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New Developments in Metastatic Breast Cancer: Integrating Recent Data into Clinical Practice

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Abstract: The treatment of metastatic breast cancer continues to be a challenging area for medical oncologists. Breast tumors are classified into several groups based on immunohistochemistry: those that are estrogen-receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative; those that are HER2–positive and either estrogen-receptor–positive or estrogen-receptor–negative; and those that are negative for the estrogen receptor, progesterone receptor, and HER2 (known as *triple-negative*). These biologic factors are an important component of the risk assessment and treatment strategy. Management goals for advanced disease are to target treatment to the specific biology in a more effective way, and to add in targeted agents that may improve the effectiveness of standard therapies, such as hormone therapy and chemotherapy. There are several new therapies that are changing outcome for patients with metastatic disease, such as eribulin, pertuzumab, and ado-trastuzumab emtansine. It is critical to understand the appropriate dosing schedules of novel agents and how best to combine them with standard therapy. Ongoing clinical trials are evaluating new treatment approaches, as well as ways to identify biologic subsets that might benefit from particular therapies. Investigational agents include glembatumumab vedotin, neratinib, and margetuximab.

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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

Patients with early-stage breast cancer are likely to achieve long-term survival, usually with tolerable treatments. Metastatic disease has been more intractable. Prognosis for these patients has recently improved with the approval of several new agents, including eribulin, lapatinib, pertuzumab, and ado-trastuzumab emtansine. Many more agents are in clinical development. Clinical trials in metastatic breast cancer largely focus on treatment of the 3 main subtypes of the disease: hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive, and triple negative (that is, negative for the estrogen receptor, progesterone receptor, and HER2). The patient's tumor biology will help guide treatment decisions. Biologic agents have toxicities that differ from those associated with chemotherapy. It is critical to understand the appropriate dosing schedules of novel agents and how best to combine them with standard therapy. Quality of life should be an important consideration when discussing management goals with patients.

Educational Objectives

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

- Discuss the latest efficacy and safety data from recently reported clinical trials on new and emerging metastatic breast cancer therapies
- Identify patients most likely to benefit from novel treatment approaches
- Integrate new and emerging agents into clinical practice
- Develop management goals based on tumor biology, treatment efficacy and safety, and quality of life concerns

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New Developments in Metastatic Breast Cancer: Introduction

Hope S. Rugo, MD

Breast cancer is the most common malignancy among women worldwide.¹ In the United States, it is diagnosed in approximately 200,000 women each year.² There have been significant improvements in understanding the biology of the disease, as well as in treatment and supportive care. The majority of women who are diagnosed with early-stage breast cancer enjoy long-term survival, usually with tolerable treatment. The prognosis for women with metastatic disease is more limited. Each year, approximately 40,000 women die of metastatic breast cancer.³ Approximately 5% to 10% of women with breast cancer are diagnosed with metastatic disease,⁴ and 15% to 20% of women with breast cancer will develop recurrent disease.⁵ Recurrent disease is usually considered either locoregional or distant. In medical oncology, the more important type of recurrence is distant disease because these patients have incurable cancer at the start. Patients with locoregional disease are at increased risk of developing distant disease, and they are often re-treated with systemic therapy.

Metastatic breast cancer can develop long after a patient is diagnosed with early-stage disease. The more aggressive proliferative cancers tend to recur within the first 5 years after diagnosis. Patients with hormone-receptor–positive disease have a longer duration of risk. Approximately 50% of recurrences in hormone receptor–disease occur more than 5 years after initial diagnosis.⁶ The subset of hormone receptor–positive–disease that is more proliferative has a higher risk of recurrence in the first 5 years.

Classically, breast tumors are classified into several groups based on immunohistochemistry: those that are estrogen-receptor–positive and human epidermal growth factor receptor 2 (HER2)-negative; those that are HER2-positive and either estrogen-receptor–positive or estrogen-receptor–negative; and those that are negative for the estrogen receptor, progesterone receptor, and HER2 (known as *triple-negative*). These biologic factors are an important component of the risk assessment and treatment strategy (Table 1).⁴

Prognosis

Evaluation of patients with recurrent breast cancer must include consideration of therapeutic goals and prognosis. The median overall survival for patients with HER2 normal disease starting chemotherapy for metastatic breast

Table 1. Metastatic Breast Cancer: Factors Pertaining to Risk Assessment and Treatment Decisions

| Disease-Related Factors |
|---|
| Disease-free interval |
| Previous therapies and response |
| Biologic therapies (hormonal receptors, HER2) |
| Tumor burden (number and site of metastases) |
| Need for control of disease/symptoms |
| Patient-Related Factors |
| Patient preferences |
| Biologic age |
| Menopausal status |
| Comorbidities and performance status |
| Socioeconomic and psychologic factors |
| Therapies available in the patient's country |

HER2, human epidermal growth factor receptor 2.

Adapted from Cardoso F et al. *Ann Oncol.* 2012;23(suppl 7):vii11-vii19.⁴

cancer is approximately 2 and a half years.⁷ Overall, this prognosis has not changed significantly in the past 10 years. However, additional therapy has changed the prognosis for patients with HER2-positive breast cancer, especially those who have not previously received HER2-targeted agents. In addition, patients who have hormone-receptor–positive, hormone-sensitive disease have a longer median survival of approximately 5 years. Approximately 5% of patients with metastatic breast cancer have a much longer survival. The disease biology of this small subset is poorly understood.

Treatment

It is important to address the goals of therapy when metastatic breast cancer is diagnosed and at every point when treatment decisions are made. For the majority of patients, the goals of therapy are to live as long as possible with the best quality of life. The patient should be an integral partner in the decision-making process regarding treatment, and her goals of therapy should be considered. For example, some patients may want to avoid drugs that cause hair loss until there are no other options. Other issues of importance to patients include treatment of brain metastases and the use of intravenous vs oral therapy.

The first treatment consideration is the disease biology (Figure 1). Treatment will be guided by the same markers

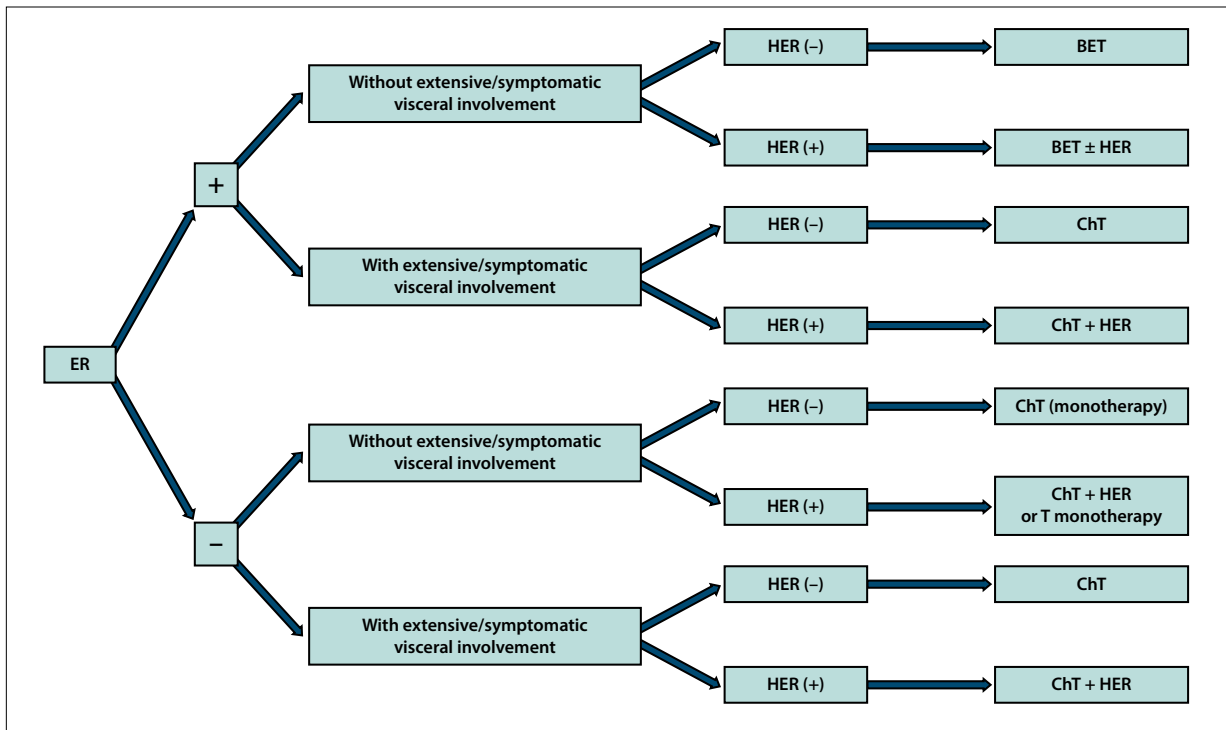


Figure 1. In metastatic breast cancer, the first treatment consideration is the disease biology. ET, endocrine therapy; ChT, chemotherapy; HER2, human epidermal growth factor receptor 2–directed therapy; T, trastuzumab. Adapted from Cardoso F et al. *Ann Oncol.* 2012;23(suppl 7):vii11-vii19.⁴

used for early-stage disease, including estrogen receptor status and HER2/neu status. (In the future, we hope to incorporate additional markers—including mutations, activation of specific pathways, proteomics, and expression analyses—but current data do not support their use.) Comparison of a metastatic patient's current markers with those present in early-stage disease appears to be extremely important. In most patients, diagnosis of metastatic disease should prompt an additional biopsy with assessment of markers to provide insight into the biology of their current disease. Metastatic breast cancer may be biologically heterogeneous, similar to the primary tumor. Therefore, tumors that express a specific clinical phenotype, but have markers that are discordant with this phenotype, should be reevaluated at every opportunity to ensure that a specific subset of breast cancer cells that might benefit from an alternative treatment has not been missed.

In addition, management choices will be based on clinical parameters such as disease-free interval and presence of visceral disease. In general, 1 year has been the disease-free interval used to assess the effectiveness of therapy. Based on recent data, however, it appears more reasonable to use a disease-free interval of approximately 2 years. Patients with a shorter disease-free interval after upfront therapy appeared to have a significantly worse prognosis and less durable responses to initial therapy.⁸ The second important clinical parameter is the extent of disease, which includes the number of visceral sites and symptoms related

to disease. For patients with hormone-receptor–positive breast cancer, the presence of limited visceral disease does not appear to affect response to hormone therapy. These patients may therefore be treated with hormone therapy upfront. Patients receive more aggressive treatment if they have visceral crises, which refers to extensive visceral disease and symptoms related to visceral involvement, such as shortness of breath, abdominal pain, or laboratory findings of organ dysfunction (eg, abnormal liver function tests).

In general, treatment is divided into hormone therapy, chemotherapy, and HER2-targeted therapy. When possible, treatment begins with oral agents and those with the least toxicity. For metastatic patients, treatment is a modification of that used in early-stage therapy to reduce toxicity. Combination chemotherapy may be appropriate as a first-line approach in patients who have very short disease-free intervals, chemotherapy-resistant disease, or, in some cases, triple-negative disease.

Treatment with hormone therapy or single-agent chemotherapy is likely to be appropriate for patients who have more indolent disease with fewer symptoms or symptoms that are easily controlled, such as bone pain. Only a subset of patients require a more aggressive approach. Patients with HER2–positive disease are generally treated with HER2-targeted therapy upfront in combination with chemotherapy, with the chemotherapy usually discontinued after the patient achieves a reason-

able radiographic and clinical response, usually after administration of 6 to 8 cycles.

Interestingly, in studies of HER2-positive disease, a complete response did not correlate with prolonged progression-free survival and, therefore, a partial response is considered adequate for discontinuation of chemotherapy.⁹ At that point, treatment with HER2-targeted therapies should continue.

Traditional management includes sequential treatment with chemotherapy, hormone therapy, and HER2-targeted agents as appropriate. If a patient has hormone-receptor-positive disease and is receiving chemotherapy, a chemotherapy holiday might be appropriate, particularly when hormone therapy can be used as a bridge. For triple-negative breast cancer, however, data have demonstrated that continuing chemotherapy results in improved survival compared to stopping chemotherapy after response and waiting for progression. For patients with HER2-positive disease, as mentioned earlier, the general approach is to treat with chemotherapy and HER2-targeted therapy and then allow a break from chemotherapy with continuation of HER2-targeted agents until disease progression. Some of these patients will have a very long progression-free survival on HER2-targeted therapy alone.

With traditional treatment approaches, patients generally experience progressively shorter progression-free survival and lower response rates until they exhaust all options or die from organ dysfunction. Management goals for advanced disease are to target treatment to the specific biology in a more effective way, and to add in targeted agents that may improve the effectiveness of standard therapies, such as hormone therapy and chemotherapy. There has already been much success in improving the response to chemotherapy and hormone therapy with HER2-targeted agents. Many of the new HER2-targeted agents have been associated with improved response, progression-free survival, and overall survival without increased toxicity. The goal moving forward is to be able to achieve this same degree of success in other subsets of breast cancer. Most excitingly, response to hormone therapy has been improved with an agent targeted to the phosphatidylinositol 3-kinase (PI3K) pathway, specifically the mammalian target of rapamycin (mTOR) inhibitor everolimus.¹⁰ There are multiple new agents targeting this pathway in clinical trials. In addition, there are new agents targeting the cyclin-dependent kinases 4 and 6 that appear to be very promising in their ability to increase responses and improve response duration in patients receiving hormone therapy for metastatic hormone receptor-positive breast cancer.

Biologic agents have toxicities that differ from those associated with chemotherapy. For example, few biologic agents, if any, cause complete alopecia. These agents may, however, have other noxious side effects that prevent their delivery in adequate doses over time. It is therefore critical to

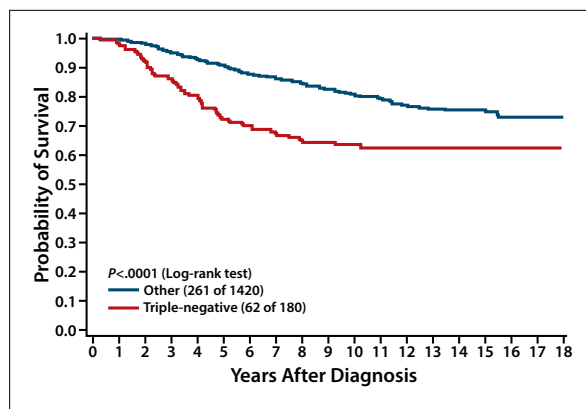


Figure 2. Patients with triple-negative disease have the shortest survival after diagnosis among all patients with metastatic disease. Adapted from Dent R et al. *Clin Cancer Res.* 2007;13:4429-4434.¹¹

understand the appropriate doses of biologic agents and how best to combine them with standard therapy. It has been difficult to identify subsets of patients within broader biologic groups that might benefit from specific targeted therapies. For example, the new HER2-targeted therapies appear to be effective in patients with HER2-positive disease, but it has not yet been possible to identify specific subgroups that benefit more. The same is true for new agents that improve response and response duration to hormone therapy. There is a small group of patients with disease that responds very poorly. A larger group of patients appears to benefit regardless of whether the specific targeted pathway, such as PI3K, is activated. Future goals are to better understand whether new biologic techniques, or perhaps evaluation of metastatic tumor tissue vs archived tissue from the initial diagnosis, can help to identify specific tumor subsets that might benefit from newer targeted agents.

Unmet Needs

Traditional treatments leave several unmet needs. The least amount of progress has been seen in the management of triple-negative breast cancers, a heterogeneous group with different biologic subtypes. There is intense study, both in the clinic and in the laboratory, to find better agents that can eventually translate into longer survival for these patients, who have the shortest survival after diagnosis of all patients with metastatic disease (Figure 2).¹¹ It has not yet been possible to identify a specific target that is expressed in the majority of these patients and that can be the focus of an effective targeted biologic agent. Some of the new chemotherapy agents are very effective in patients with triple-negative breast cancer. We are trying to understand the value of DNA-damaging agents and whether patients most likely to benefit from these agents can be identified through specific tests, such as the homologous recombination defect

efficiency test. The study of PARP inhibitors is ongoing, particularly in patients with BRCA-mutated tumors.

Other unmet needs are to adequately control treatment toxicity and to provide appropriate supportive care for fatigue and peripheral neuropathy. A better understanding is needed to better identify which patients are at risk for peripheral neuropathy and to provide them with protective therapies or alternative therapies. In addition, agents are needed to prevent the development of brain metastases and to treat them more effectively to prevent continued progression.

Summary

The treatment of metastatic breast cancer continues to be a challenging area for medical oncologists. However, there are several exciting new therapies that have changed outcome for patients with this disease. In addition, ongoing clinical trials are evaluating new treatment approaches, as well as ways to identify biologic subsets that might benefit from particular therapies.

Acknowledgment

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Practice-Changing Data in Metastatic Breast Cancer

Edith A. Perez, MD

Many advances continue to be made in the field of metastatic breast cancer, especially in the context of managing patients according to a better understanding of the underlying biology of the disease. Results from a number of clinical studies have recently been reported, and the field eagerly awaits the findings of many ongoing trials. Some of these studies are attempting to correlate molecular signatures or abnormalities in the breast tumor with the way patients respond to particular interventions. Hopefully, these findings will guide clinicians in better management and treatment decisions.

In the interim, many of the findings reported by recent clinical trials are applicable to the care of patients with metastatic breast cancer. Clinical trials in metastatic breast cancer largely focus on treatment of the 3 main subtypes

of the disease: hormone receptor–positive, HER2-positive, and triple negative (that is, negative for the estrogen receptor, progesterone receptor, and HER2; Table 2). When interpreting the results from these studies, it is important to recognize the significant and clinically meaningful heterogeneity that exists among even these 3 subtypes.

Agents Targeting HER2-Positive Metastatic Breast Cancer

HER2 overexpression is a frequent event in breast cancer, occurring in approximately 15% to 20% of all breast cancers.^{1,2} The treatment of HER2-positive metastatic breast cancer was revolutionized in 1998 with the US Food and Drug Administration (FDA) approval of

Table 2. Treatment According to Subtype of Metastatic Breast Cancer

| | Incidence | Therapy |
|-----------------|-----------|---------------------------|
| ER+, ER-, PR+ | 75% | Endocrine Chemotherapy |
| HER+ | 15%–30% | Anti-HER2 |
| Triple-negative | 10%–20% | Chemotherapy |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

trastuzumab, a HER2-directed recombinant humanized monoclonal antibody. Nearly a decade later, in 2007, the FDA approved use of the small-molecule tyrosine kinase inhibitor lapatinib (in combination with capecitabine) for patients with HER2-positive metastatic breast cancer previously treated with an anthracycline, a taxane, and trastuzumab. Subsequently, in 2010, lapatinib was approved in combination with letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer overexpressing HER2. More recently, 2 other drugs were approved for this disease setting: pertuzumab (in 2012) and ado-trastuzumab emtansine (T-DM1; in 2013).

Like trastuzumab, pertuzumab is a (fully) humanized monoclonal antibody directed against HER2. However, slight but significant differences exist between the 2 antibodies.³ For example, although the mechanism of action of pertuzumab is complementary to trastuzumab, it is not identical. The primary mechanism of action of trastuzumab has been attributed to inhibition of HER2-dependent signal transduction, but pertuzumab is thought to act primarily by inhibiting ligand-induced dimerization between HER2 and other HER family members, such as HER3. This difference is attributed to the fact that pertuzumab recognizes and binds a different epitope on the HER2 receptor. A number of other mechanisms of action have been attributed to both antibodies, including antibody-dependent cell-mediated cytotoxicity (ADCC).

Pertuzumab is indicated for use in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.⁴ Approval of pertuzumab was based primarily on the positive results of the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) study, an international, randomized, double-blind, placebo-controlled phase 3 trial.^{5,6} A total of 808 metastatic breast cancer patients were enrolled and randomized in a 1:1 fashion to receive pertuzumab, trastuzumab, and docetaxel or placebo, trastuzumab, and docetaxel as first-line therapy. Treatment was continued until time of disease progression or development of unmanageable toxicity. The baseline demographic characteristics were

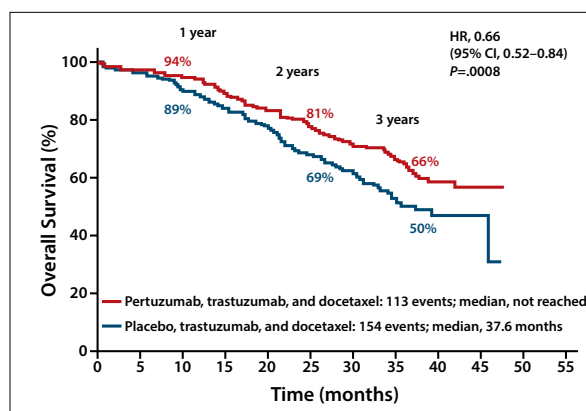


Figure 3. Overall survival in the CLEOPATRA trial. CLEOPATRA, Clinical Evaluation of Pertuzumab and Trastuzumab. Adapted from Swain SM et al. *Lancet Oncol.* 2013;14(6):461-471.⁷

well balanced between the treatment arms. In both arms, the median age was 54.0 years, and 99% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Other similar characteristics included hormone receptor-positive status (47.0% and 49.0% in the pertuzumab and placebo arms, respectively) and use of prior adjuvant or neoadjuvant therapy (45.8% and 47.3% in the pertuzumab and placebo arms, respectively). Notably, trastuzumab was a component of prior adjuvant or neoadjuvant therapy in 11.7% of patients in the pertuzumab arm and 10.1% of patients in the placebo arm. These rates are lower than those typically observed in most real-world clinical settings, in which a large majority of HER2-positive metastatic breast cancer patients have previously received adjuvant or neoadjuvant trastuzumab based on its high efficacy.

The primary study endpoint—progression-free survival—was significantly improved among patients in the pertuzumab group compared with the placebo group (median independently reviewed progression-free survival, 18.5 vs 12.4 months; hazard ratio for progression or death, 0.62; 95% CI, 0.51-0.75; $P < .001$).^{5,6} Importantly, this benefit in progression-free survival occurred across all patient subgroups, including age, race/ethnicity and geographic region, visceral vs nonvisceral disease, hormone receptor status, and use of prior adjuvant therapy. The objective response rate was also improved in the pertuzumab arm compared with the placebo arm (80.2% vs 69.3%; $P = .001$). This difference was caused primarily by an increase in the number of partial responses (74.6% vs 65.2%); the proportion of complete responses was similar between the 2 arms (5.5% vs 4.2%).

In a second interim analysis of overall survival, the median overall survival was 37.6 months in the placebo group and was not reached in the pertuzumab group (hazard ratio, 0.66; 95% CI, 0.52-0.84; $P = .0008$; Figure 3).⁷ Estimated

overall survival rates were as follows for the pertuzumab and placebo arms, respectively: 94.4% vs 89.0% at 1 year, 80.7% vs 69.4% at 2 years, and 65.8% vs 50.4% at 3 years.

An exploratory analysis of biomarkers in CLEOPATRA did not identify any that were predictive of response to therapy or prognostic of outcome.⁶ The investigators concluded that HER2 was the only currently available biomarker suitable for selecting patients for HER2-directed therapy.

All-grade adverse events occurring at a greater frequency (by at least 5 percentage points) in the pertuzumab-treated arm included diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin.^{5,6} Rates of grade 3 or higher febrile neutropenia and diarrhea were at least 2 percentage points higher in the pertuzumab arm. A higher incidence of any-grade left ventricular systolic dysfunction occurred in the placebo arm compared with the pertuzumab arm (8.3% vs 4.4%). In a follow-up analysis of cardiac tolerability, the overall incidence of all-grade cardiac adverse events was 14.5% in the pertuzumab arm and 16.4% in the placebo arm; most of these events were reversible.⁸ Importantly, it was concluded that the addition of a second HER2-directed monoclonal antibody to trastuzumab did not increase risk for cardiac toxicity.

To maintain or improve upon the efficacy—and minimize the toxicity—observed with the triple combination in CLEOPATRA, the pertuzumab plus trastuzumab combination is being evaluated with other chemotherapy backbones. For example, the VELVET (A Combination of Pertuzumab, Trastuzumab, and Vinorelbine for First-Line Treatment of Patients With HER2-Positive Metastatic Breast Cancer: An Open-Label, Two-Cohort, Phase II Study) trial is a phase 2 evaluation of pertuzumab and trastuzumab plus vinorelbine in 210 previously untreated HER2-positive metastatic breast cancer patients.⁹ Included in this study design is an evaluation of antibody administration that is sequential vs combined (in a single infusion bag), with the purpose of determining the feasibility of the latter approach to minimize the infusion time. The primary endpoint of this study is overall objective response, although tolerability and progression-free survival are also being evaluated. Future studies are needed in metastatic breast cancer to evaluate pertuzumab in combination with chemotherapy for treatment of HER2-positive tumors that are refractory to trastuzumab.

T-DM1 is an antibody-drug conjugate in which trastuzumab is conjugated to the potent tubulin-targeted cytotoxic agent maytansinoid DM1. The mechanism of T-DM1 is thought to rely upon targeted delivery of the T-DM1 molecule to HER2-overexpressing breast cancer cells via the trastuzumab antibody.¹⁰ Once bound, T-DM1 is internalized and the DM1 moiety is released, freeing

it to bind to tubulin and disrupt microtubule dynamics. In addition, T-DM1 has been shown to exhibit the mechanisms of action typically associated with trastuzumab, including inhibition of HER2 signal cascades and ADCC.

T-DM1 is now approved by the FDA, with an indication as a single agent for the treatment of HER2-positive metastatic breast cancer patients who previously received trastuzumab and a taxane separately or in combination.¹¹ The approval was largely based on results from 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) study, an open-label, international, phase 3 trial that randomized 991 patients in a 1:1 ratio to receive either T-DM1 or the combination of lapatinib plus capecitabine.¹² Eligible patients had received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. The HER2-positive metastatic breast cancer patients had previously received therapy with trastuzumab and a taxane, and the lapatinib plus capecitabine combination used in the control arm is a standard regimen for this patient population. Prior to randomization, patients were stratified according to world region, number of prior chemotherapy regimens, and extent of disease involvement. The baseline characteristics were balanced between the 2 treatment groups. They included median age (53 years in each arm), ECOG performance status of 0 or 1 (99% in the T-DM1 arm and 98% in the lapatinib plus capecitabine arm), hormone receptor-positive status (57% in the T-DM1 arm and 53% in the lapatinib plus capecitabine arm), and more than 1 prior chemotherapy regimen for locally advanced or metastatic disease (39% in each arm).

One of the primary study endpoints—progression-free survival—was significantly prolonged in patients who received T-DM1 compared with patients who received lapatinib plus capecitabine (median progression-free survival, 9.6 vs 6.4 months; hazard ratio, 0.65; 95% CI, 0.55-0.77; $P < .001$; Figure 4).¹² The objective response rate was also increased in the T-DM1 group vs the lapatinib plus capecitabine group (43.6% vs 30.8%; $P < .001$). Responses with T-DM1 proved to be more durable, with a median duration of response of 12.6 months in the T-DM1 arm vs 6.5 months in the lapatinib plus capecitabine arm.

Overall survival was another primary study endpoint of the EMILIA trial.¹² In a second interim analysis, the median overall survival was greater in the T-DM1 arm vs the lapatinib plus capecitabine arm, and crossed the stopping boundary for efficacy (30.9 vs 25.1 months; hazard ratio, 0.68; 95% CI, 0.55-0.85; $P < .001$).

More grade 3 or higher adverse events were reported in the lapatinib plus capecitabine arm (57.0%) compared

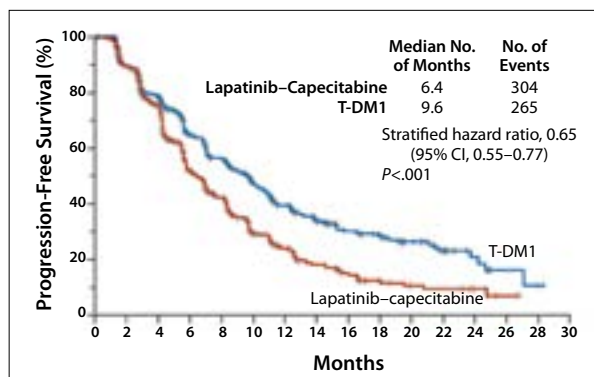


Figure 4. In the EMILIA trial, progression-free survival was prolonged in patients who received T-DM1 as compared with patients who received lapatinib plus capecitabine. EMILIA, An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine Plus Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer; T-DM1, ado-trastuzumab emtansine. Adapted from Verma S et al. *N Engl J Med.* 2012;367(19):1783-1791.¹²

with the T-DM1 arm (40.8%).¹² The most frequently reported grade 3 or 4 adverse events among T-DM1-treated patients were thrombocytopenia (12.9%) and elevated levels of aspartate aminotransferase (4.3%) and alanine aminotransferase (2.9%).

With the approval of T-DM1 in the setting of previously treated metastatic breast cancer, effort has now turned to assessing this agent in the first-line treatment of metastatic disease. One recent phase 2 randomized trial compared single-agent T-DM1 with trastuzumab plus docetaxel for the first-line treatment of 137 patients with HER2-positive metastatic breast cancer (or locally advanced recurrent breast cancer).¹³ Median progression-free survival increased from 9.2 months with trastuzumab plus docetaxel to 14.2 months with T-DM1 (hazard ratio, 0.59; 95% CI, 0.36-0.97). The objective response rate with T-DM1 was also higher compared with trastuzumab plus docetaxel (64.2% vs 58.0%). These promising data have heightened the anticipation of results from the MARIANNE (A Study of Trastuzumab Emtansine [T-DM1] Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer) study, an ongoing phase 3 trial comparing 3 regimens in first-line metastatic breast cancer treatment: T-DM1, T-DM1 plus pertuzumab, and a taxane plus trastuzumab.^{14,15}

Together, the CLEOPATRA and EMILIA trials provide new data demonstrating significant and clinically meaningful improvements in both progression-free survival and overall survival for patients with HER2-positive metastatic breast cancer. These studies have changed the standard of care for management of patients with HER2-positive advanced breast cancer.

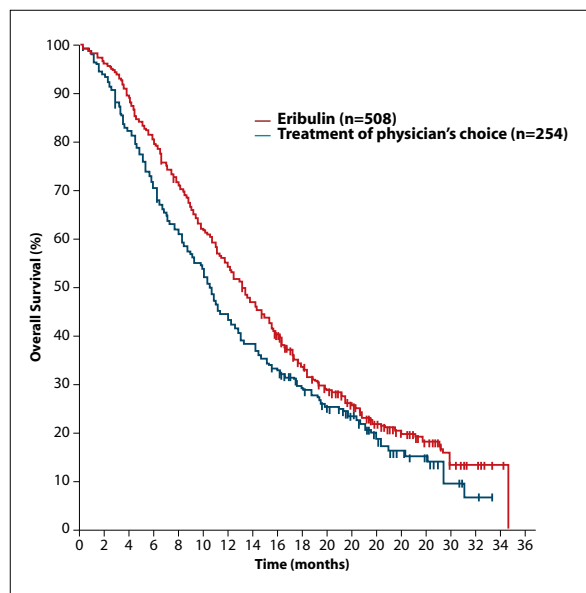


Figure 5. An updated analysis of the EMBRACE trial showed median overall survival was increased in the eribulin arm compared with the treatment of physician's choice arm remained significant in an updated analysis. EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin. Adapted from Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2013.¹⁶

Novel Strategy for Targeting Microtubules in Metastatic Breast Cancer

Eribulin mesylate is a synthetic analogue of halichondrin B, an antineoplastic agent produced by marine sponges. Eribulin binds to tubulin, inhibiting tubulin polymerization and thus microtubule assembly. Eribulin has gained FDA approval for the treatment of metastatic breast cancer patients who have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting and at least 2 chemotherapeutic regimens for the treatment of metastatic disease.¹⁶ This approval was based on results from the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin) trial, a phase 3, global, multicenter, open-label randomized trial that compared eribulin with a treatment of the physician's choice in 762 women with heavily pretreated locally recurrent or metastatic breast cancer.¹⁷ The baseline patient characteristics were well balanced between the treatment arms. Most patients had an ECOG performance status of 0 or 1 (42% and 49%, respectively). A majority of the study population was HER2-negative (74%), and most patients were hormone receptor-positive (64%). A total of 19% of the patients had triple-negative disease. The median number of prior chemotherapy regimens was 4 (range, 1-7), with capecitabine the most common agent.

The EMBRACE study met its primary endpoint by demonstrating a significantly improved median overall

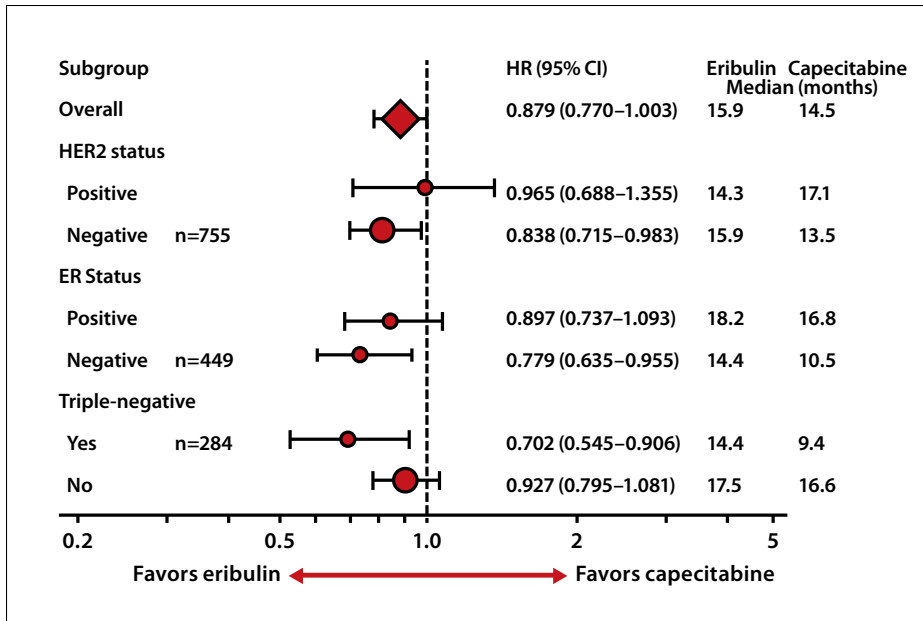


Figure 6. In Study 301, a phase 3 trial of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes, prespecified subgroup analyses suggested that eribulin was favored in patients with HER2-negative disease, ER-negative disease, and triple-negative breast cancer.

CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio. Adapted from Kaufman PA et al. SABCS abstract S6-6. *Cancer Res.* 2012;72(suppl 3).¹⁸

survival in the eribulin arm compared with the treatment of physician's choice arm (13.1 vs 10.6 months; hazard ratio, 0.81; 95% CI, 0.66-0.99; $P=.041$).¹⁷ The increase in median overall survival observed in the eribulin arm compared with the treatment of physician's choice arm remained significant in an updated analysis (13.2 vs 10.5 months; hazard ratio, 0.81; 95% CI, 0.67-0.96; $P=.014$; Figure 5).¹⁶ The 1-year overall survival rate was 54.5% in the eribulin group and 42.8% in the treatment of physician's choice group.

An independent review showed a trend toward improved median progression-free survival with eribulin compared with the treatment of physician's choice; however, this difference did not reach statistical significance (3.7 vs 2.2 months; hazard ratio, 0.87; 95% CI, 0.71-1.05; $P=0.137$).¹⁷ Statistical significance was achieved when an investigator review was conducted (hazard ratio, 0.76; 95% CI, 0.64-0.90; $P=.002$). The rate of objective response was significantly improved with eribulin vs treatment of physician's choice (12% vs 5%; $P=.002$).

Most adverse events occurring in both arms were mild or moderate (grade 1/2).¹⁷ Grade 3 or 4 adverse events occurring more frequently in the eribulin arm vs the treatment of physician's choice arm were neutropenia, leukopenia, and peripheral neuropathy. Grade 3 and 4 peripheral neuropathy occurred at a rate of 8% in the eribulin arm and less than 1% in the control arm.

A complementary trial, Study 301, was a global, open-label, randomized, multicenter, phase 3 study in

1,102 women with locally advanced or metastatic breast cancer.¹⁸ Patients were randomized 1:1 to receive either eribulin or capecitabine; prior to randomization, patients were stratified by geographic region and HER2 status. Enrolled patients had received 3 or fewer prior chemotherapy regimens, up to 2 of which for advanced disease. All patients had received a prior anthracycline and taxane, either in the adjuvant or neoadjuvant setting or for locally advanced or metastatic disease. Baseline demographics were well balanced between the treatment arms. The median age was 53 to 54 years, and most patients had an ECOG performance score of either 0 or 1 (97%-98%). Approximately half of patients (50%-53%) had received 1 prior chemotherapy regimen, and 27% to 28% had received 2 prior chemotherapy regimens. The majority of patients were HER2-negative (68%-69%), and 25% to 27% had triple-negative disease.

The primary study endpoints were overall survival and progression-free survival.¹⁸ There was not a statistically significant improvement in overall survival with eribulin vs capecitabine (15.9 vs 14.5 months; hazard ratio, 0.879; 95% CI, 0.770-1.003; $P=.056$). Interestingly, however, the yearly overall survival rates showed a consistent trend for benefit with eribulin vs capecitabine at 1 year (64.4% vs 58.0%; $P=.035$), 2 years (32.8% vs 29.8%; $P=.324$), and 3 years (17.8% vs 14.5%; $P=.175$). A subgroup analysis suggested that eribulin may increase survival over capecitabine in patients with certain tumor subtypes, such as triple-

negative tumors (14.4 vs 9.4 months; hazard ratio, 0.702; 95% CI, 0.545-0.906; Figure 6).

Median progression-free survival was also not significantly different between the eribulin and capecitabine treatment groups (investigator review, 4.2 vs 4.1 months; hazard ratio, 0.977; 95% CI, 0.857-1.114; $P=0.736$; independent review, 4.1 vs 4.2 months; hazard ratio, 1.079; 95% CI, 0.932-1.250; $P=.305$).¹⁸ Objective response was also similar between the eribulin and capecitabine arms (11% vs 12%; $P=.849$).

Although Study 301 did not demonstrate a significant superiority with eribulin vs capecitabine in either overall survival or progression-free survival, it did show that both agents had similar activity.¹⁸ Notably, certain adverse events occurred with less frequency in the eribulin arm vs the capecitabine arm, including hand-foot syndrome and diarrhea. However, grade 3/4 neutropenia and leukopenia were more frequent with eribulin. The suggestion that eribulin may be more effective in certain patient subgroups—such as those with triple-negative metastatic breast cancer—should be explored in future clinical studies.

Etirinotecan Pegol

The novel agent etirinotecan pegol (NKTR-102) was examined in a randomized phase 2 study of patients with refractory metastatic breast cancer who had received prior therapy with anthracyclines and taxanes (capecitabine was allowed).¹⁹ The study evaluated 2 schedules. It showed a response rate of 29%, and disease stability in approximately 35% of patients at 6 months. The toxicity profile was fairly tolerable; the main issue was diarrhea, which occurred in approximately one-quarter of the patients, but it tended to occur later in the therapy (after a median of 3 months on therapy). This late occurrence reflects the fact that this toxicity was observed mainly in patients who were otherwise deriving clinical benefit from the treatment. This trial led to the ongoing BEACON (Breast Cancer Outcomes With NKTR-102) phase 3 trial, which recently completed accrual.²⁰ BEACON is a global study evaluating NKTR-102 vs physician's choice of single-agent chemotherapy in patients with metastatic breast cancer previously treated with anthracyclines, taxanes, and capecitabine. Results are expected in 2014 or 2015.

Acknowledgment

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

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Novel Data in Metastatic Breast Cancer

Linda T. Vahdat, MD

Data from recent and ongoing clinical trials in metastatic breast cancer are providing insight into the use of existing agents and identifying novel agents with activity in this setting. Management of metastatic breast cancer will likely evolve over the next few years as these data are incorporated into clinical care.

New Data for Everolimus

Everolimus is an agent that targets the mTOR protein for inhibition. In 2012, it gained approval for use in combination with exemestane for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer, following failure of treatment with either letrozole or anastrozole.¹ Both the mTOR and the related PI3K pathways have been implicated in the development of resistance to endocrine therapy in patients with hormone receptor-positive disease, and therefore targeting 1 or both of these pathways is likely a reasonable strategy.² This approach was successful in the phase 3 BOLERO-2 (Breast Cancer Trials of Oral Everolimus-2) trial, which randomized patients to receive either exemestane plus everolimus or exemestane plus placebo.³ The resulting median progression-free survival was 7.8 months for exemestane plus everolimus compared with 3.2 months for exemestane plus placebo (hazard ratio, 0.45; 95% CI, 0.38-0.54; $P < .0001$; Figure 7).⁴ The overall response rates were 12.6% for patients receiving exemestane plus everolimus vs only 1.7% in patients receiving exemestane plus placebo. In a planned interim analysis, overall survival was not significantly different between the treatment groups (hazard ratio, 0.77; 95% CI, 0.57-1.04).

In the BOLERO-3 follow-up study, 569 patients with HER2-positive trastuzumab-resistant locally advanced or metastatic breast cancer were randomized to receive vinorelbine plus trastuzumab, given with either everolimus or placebo.⁵ Although overall survival data were not yet available, a significant improvement in median progression-free survival was observed in the everolimus group compared with the placebo group (7.0 vs 5.78 months, hazard ratio, 0.78; 95% CI, 0.65-0.95; $P = .0067$).

Investigational Agents in Clinical Development

Glebatumumab Vedotin

Glebatumumab vedotin (CDX-011) is a novel antibody-drug conjugate consisting of a fully human monoclonal antibody directed against an extracellular domain of the glycoprotein non-metastatic melanoma protein

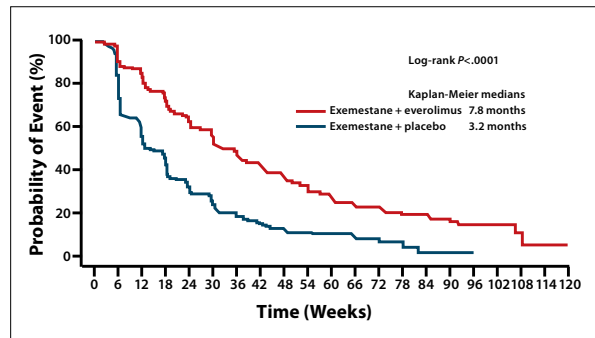


Figure 7. In the final progression-free survival analysis of the BOLERO-2 trial, progression-free survival was longer with exemestane plus everolimus compared with exemestane plus placebo. BOLERO-2=Breast Cancer Trials of Oral Everolimus. Adapted from Piccart M et al. SABCS abstract P6-04-02. *Cancer Res.* 2012;72(suppl 3).⁴

B (GPNMB), and the potent microtubule inhibitor monomethyl auristatin E.⁶ GPNMB is a transmembrane glycoprotein important for cellular invasion and migration. Patients with tumors that express high amounts of GPNMB have shorter metastasis-free survival and overall survival (Figures 8 and 9).⁷ In a phase 1/2 trial that enrolled 42 patients, glebatumumab vedotin treatment resulted in an objective response rate of 17%. Interestingly, in a small subset of patients with triple-negative breast cancer, the objective response rate appeared to be slightly higher, at 25%. Dose-limiting toxicities were grade 3 peripheral neuropathy (in 10%) and rash (in 6%). An interesting observation in this study was that patients with GPNMB overexpression, as assessed by immunohistochemistry, appeared to derive a greater benefit from glebatumumab vedotin treatment.⁸

To build upon these data, the EMERGE (A Study of CDX-011 [CR011-vcMMAE] in Patients With Advanced GPNMB-Expressing Breast Cancer) study was conducted to further characterize the safety and efficacy of glebatumumab vedotin in 120 patients with locally advanced or metastatic breast cancer and GPNMB overexpression.⁹ Patients were randomized in a 2:1 fashion to treatment with either glebatumumab vedotin or treatment of the physician's choice. All patients had received between 2 and 7 prior therapies, including an anthracycline, a taxane, and capecitabine. Crossover was allowed at the time of disease progression for patients randomized to the treatment of physician's choice arm. Patients were confirmed to have GPNMB

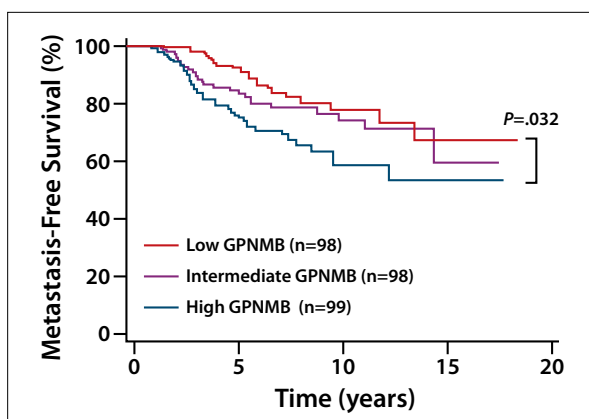


Figure 8. Patients with tumors that express high amounts of GPNMB have shorter metastasis-free survival. GPNMB, glycoprotein non-metastatic melanoma protein B. Adapted from Rose AA et al. *Clin Cancer Res.* 2010;16(7):2147-2156.⁷

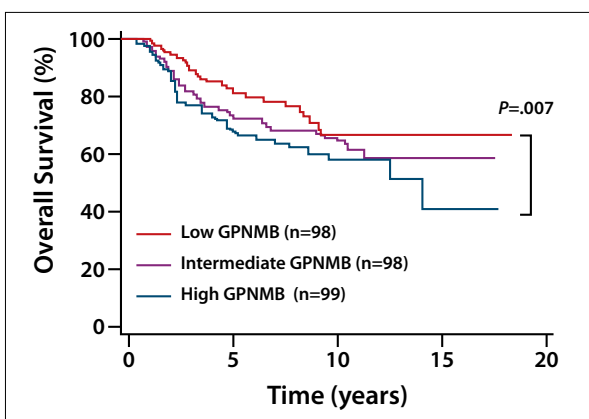


Figure 9. Patients with tumors that express high amounts of GPNMB have shorter overall survival. GPNMB, glycoprotein non-metastatic melanoma protein B. Adapted from Rose AA et al. *Clin Cancer Res.* 2010;16(7):2147-2156.⁷

overexpression using a centralized immunohistochemistry method. GPNMB overexpression, which was required for eligibility, was defined as more than 5% expression in either the epithelial or stromal component of a tumor block specimen; as a result, enrolled patients had varying levels of GPNMB overexpression. Interestingly, it became clear in the study analysis that patients with triple-negative metastatic breast cancer tended to show greater levels of GPNMB overexpression.

At baseline, patients in both arms had received a median of 6 prior treatment regimens. In addition to anthracyclines, taxanes, and capecitabine (which were required for study enrollment), other prior therapies included gemcitabine, bevacizumab, and vinorelbine. Overall, these patients seemed to be fairly representative of a heavily pretreated metastatic breast cancer population.

The objective response rate achieved with glembatumumab vedotin was 19% vs 14% with treatment of physician's choice. When the subgroup of patients with triple-negative disease was assessed separately, the objective response rates were 21% with glembatumumab vedotin and 0% with the control. Patients with triple-negative disease who had high levels of GPNMB overexpression achieved a 36% objective response rate with glembatumumab vedotin, compared with 0% with treatment of physician's choice. In this subgroup of patients with high GPNMB overexpression and triple-negative breast cancer, the median progression-free survival was 3.5 months with glembatumumab vedotin vs 1 month with treatment of physician's choice.

There were no new toxicities apparent with glembatumumab vedotin in the EMERGE trial. Overall, this agent was well tolerated. Adverse events included grade 3/4 neutropenia (in 24%), grade 3/4 rash (in 4%), and grade 3/4 peripheral neuropathy (in 3%).

Glembatumumab vedotin will be evaluated as an earlier line of treatment in a randomized phase 2 trial. This study is expected to focus especially on the subset of metastatic breast cancer patients with both high levels of GPNMB overexpression and triple-negative disease.

Neratinib

Neratinib (HKI-272) is a potent tyrosine kinase inhibitor active against HER1, HER2, and HER4.^{10,11} In an open-label, multicenter, phase 2 trial evaluating single-agent neratinib in patients with HER2-positive metastatic breast cancer, the 16-week progression-free survival rate was 59% among women with prior exposure to trastuzumab and 78% among women with no prior trastuzumab therapy.¹¹ The respective median progression-free survival was 22.3 weeks and 39.6 weeks, respectively, and the objective response rates were 24% and 56%. Single-agent neratinib was compared against lapatinib plus capecitabine in a randomized phase 2 trial, which found that neither inferiority nor noninferiority could be established.¹²

Of particular interest is a phase 1/2 trial investigating the combination of the mTOR inhibitor temsirolimus with neratinib in trastuzumab-refractory HER2-positive metastatic breast cancer.¹³ At baseline, the median number of prior therapies was 3, and 52% of the 27 patients had hormone receptor-positive disease. The combination was associated with a 44% rate of partial responses, although no complete responses were reported. Patients who experienced a partial response with neratinib plus temsirolimus showed a maximum change in the size of their target lesions of between 33% and 83%. Median progression-free survival of the 27 evaluable patients was 18 weeks. The combination of

neratinib and temsirolimus had acceptable tolerability. The most frequent severe adverse events were grade 3 diarrhea (22%), grade 3 mucositis (15%), grade 3 hyperglycemia (4%), grade 3 leukopenia (4%), and grade 3 fatigue (4%).

Margetuximab

Margetuximab (MGAH22) is an Fc-modified chimeric monoclonal antibody directed against the HER2 receptor. Unlike other HER2-targeted antibodies, the Fc region of margetuximab has been modified to enhance the ADCC activity of the molecule. A recent phase 1 trial of margetuximab in patients with advanced solid tumors showed promising activity.¹⁴ A phase 2 trial is now initiating, which will enroll HER2-positive metastatic breast cancer patients.

Hsp90 Inhibitors

Heat shock protein 90 (Hsp90) is a molecular chaperone protein required for the proper maturation and activation of numerous client proteins. Many of these Hsp90 client proteins play critical roles in cell growth, differentiation, and survival. Relative to normal cells, cancerous cells rely more heavily on Hsp90 activity. Inhibitors of Hsp90 are particularly interesting in HER2-positive metastatic breast cancer, as HER2 is known to be a client protein of Hsp90.¹⁵ Several ongoing clinical trials are evaluating these agents both as monotherapy and in combination with trastuzumab.

PARP Inhibitors

Inhibitors of the poly(ADP-ribose) polymerase (PARP) showed significant promise a few years ago. In a randomized phase 2 trial of patients with triple-negative metastatic breast cancer, the PARP inhibitor iniparib demonstrated improved outcomes (including response rate, progression-free survival, and overall survival) when combined with gemcitabine and carboplatin. These results failed to be reproduced in a similarly designed phase 3 trial.^{16,17} Despite these disappointing results, a number of recently published reports point to a potential for the use of PARP inhibitors in patients with *BRCA* mutations.¹⁸⁻²⁰

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New Developments in Metastatic Breast Cancer: General Discussion

Edith A. Perez, MD What are some unmet needs in metastatic breast cancer?

Linda T. Vahdat, MD One issue that I think is particularly relevant for the metastatic breast cancer field is the need to increase the number of patients enrolled in clinical trials. That stated, there is also a need for better-designed clinical studies. New drugs must be moved through the clinical development process as quickly as possible, but it is also important to have better judgment in how these drugs are evaluated in the clinical trial setting. It would be very helpful if more of these new agents could be moved into the neoadjuvant and adjuvant setting. In addition, there is a great need to assess molecular targets of predictive or prognostic significance for these newer agents.

Hope S. Rugo, MD One issue with clinical trial development is collaboration between drug manufacturers to facilitate testing active combinations in the clinic as early as possible. Often studies are limited by a specific company's drug portfolio, so that important potential combinations are lost or poorly studied. The neoadjuvant setting has emerged as a mechanism for studying agents at an early stage of development, using pathologic complete remission as a surrogate endpoint, and providing accessible tissue for biomarker development.

Linda T. Vahdat, MD An important question in the management of these patients is when to repeat biopsies. Many metastatic breast cancer patients actually want to be rebiopsied. Often they also request it after second-line or third-line therapy. In some cases I agree, but in others I do not.

Edith A. Perez, MD The issue of repeated biopsies is one that will be very important for research. The more trials we have to target these abnormalities, the better it will be for our patients. There has been an increasing reliance on the use of biopsies in the metastatic setting as part of the standard of care. In fact, I see this happening in our own practice. This is very different compared to a decade ago, when biopsies were almost never performed in metastatic breast cancer patients. Some clinicians are now recommending biopsies before they decide on a first-line treatment regimen, in order to assess if there has been a change in biomarkers that may lead to a better utilization

of targeted therapies. More and more data are becoming available regarding changes in the 3 primary biomarkers in breast cancer—estrogen receptor, progesterone receptor, and HER2—that occur between the primary setting and the appearance of metastatic disease. Overall, these data support obtaining a biopsy when a patient presents with metastatic breast cancer, especially in cases where the biomarkers were initially negative, because a shift to positive would vastly increase the therapeutic options. We can also extend this discussion to the next level, whereby there may be a cause to evaluate biomarkers that may be of importance for novel agents in clinical development, especially if it is feasible that the patient could then participate in a trial depending on the results of her biopsy.

Technologies are becoming more readily commercially available, allowing physicians to send a patient's biopsy specimens to be assayed for any number of genes. But one of the challenges we have is the growing number of technologies, coupled with the fact that the expression of the single gene itself may not be what is important. Even in the setting of HER2-positive breast cancer, the single-agent activity of trastuzumab is in the range of 20% to 25%. Therefore, just because a patient has the HER2 biomarker does not necessarily mean that she will automatically have a robust response to HER2-directed therapy.

One of my concerns is that the community will assume that if a biopsy reveals the presence of a particular biomarker of interest, such as a mutation in PI3K, it will result in an easy treatment decision for targeted therapy. As was shown in BOLERO-2, there was no correlation between the presence of PI3K mutations and benefit with everolimus. So although the field is complex, we at least have growing access to the technology that will eventually help us to better understand the clinical importance of patterns of gene expression.

Linda T. Vahdat, MD Yes, I completely agree with you. One strategy I have been relying upon recently, especially in difficult-to-treat metastatic breast cancers, is to use genomic studies to see if they can help suggest a particular direction for treatment. There is a great deal of technology available, but how best to use the information it provides in clinical practice is not yet known. Every so often, I come across an unsuspected *BRCA* mutation or a HER2-activating mutation, which can be used to drive treatment decisions.

Hope S. Rugo, MD I agree that we must be cautious applying genomic data to clinical practice. We do not have the data to demonstrate that mutations in specific genes correlates with response to an added or targeted agent. Indeed, patients whose tumors have either mutated or wild-type PI3K appear to have similar responses to agents targeting this pathway. One comment about obtaining multiple biopsies in metastatic disease is that this will be challenging in several ways. First is obtaining adequate tissue, which can be quite difficult depending on the source. The second is obtaining tissue that represents the majority of the tumor, given that significant heterogeneity may exist. Last is the discomfort, risk, and cost associated with these procedures.

Edith A. Perez, MD This technology will be particularly intriguing when it can be used in every patient. An important issue to be aware of is that biopsy samples may receive divergent results from different companies. Another area of interest in the area of biopsy gene profiling is the identification of novel transcripts in breast cancer. These transcripts need to be explored further to determine whether they can predict therapeutic benefit.

I would like to echo your comment on the importance of clinical trials, as this remains a major issue in the metastatic breast cancer field. Hopefully, as phase 2 trials are becoming more well designed, there will be a greater likelihood of

having these studies approved more rapidly. This will greatly increase the opportunities available for our patients.

Linda T. Vahdat, MD Yes. For example, right now it is better to manage women with triple-negative metastatic disease in a clinical trial, as opposed to giving them standard cytotoxic chemotherapeutic options, because we know these drugs do not work in these patients. That said, there should be more studies available for these patients.

Hope S. Rugo, MD Indeed this is true, but trials may not be accessible or feasible for all patients. Certainly standard chemotherapy agents, either alone or in combination, have activity in a number of triple-negative tumors. However, clinical trials are an important option to consider if they are available, as each new option provides an additional opportunity for disease control.

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Slide Library

Breast Cancer Subtypes

- Estrogen-receptor-positive and HER2-negative
- HER2-positive and either estrogen-receptor-positive or estrogen-receptor-negative
- Triple-negative (negative for the estrogen receptor, progesterone receptor, and HER2)

HER2, human epidermal growth factor receptor 2

Results From the EMILIA Trial

- PFS was significantly prolonged in patients who received T-DM1 compared with patients who received lapatinib plus capecitabine (median PFS, 9.6 vs 6.4 months; HR, 0.65; 95% CI, 0.55-0.77; $P < .001$)
- The objective response rate was increased in the T-DM1 arm vs the lapatinib plus capecitabine arm (43.6% vs 30.8%; $P < .001$)
- The median overall survival was greater in the T-DM1 arm vs the lapatinib plus capecitabine arm (30.9 vs 25.1 months; HR, 0.68; 95% CI, 0.55-0.85; $P < .001$)

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. See from Slamon T et al. N Engl J Med. 2012;367(16):1783-1791.

Recent Approved Agents in Metastatic Breast Cancer

- Lapatinib
- Eribulin
- Pertuzumab
- Ado-trastuzumab emtansine (T-DM1)

Results From the EMBRACE Trial

- Median overall survival was improved in the eribulin arm compared with the treatment of physician's choice arm (13.1 vs 10.6 months; HR, 0.81; 95% CI, 0.66-0.99; $P = .041$)
- The increase in median overall survival observed in the eribulin arm compared with the treatment of physician's choice arm remained significant in an updated analysis (13.2 vs 10.5 months; HR, 0.81; 95% CI, 0.67-0.96; $P = .014$)
- The 1-year overall survival rate was 54.5% in the eribulin arm and 42.8% in the treatment of physician's choice arm

EMBRACE, Oral Metastatic Breast Cancer Study Assessing Physician's Choice versus Eribulin. Data from Metastatic Breast Cancer International Group (MBCIG). See from Finn RS et al. Lancet. 2011;377(9743):944-952.

Results From the CLEOPATRA Trial

- PFS was improved in the pertuzumab arm compared with the placebo arm (median independently reviewed PFS, 18.3 vs 12.4 months; HR for progression or death, 0.62; 95% CI, 0.51-0.75; $P < .001$)
- The objective response rate was improved in the pertuzumab arm compared with the placebo arm (80.2% vs 69.3%; $P < .001$)
- The median overall survival was 37.6 months in the placebo arm and not reached in the pertuzumab arm (HR, 0.64; 95% CI, 0.52-0.84; $P < .0008$)
- Estimated overall survival rates were as follows for the pertuzumab and placebo arms, respectively: 94.4% vs 89.9% at 1 year, 80.7% vs 69.4% at 2 years, and 65.9% vs 50.4% at 3 years

CLEOPATRA, Clinical Evaluation of Pertuzumab and Trastuzumab. HR, hazard ratio; PFS, progression-free survival. See from Slamon T et al. N Engl J Med. 2012;366(2):109-126 and Slamon T et al. Lancet Oncol. 2012;13(5):461-471.

Results From Study 301

- There was no statistically significant improvement in overall survival with eribulin vs capecitabine (15.9 vs 14.3 months; HR, 0.879; 95% CI, 0.770-1.003; $P = .056$)
- The yearly overall survival rates showed a consistent trend for benefit with eribulin vs capecitabine at 1 year (64.4% vs 58.0%; $P = .033$), 2 years (32.8% vs 29.8%; $P = .324$), and 3 years (17.8% vs 14.5%; $P = .175$)
- A subgroup analysis suggested that eribulin may increase survival over capecitabine in patients with certain tumor subtypes, such as triple-negative tumors (14.4 vs 9.4 months; HR, 0.702; 95% CI, 0.545-0.908)

See from Kaufman PL et al. Semin Oncol 2011;38(4):509-519.

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<http://www.hematologyandoncology.net>

New Developments in Metastatic Breast Cancer: Integrating Recent Data into Clinical Practice

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

1. Approximately how many women with breast cancer will develop recurrent disease?
 - a. 15% to 20%
 - b. 25% to 30%
 - c. 35% to 40%
 - d. 45% to 50%
2. Approximately how many recurrences in hormone receptor–disease occur more than 5 years after initial diagnosis?
 - a. 20%
 - b. 30%
 - c. 50%
 - d. 60%
3. Approximately how many breast cancer patients have HER2 overexpression?
 - a. 15% to 20%
 - b. 25% to 30%
 - c. 35% to 40%
 - d. 45% to 50%
4. In the second interim analysis of overall survival in the CLEOPATRA trial, what was the median overall survival in the pertuzumab arm?
 - a. 30.9 months
 - b. 41.7 months
 - c. 50.8 months
 - d. Not reached
5. In a second interim analysis of the EMILIA trial, what was the median overall survival in the T-DM1 arm?
 - a. 30.9 months
 - b. 41.7 months
 - c. 50.8 months
 - d. Not reached
6. In the EMBRACE trial, what was the 1-year overall survival rate in the eribulin arm?
 - a. 38.7%
 - b. 42.8%
 - c. 54.5%
 - d. 61.2%
7. In a randomized phase II study, etirinotecan pegol showed a response rate of:
 - a. 29%
 - b. 37%
 - c. 41%
 - d. 53%
8. In the BOLERO-2 trial, what was the median progression-free survival for patients receiving exemestane plus everolimus?
 - a. 5.6 months
 - b. 6.5 months
 - c. 7.8 months
 - d. 8.7 months
9. Which agent is approved for use in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease?
 - a. Ado-trastuzumab emtansine
 - b. Eribulin
 - c. Lapatinib
 - d. Pertuzumab
10. Which investigational agent is a potent tyrosine kinase inhibitor active against HER1, HER2, and HER4?
 - a. Etirinotecan pegol
 - b. Glembatumumab vedotin
 - c. Margetuximab
 - d. Neratinib

Evaluation Form: New Developments in Metastatic Breast Cancer: Integrating Recent Data into Clinical Practice

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 9285**. 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, Medical Oncology, Radiation 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:

Discuss the latest efficacy and safety data from recently reported clinical trials on new and emerging metastatic breast cancer therapies

- Strongly Agree Agree Neutral Disagree Strongly Disagree

Identify patients most likely to benefit from novel treatment approaches

- Strongly Agree Agree Neutral Disagree Strongly Disagree

Integrate new and emerging agents into clinical practice

- Strongly Agree Agree Neutral Disagree Strongly Disagree

Develop management goals based on tumor biology, treatment efficacy and safety, and quality of life concerns

- 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:

Request for Credit (*required fields)

Name* _____

Degree* _____

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Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax _____

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Signature* _____ Date* _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

- I participated in the entire activity and claim 1.25 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 |
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| | | | | | | | | | |