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# New Frontiers and Treatment Paradigms for Metastatic Breast Cancer

A Review of an Adjunct Symposium of the 2011 American Society of Clinical Oncology Annual Meeting
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## Statement of Need/Program Overview

The treatment of breast cancer has evolved rapidly as surgical and radiologic techniques have been refined and more active chemotherapeutic and biologic strategies are investigated and become available. Several new agents have recently demonstrated promising benefits in both the early stage and advanced disease settings. In addition, research efforts now focus on identifying predictive and prognostic markers as well as exploring novel combinations and dosing schedules of new and existing agents in an effort to optimize patient outcomes. Results from recently reported clinical trials have the potential to change the clinical practice of treating breast cancer. This monograph provides a comprehensive overview of recent advances in the treatment of breast cancer.

## Educational Objectives

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

- Describe the importance of new study findings and clinical trial data in the natural history of breast cancer patients
- Explain the results of new study findings, including current clinical trials evaluating therapy in the treatment of breast cancer
- Describe how to integrate into clinical practice the latest knowledge on emerging therapies and methods for treating breast cancer
- Identify future research directions for various therapies in breast cancer
- Employ different methods for treating breast cancer patients in an effort to improve current prognosis

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# Table of Contents



*This monograph was authored by an independent medical writer, Melinda Tanzola, PhD, based on presentations given at "New Frontiers and Treatment Paradigms for Metastatic Breast Cancer," an adjunct symposium of the 2011 American Society of Clinical Oncology Annual Meeting, held on June 4, 2011.*

# Evolving Paradigms for Optimizing Management of Metastatic Breast Cancer

Edith A. Perez, MD

The most basic therapeutic goal for individuals living with metastatic breast cancer is to extend survival. More complex, subjective treatment goals including improvement of quality of life through palliation, delay of symptoms, and attaining a favorable treatment risk/benefit profile, in which treatments have a manageable toxicity, convenience, and cost. These goals are becoming more attainable as new agents are developed for the treatment of metastatic breast cancer. The introduction of these agents—both chemotherapeutic and hormonal—has significantly improved survival for individuals with breast cancer.[1,2] At the level of individual therapies, however, few phase III trials have shown a survival improvement with a single agent or regimen. One challenge in conducting clinical trials is that survival outcomes are confounded by crossover, which complicates the analysis. Therefore, although overall survival (OS) remains the gold-standard endpoint from the perspective of the US Food and Drug Administration (FDA)—both as a safety and efficacy parameter—progression-free survival (PFS) may be an acceptable alternative, provided that it is properly measured and of "sufficient magnitude." Survival remains an important endpoint, however, to understand the effects of treatments.

Clinicians treating patients with metastatic breast cancer are presented with the challenge of individualizing therapy based on multiple factors (Table 1). A greater understanding of molecular biology has shown that metastatic breast cancer is a multifaceted disease characterized by subtypes that differ in their clinical, pathologic, and molecular features. These differences have significance for a patient's prognosis and for developing the optimal treatment strategy. As clinicians weigh the different treatment options, they must balance the anticipated efficacy against the potential toxicity of different approaches. Factors that will weigh into the decision include disease-specific factors (hormone receptor status, human epidermal growth factor receptor 2 [HER2] status, and tumor burden), and patient-specific factors (age, disease-associated symptoms, performance status, comorbidities, prior treatment history, and patient preference).

## Evolving Approaches in Hormone Receptor-Positive Metastatic Breast Cancer

Multiple factors influence the sensitivity of hormone receptor–positive tumors to hormonal therapy. One tumor-related factor is percent staining positivity. The benefit of hormonal therapy according to staining positivity remains a controversial issue. Other factors that influence sensitivity to hormonal therapy include disease grade and the presence of other biomarkers.

In general, the treatment paradigm for patients with hormone receptor–positive metastatic breast cancer is based on HER2 status. Today, patients with HER2-positive disease most often receive chemotherapy plus HER2-targeted therapy. In some cases, patients may receive an aromatase inhibitor alone or in combination with anti-HER2 therapy. If there is evidence of tumor progression following the initial treatment, patients receive additional chemotherapy plus anti-HER2 therapy.

For patients with hormone receptor–positive and HER2-negative disease, the most common initial treatment approach is hormonal therapy. In a small proportion of cases, it may be desirable to use chemotherapy first, even if the tumor is hormone receptor–positive.

**Table 1.** Metastatic Breast Cancer: Overview

**Multifaceted disease with different subtypes**
- Varied spectrum of clinical, pathologic, and molecular features with different prognostic and therapeutic implications

**Prognostic and predictive factors constitute important tools for therapeutic personalization**
- To provide efficient treatment
- To spare patients from unwanted side effects of overtreatment

**Effective therapies that target relevant processes**

However, when possible, chemotherapy is withheld until it becomes more necessary. In regard to specific agents, postmenopausal women can receive any of the aromatase inhibitors or tamoxifen. In the second-line setting, data support the use of exemestane or fulvestrant, depending on the patient's preference in regards to convenience.

The management of patients with hormone receptor–positive metastatic breast cancer continues to evolve. Although the treatment of patients with HER2-positive disease is not likely to change in the next few years, new strategies are being evaluated in HER2-negative disease that may change the treatment approach for these patients. A randomized, phase III trial is comparing letrozole versus tamoxifen with or without bevacizumab.[3] The randomized, double-blind, placebo-controlled BOLERO-2 (Breast Cancer Trials of Oral Everolimus-2) trial is comparing the efficacy and safety of the mammalian target of rapamycin (mTOR) inhibitor everolimus plus exemestane in the treatment of patients with estrogen receptor–positive, locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole.[4] These studies may lead to an evolution in the management of patients with hormone receptor–positive metastatic breast cancer.

Other novel strategies are being evaluated in the treatment of hormone receptor–positive metastatic breast cancer. Histone deacetylase (HDAC) inhibitors may resensitize endocrine-resistant cells to further hormonal manipulation. Src inhibitors may improve responses to hormonal therapy by interfering with estrogen receptor signaling or with bypass resistance mechanisms. Inhibitors of the insulin growth factor receptor (IGF-1R) are being evaluated because activation of IGF-1R-mediated signaling pathways is associated with resistance to endocrine therapy.

## Evolving Approaches in Triple-Negative Breast Cancer

Approximately 15% of breast cancers lack expression of estrogen-receptor, progesterone-receptor, or HER2. One challenge in the management of triple-negative disease is first defining the cutoff for negative expression of each marker. The American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for HER2 testing[5] can be misinterpreted. It is recommended that HER2 negativity be defined as a fluorescence in situ hybridization (FISH) ratio of less than 2 or a percent positivity below 10% by immunohistochemistry.

Today, these triple-negative cancers are managed in the adjuvant setting with chemotherapy. If there is evidence of recurrence or metastatic disease, systemic chemotherapy is used either with or without bevacizumab. However, the role of bevacizumab may change depending on whether the 2008 accelerated approval of this agent is revoked by the FDA.

Patients with hormone receptor–positive and HER2-negative disease who have resistance to hormonal therapy share similarities with patients who have triple-negative disease. Because these patients are HER2-negative and do not respond to hormonal therapy, they essentially have triple-negative disease. Ongoing research is investigating the molecular mechanisms of resistance to define differences between patients with true triple-negative disease and those with HER2-negative disease and resistance to hormonal therapy. In regard to treatment decisions, however, these patients are approached with the same strategy.

Several agents are being evaluated for use in patients with triple-negative disease. Isakoff and colleagues[6] conducted a multicenter, phase II study of cisplatin or carboplatin in 86 patients with metastatic triple-negative breast cancer. Single-agent platinum therapy was associated with an overall response rate (ORR) of 31.7% in the first-line setting and 20% in the second-line setting, suggesting that platinum-based agents are as effective as the other agents available for these patients. Another important question that will shape future therapy concerns the availability of bevacizumab and multikinase inhibitors.

## Evolving Approaches in HER2-Targeted Therapy

HER2-positive breast cancer accounts for 15–20% of all invasive breast cancers; of these, half are estrogen receptor–positive. Clinical trials are evaluating novel HER-targeted agents, including both antibodies and small-molecule tyrosine kinase inhibitors. These trials may expand the number of HER2-targeted agents available.

## Measuring Responses to Therapy in Breast Cancer

In 1981, the World Health Organization[7] first published recommendations for reporting results of cancer treatment. The Response Evaluation Criteria in Solid Tumors (RECIST)[8] were developed nearly 20 years later, in 2000, followed by the revised RECIST criteria[9] in 2009 (Table 2). A major change from the original RECIST criteria to the revised criteria was a reduction in the number of targets measured from 10 (5 per organ) to 5 (2 per organ). It is important that medical oncologists work together with radiologists to attain measurements of the recommended number of lesions. Other changes to the criteria were related to lymph node measurements, the definition of progression, the definition of nonmeasurable progressive disease, requirements for confirmation of response, and interpretation of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning.

**Table 2.** Summary: What Has Changed in RECIST 1.1

| | RECIST 1.0 | RECIST 1.1 |
|---|---|---|
| Measuring tumor burden | 10 targets<br>5 per organ | For response: 5 targets<br>(2 per organ) |
| Lymph node | Measure long axis as for other lesions<br>Silent on normal size | Measure short axis<br>Define normal size |
| Progression definition | 20% increase in sum | 20% increase and at least 5 mm absolute increase |
| Nonmeasurable progressive disease | "Must be unequivocal" | Expanded definition to convey impact on overall burden of disease |
| Confirmation | Required | Required when response is the primary endpoint, but not PFS |
| New lesions | — | New section that includes comment on FDG PET interpretation |

FDG PET=fluorodeoxyglucose positron emission tomography; PFS=progression-free survival; RECIST=Response Evaluation Criteria In Solid Tumors.

Data from Therasse P et al. *J Natl Cancer Inst.* 2000;92:205-216[8] and Eisenhauer EA et al. *Eur J Cancer.* 2009;45:228-247.[9]

It is important to measure multiple lesions for several reasons. First, the largest lesion may not be the most reproducible. Moreover, there may not be a synchronous response between different lesions. For example, whereas one lesion may appear stable, another lesion may show an increase in size. Therefore, measurement of multiple lesions allows for a more accurate assessment of response.

Another important issue concerns the use of biopsy for suspected metastases. Biopsy of suspected metastases should be considered when feasible, as it can provide important information. First, the biopsy can confirm that the lesion does not represent a different malignancy, such as primary lung cancer, bronchial carcinoid, a liver metastasis from a gastrointestinal tumor, or lymphoma. Moreover, the biopsy can be used to determine breast cancer characteristics, particularly to identify predictive factors for individualizing therapy. Studies have shown discordance between the primary tumor and recurring disease in relation to hormone receptor and HER2 status.[10]

## Future Directions in Breast Cancer

The molecular characterization of cancer is a major focus of ongoing research to develop novel strategies in breast cancer treatment. Each tumor has hundreds to thousands of genomic alterations, including chromosomal changes, epigenetic changes, and mutations. Perez and colleagues are involved in a collaborative effort to investigate molecular characteristics of breast cancer, including messenger RNAs, microRNAs, and the implications of gene copy number and epigenetic modifications. The researchers are working toward a goal of personalized medicine in the treatment of patients with metastatic breast cancer. Investigators aim to develop a molecular screening program to enrich clinical trials in breast cancer based on molecular alterations. They also hope to identify surrogate markers using specimens or imaging. Another future goal is image-guided drug delivery, in which imaging techniques are used in quantitative assessments of tumor-targeted therapeutic delivery, distribution, uptake, and response. Overall, these novel strategies should lead to better outcomes for patients living with metastatic breast cancer.

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# Microtubules as a Target for Anticancer Drugs

Susan L. Mooberry, PhD

Microtubules are dynamic structural proteins that are essential for numerous cell functions, including maintenance of cell shape, motility, intracellular transport and secretion, signal transduction, and mitotic chromosome separation.[1] Given the central role of microtubules in cellular processes, microtubule dynamics are regulated in a precise and rapid manner. This regulation, which occurs through the activity of many endogenous proteins, is critical for cell viability and proper cell division.

Microtubules are formed from heterodimers of alpha and beta tubulin. Although many different alpha and beta sequences have been identified, the 2 subunits never exist alone; they are folded together during formation in the ribosome. Alpha-beta tubulin heterodimers assemble in a head-to-tail fashion to form linear protofilaments. These protofilaments further polymerize to form a hollow tubular structure consisting of 13 protofilaments joined together. The structure contains a polar organization, in which the alpha-tubulin subunit is located at the negative end and the beta tubulin subunit is exposed at the positive end. Microtubule dynamics—the growth and shortening of microtubules—occur at the positive end of microtubules.

The regulation of microtubule length occurs through a process called dynamic instability, in which microtubules switch between elongation, pause (no change), and catastrophe, which is a rapid change from growth to shrinkage. Stabilization of microtubules occurs through the binding and hydrolysis of guanosine-5'-triphosphate (GTP) to beta-tubulin. This GTP cap stabilizes the end of the microtubule, allowing new alpha-beta heterodimers to be added. Conversely, loss of the GTP cap destabilizes the microtubule, resulting in catastrophe. Microtubules can also exist in a state of treadmilling, which is characterized by controlled loss of tubulin subunits from the negative end and gain of tubulin subunits at the positive end, resulting in no net change in the microtubule length.

Microtubule-targeted agents have an important role in the treatment of patients with metastatic breast cancer (Table 1). These agents differ in their specific effects on microtubule dynamics, their sensitivity to different tubulin isotypes, their tissue and tumor susceptibility, their reversibility, and their forms of resistance. In general, microtubule-targeted agents disrupt normal microtubule dynamics through 2 major mechanisms.[1-3] The microtubule destabilizers inhibit the polymerization of tubulin, resulting in the loss of cellular microtubules. Destabilizing agents include the vinca alkaloids (vinblastine, vincristine, and vinorelbine), the halichondrins, and eribulin, the semisynthetic derivative of halichondrin B. The second class of microtubule targeting agents is the microtubule stabilizers. These agents stimulate polymerization, increasing the density of cellular microtubules. Examples of microtubule stabilizers include the taxanes (such as paclitaxel, docetaxel, and nab-paclitaxel) and the epothilones, such as ixabepilone.

At the lowest concentrations, however, they have a similar effect and are classified as antimitotic agents. By inhibiting microtubule dynamics, these agents compro-

**Table 1.** Microtubule-Targeted Agents

- Suppress normal microtubule dynamics
- Disrupt microtubules
- Prevent normal mitosis
- Result in apoptosis

**Table 2.** Microtubule-Targeted Agents Are Not the Same

- Bind to different binding sites on tubulin and on microtubules
- Different sensitivities to tubulin isotypes
- Different tissue and tumor susceptibilities
- Different forms of resistance
- Suppress microtubule dynamics by different mechanisms
- Have different degrees of reversibility-cellular persistence

**Table 3.** Eribulin: Preclinical Mechanistic Data

**Eribulin is a new microtubule destabilizer with a unique mechanism of inhibiting microtubule dynamics**

- It is an "end poison" binding with high affinity to the positive ends of microtubules to inhibit microtubule growth
- One eribulin molecule bound per microtubule is sufficient to inhibit growth
- Disrupts mitotic spindle function leading to mitotic arrest and, ultimately, apoptosis

**In vivo antitumor activity in multiple human xenografts**

Data from Jordan M et al. *Mol Cancer Ther.* 2005;4:1086-1095,[4] Smith J et al. *Biochemistry.* 2010;19:1331-1337,[5] and Towle MJ et al. *Cancer Res.* 2001,61:1013-1021.[7]

mise the ability of the mitotic spindle to be dynamic, resulting in antimitotic activity.[1-3]

## Differences Between Microtubule Targeted Agents

Microtubule targeted agents differ in their binding specificity; this includes their binding site on the individual beta-tubulin subunit and their binding location within the microtubule structure (Table 2). Vinblastine binds both at the positive end of the microtubule and along the length of the microtubule. At the end of the microtubule, vinblastine acts like a GTP cap, stabilizing the end and preventing depolymerization. Along the length of the microtubule, vinblastine binds to the protofilaments, preventing depolymerization at that point. Conversely, paclitaxel and related taxanes bind to beta-tubulin subunits along the inside of the microtubule.

Eribulin represents a new class of microtubule-disrupting agents that differs from other agents in its binding, its effects on dynamic instability, and the irreversibility of its antimitotic activity. A synthetic analogue of the marine sponge natural product halichondrin B, eribulin is a potent inhibitor of cell proliferation.[4] The antiproliferative activity of eribulin correlates with its effects on mitosis.[4] Eribulin disrupts mitotic spindle organization, resulting in mitotic arrest and apoptosis (Table 3).

Eribulin binds at the positive end of microtubules with high affinity. It therefore acts as a competitive inhibitor of the vinca alkaloids, which also bind at the positive end. However, eribulin, unlike the vinca alkaloids, does not appear to bind along the length of the microtubule. Instead, eribulin exerts its effects through binding at a single site on the microtubule, as binding studies indicate that a maximum of 14.7 molecules of eribulin bind to a single microtubule.[5] However, few molecules are needed to inhibit microtubule growth. At the concentration of eribulin that inhibits microtubule growth by 50%, only 0.5 molecules of eribulin are bound per microtubule. This suggests that a single molecule of eribulin bound to the end of a microtubule is sufficient to prevent normal dynamic instability.

In vitro studies have revealed several important differences between different microtubule-targeted agents. Several studies have shown that eribulin inhibits microtubule growth but has no effect on the rate of microtubule shortening.[4] This differs from other microtubule-targeting agents, which affect both shortening and growth of microtubules. Another study showed that agents differ in the reversibility of the mitotic block they induce.[6] In this study, researchers treated cells with microtubule-targeting agents for 12 hours, which was followed by a 10-hour washout period. They then evaluated the effects on mitotic arrest. Cells treated with eribulin remained in mitotic arrest even after 10 hours, whereas cells treated with paclitaxel required a 14-fold higher initial concentration to cause persistence of mitotic arrest. Thus, eribulin appears to induce irreversible mitotic blockade, a finding that may have implications for dosing strategies. Vincristine also showed an irreversible mitotic block, while vinblastine required a 65-fold increased concentration to attain the same mitotic block.

Other preclinical studies provided other information on the antitumor activity of eribulin. In 2001, Towle and colleagues reported the activity of eribulin in the MDA-MB-435 human xenograft model.[7] Eribulin was found to inhibit tumor growth by more than 95% at 42 days, and with 100-fold greater potency than paclitaxel. Moreover, eribulin showed activity across a broad range of concentrations.

## Conclusion

The microtubule-disrupting agents have demonstrated significant efficacy in the treatment of breast cancer. Although these agents differ mechanistically, they all suppress microtubule dynamics, leading to mitotic arrest and, ultimately, apoptosis. Researchers have continued to explore the effects of microtubule-targeting agents on tumor cells. One recent hypothesis suggests that mitosis may not be the only important target of microtubule agents.[8] Instead, the effects of these drugs on interphase microtubules may also be important. As more is understood about the mechanisms of these drugs, they can be used more effectively to improve outcomes for patients with breast cancer.

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*Dr. Mooberry is a consultant for Eisai, Inc.*

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# Survival Prolongation in Metastatic Breast Cancer: The Role of Nontaxane Microtubule Dynamics Inhibitors

Christopher Twelves, MD

The prognosis for women with breast cancer has improved in recent decades, a period of time in which many new cytotoxic agents have been introduced. Although population-based studies have shown a trend toward improved survival in recent years,[1] few individual clinical trials have shown an improvement in OS with any single regimen. This is particularly true in heavily pretreated patients. In 1999, Nabholtz and colleagues[2] provided the first demonstration of a significant survival benefit with a new cytotoxic agent, showing a significant improvement in median OS from 8.7 months with mitomycin plus vinblastine to 11.4 months with docetaxel (*P*=.0097) in patients already treated with anthracyclines. Several years later, O'Shaughnessy and colleagues[3] reported an incremental improvement with the addition of capecitabine to docetaxel.

One challenge in clinical trial design has been endpoint selection (Table 1). Although PFS is often used as a clinical trial endpoint, there has been an ongoing debate as to whether PFS is an appropriate surrogate for survival. At the 2011 ASCO meeting, Cortazar and colleagues[4] from the FDA presented an analysis correlating PFS and OS outcomes from FDA-reviewed data from 14 randomized clinical trials in 9,819 patients with metastatic breast cancer. The analysis failed to show a significant association between PFS and OS among all patients. The calculated $R^2$ of 0.067 suggests that PFS accounts for less than 10% of the variability in OS. The association between PFS and OS was stronger among the subset of patients with triple-negative breast cancer ($R^2$=0.399), suggesting that a substantial proportion of the variability in survival among those patients may indeed relate to PFS.

**Table 1.** Endpoints in Metastatic Breast Cancer

**Reviewed 76 phase II trials in metastatic breast cancer published from 1998–2007 in 11 leading journals**

- OS was the primary endpoint in only 5 trials; it was a secondary endpoint in 64 trials
- OS gain was seen in 15 trials, but none of those in which it was a primary endpoint
  - Trials with a gain in OS
    - Tended to be larger
    - More often in second- or third-line setting

OS=overall survival.

Data from Saad ED, Katz A, Buyse M. *J Clin Oncol.* 2010;28:1958-1962.[6]

The association between PFS and OS was also evaluated by Broglio and colleagues,[5] who found that the duration of survival after progression on study treatment relates to the strength of PFS as a surrogate for OS. As patients survive longer after progression on study treatment, the association between PFS and OS becomes weaker. The investigators concluded that OS is a reasonable primary endpoint when postprogression survival is short (approximately 6 months) but becomes increasingly difficult to use as an endpoint when postprogression survival is longer (approximately 12 months or longer).

Another analysis investigating the association between PFS and OS was reported by Saad and colleagues,[6] who evaluated the frequency of OS gains and the relationship between PFS and OS among all randomized, phase III clinical trials of patients with metastatic breast cancer published between 1998 and 2007. The researchers found that of 76 trials, 15 trials (20%) reported OS gains, although OS was not the primary endpoint in any of these trials. Conversely, OS was the primary endpoint in 5 trials, none of which showed a significant survival benefit. Trials showing a survival benefit were more likely to be larger and to be in the second- or third-line setting. Overall, these analyses highlight the challenges in showing a survival benefit in metastatic breast cancer.

Microtubules are among the most clinically validated targets in the treatment of metastatic breast cancer. Microtubule-targeting agents have figured prominently among the drugs receiving FDA approval for the treatment of patients with previously treated metastatic breast cancer, from paclitaxel in 1994 to ixabepilone in 2007 and, most recently, eribulin in 2010. Taxanes, ixabepilone, and eribulin share the same general mechanism of action, interfering with microtubule dynamics, but they act on distinct targets within the microtubule structure. The 2 nontaxane microtubule-targeting agents that have demonstrated a clinical benefit in patients with heavily pretreated metastatic breast cancer are ixabepilone and eribulin.

## Nontaxane Microtubule-Targeting Agents: Ixabepilone

Ixabepilone is a semi-synthetic analogue of epothilone B, a natural macrolide derived from the myxobacterium *Sorangium cellulosum.* In preclinical studies, ixabepilone showed activity in paclitaxel-resistant cells and demonstrated synergy with bevacizumab, capecitabine, and trastuzumab.

Four phase II studies were undertaken to evaluate the efficacy and safety of ixabepilone in different patient populations. Single-agent ixabepilone was associated with an ORR ranging from 11.5% in patients with disease resistant to anthracyclines, taxanes, or capecitabine to 57% in patients with no previous taxane treatment.[7-10] No biomarkers that significantly predict responses to ixabepilone have been identified.

The activity of ixabepilone demonstrated in the phase II trials led to the development of 2 randomized, phase III trials of ixabepilone in patients with previously treated metastatic breast cancer. Study 046[11] randomized 752 patients with resistance to previous anthracycline and taxane therapy and measurable disease. Study 048[12] randomized 1,221 patients who were pretreated with anthracycline and taxane but who did not necessarily have chemotherapy resistance and could have measurable or nonmeasurable disease. Both trials compared ixabepilone 40 mg/m$^2$ every 3 weeks plus capecitabine 1,000 mg/m$^2$ twice daily for 14 days of an every 21-day cycle versus capecitabine 1,250 mg/m$^2$ twice daily for 14 days of an every 21-day cycle. The primary endpoint of Study 046 was time-to-progression (TTP), with secondary endpoints including OS and objective response rate. The primary endpoint of Study 048 was OS, with secondary endpoints including TTP and objective responses.

In both trials, the addition of ixabepilone to capecitabine was associated with a significant improvement in PFS. The median PFS with ixabepilone plus capecitabine versus capecitabine alone was 5.26 versus 3.81 months ($P$=.001) in Study 046 and 6.24 versus 4.40 months ($P$=.0005) in Study 048.[13] This difference was irrespective of performance status.

In Study 048, there was no significant difference in OS with ixabepilone plus capecitabine versus capecitabine alone, and thus the study did not meet its primary endpoint.[12] However, the investigators did note some imbalances between the 2 arms that may have influenced outcomes: compared with patients in the control arm, those in the ixabepilone arm had a worse performance status at baseline and were less likely to receive taxanes

**Table 2.** Ixabepilone in Metastatic Breast Cancer

**Single-agent activity in pretreated metastatic breast cancer**
- Response rate of 11.5% and progression-free survival of 3.1 months in heavily pretreated patients
- No phase III single-agent data have been published

**In combination with capecitabine vs single-agent capecitabine**
- Higher response rate (43% vs 26%)
- Significant prolongation of progression-free survival (6.0 months vs 4.4 months)
- No improvement in overall survival (16.7 months vs 16.2 months; *P*=.81)
  - Possible benefit in patients with KPS 70–80 (12.3 months vs 9.5 months; *P*<.05)

**Grade 3/4 peripheral neuropathy common as a single-agent (2–21%) and in combination with capecitabine (23%)**

KPS=Karnofsky Performance Scale; PFS=progression-free survival.

as post-protocol therapy. In a planned secondary analysis adjusting for prognostic factors, ixabepilone did provide a significant survival benefit (*P*=.02). Subgroup analyses did not reveal any group that benefitted from ixabepilone more than another.

Study 046 met its primary endpoint, showing a significant improvement in PFS with the addition of ixabepilone to capecitabine, leading to the FDA approval of ixabepilone in this indication. OS data, published in 2010,[14] showed a nonsignificant trend toward an improvement in OS with the addition of ixabepilone to capecitabine (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.77–1.05; *P*=.19). The trend remained nonsignificant after adjusting for prognostic factors (*P*=.08). However, subgroup analyses did show a significant survival benefit with ixabepilone plus capecitabine versus capecitabine alone in the subset of patients with a reduced Karnofsky Performance Score (KPS) of 70–80 (HR, 0.75; 95% CI, 0.58–0.98). However, although these analyses were preplanned, interpreting outcomes in individual subgroups is challenging.

Recently, Roché and colleagues[13] published combined OS data from the 2 phase III trials of ixabepilone with outcomes pooled according to performance status. Again, ixabepilone plus capecitabine was associated with an improvement in OS versus capecitabine alone in patients with a KPS of 70–80 (HR, 0.75; *P*=.0015), but not in patients with a KPS of 90–100 (*P*=.81).

Finally, Perez and colleagues[15] conducted a retrospective analysis of the efficacy and safety of ixabepilone among patients with triple-negative disease enrolled across 5 phase II studies and the 2 phase III trials. Overall, 556 of the 2,261 patients enrolled on these trials (24.5%) had triple-negative tumors. Overall response rates in the patients with triple-negative disease were comparable to those observed in the overall population. In the phase III trials, a regimen of ixabepilone plus capecitabine was associated with an ORR of 31% in patients with triple-negative disease. The median PFS in these patients was significantly longer with ixabepilone plus capecitabine versus capecitabine alone (4.2 vs 1.7 months). Moreover, toxicity was not increased in patients with triple-negative disease.

The toxicity profile of ixabepilone is well defined. The most common grade 3/4 adverse event associated with ixabepilone is neutropenia, observed in 68% of patients receiving ixabepilone plus capecitabine versus 11% in patients receiving capecitabine alone in Study 048.[11] Other notable grade 3/4 adverse events more common with the addition of ixabepilone are leukopenia (57% vs 6%), peripheral neuropathy (22.0% vs 0%), and febrile neutropenia (4.8% vs 0.5%).[11]

Overall, ixabepilone has clearly demonstrated activity in the treatment of patients with previously treated metastatic breast cancer (Table 2). The addition of ixabepilone to capecitabine is associated with an improvement in response rate and PFS, although its effect on OS is not yet clear. In regard to toxicity, a common issue is peripheral neuropathy, which develops at grade 3/4 severity in approximately 20% of patients receiving ixabepilone.

## Nontaxane Microtubule-Targeting Agents: Eribulin

Eribulin mesylate is a synthetic analog of halichondrin B, a natural marine sponge product. This nontaxane microtubule dynamics inhibitor uses a novel mode of action, binding with high affinity at the positive end of microtubules.[16,17] Eribulin has demonstrated potent antiproliferative activity in vitro and in vivo, and it retains activity against β-tubulin-mutated cell lines.[18,19] Moreover, in mice, eribulin has been shown to induce less neuropathy than paclitaxel.[20]

Two phase II trials[21,22] were undertaken to evaluate eribulin in patients with heavily pretreated metastatic breast cancer. The studies enrolled a total of 356 evaluable patients who had received a median of 4 prior therapies (range, 1–11). In these studies, eribulin was associated with response rates of 9.3% and 11.5%.

The encouraging responses in the phase II studies led to the design of the global, randomized, open-label

**Table 3.** Eribulin in Metastatic Breast Cancer

**Phase II single-agent activity in heavily pretreated metastatic breast cancer**
- Response rate of 10%, progression-free survival of 2.6 months, and overall survival of 9.0/10.4 months

**In the phase III EMBRACE study vs treatment of physician's choice**
- Higher response rates (12.2% vs 4.7%)
- Prolongation of progression-free survival (3.6/3.7 months vs 10.6 months)
- Significant improvement in overall survival (13.2 months vs 10.6 months; *P*=.014)
  - Maintained across subgroups

**Grade 3/4 peripheral neuropathy not common (8%)**

**Results of phase III study 301 (eribulin vs capecitabine) awaited**

EMBRACE=Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389.

phase III EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) trial (Table 3).[23] The study enrolled 762 patients with locally recurrent or metastatic breast cancer who had received 2–5 prior chemotherapies for advanced disease, including an anthracycline and a taxane. Patients were eligible if they had progressed within 6 months of their last regimen, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and had no grade 3/4 neuropathy at baseline.

Patients were randomly assigned 2:1 to eribulin mesylate (1.4 mg/m$^2$ administered intravenously over 2–5 minutes on days 1 and 8 every 21 days; 508 patients) or treatment of physician's choice (TPC). The TPC arm was developed to account for the fact that when the study was designed, no single agent was approved for use in patients who had progressed on an anthracycline and a taxane. Moreover, individual oncologists varied widely in their preferred treatment strategy for these patients. Therefore, the control arm allowed patients to receive any monotherapy approved for the treatment of cancer (chemotherapy, hormonal, biologic) or supportive care only. Patients were stratified based on prior capecitabine therapy, HER2 status, and geographic area—an attempt to account for potential regional differences in choice of treatment in the TPC arm.

Overall, 96% of patients in the TPC arm received chemotherapy. The most commonly used agents were vinorelbine, gemcitabine, and capecitabine, although some patients received taxanes, anthracyclines, or other agents. No physicians opted to use biologic therapies or best supportive care. This variability in treatment strategies is representative of real-life clinical practice, and reflects the lack of clarity regarding the optimal treatment of these patients. However, the use of this control arm does complicate the analysis by creating a heterogeneous control population.

In the EMBRACE trial, eribulin was associated with a significant 2.5-month improvement in OS compared with TPC, with a median OS of 13.1 versus 10.6 months (HR, 0.81; 95% CI, 0.66–0.99; *P*=.041); 12-month survival rates were 53.9% and 43.7%, respectively.[23] Thus, the trial met its primary endpoint, showing a significant benefit in OS with a single agent. At the time of the primary analysis, at which point approximately 55% of events had occurred, the *P* value had just reached statistical significance at .041, and the Kaplan-Meier analysis showed the 2 survival curves coming together. Therefore, an updated, unplanned survival analysis was conducted after 77% of events had occurred. This analysis, mandated by regulatory authorities, confirmed the original findings, showing maintained separation of the survival curves and a reduction in the *P* value to .014. It has been reassuring to see the data become more robust, rather than weaker, over time.

Subset analyses showed a benefit of eribulin over TPC irrespective of hormone receptor status, including in triple-negative disease.[23] Some differences in the benefit of eribulin were noted according to geography, with the greatest benefit observed in patients in North America, Western Europe, and Australia. There was also a suggestion that patients already treated with capecitabine may have benefitted more from eribulin. An exploratory analysis of survival according to the number of prior regimens showed a greater benefit with eribulin among patients who were less heavily pretreated. Among patients who had received no more than 3 prior chemotherapy regimens, the median OS with eribulin and TPC was 13.5 months and 11.7 months, respectively (*P*=.04).

Eribulin was also more effective than TPC, according to median PFS as assessed by investigator review (3.6 vs 2.2 months; HR, 0.76; 95% CI, 0.64–0.90; *P*=.002).[23] By independent review, there was a nonsignificant trend toward an improved median PFS with eribulin versus TPC (3.7 vs 2.2 months; HR, 0.87; 95% CI, 0.87–1.05; *P*=.14). There may be a methodologic explanation for the difference in the 2 analyses. The response rate favored eribulin over TPC in both the independent review (12.2% vs 4.7%; *P*=.002) and in the investigator review (13.2% vs 7.6%; *P*=.028).

In regard to toxicity, eribulin is associated with myelosuppression. The most frequent grade 3/4 toxicity in the EMBRACE trial was neutropenia, reported in 45.2% of patients receiving eribulin and 21.1% of patients receiving TPC.[23] However, febrile neutropenia rates were relatively low, at 4.2% and 1.2%, respectively. Grade 3/4 peripheral neuropathy developed in 8.2% of patients receiving eribulin and 2.0% of patients receiving TPC. Neuropathy led to treatment discontinuation in less than 5% of patients. Thus, eribulin appears to cause less neuropathy than ixabepilone.

Eribulin has been approved for use in Europe and in the United States, and it is currently undergoing cost effectiveness analysis in the United Kingdom. However, additional studies are needed to further assess the safety and efficacy of eribulin. One potential limitation of the EMBRACE trial was the lack of quality-of-life assessments, which are being included in other studies.

The ongoing Study 301, which completed enrollment in September 2009, is comparing eribulin administered at 1.4 mg/m$^2$ given intravenously over 2–5 minutes on days 1 and 8 every 21 days versus capecitabine 2.5 g/m$^2$/day administered orally twice daily in 2 equal doses on days 1–14 every 21 days. The study has enrolled 1,102 patients with locally advanced or metastatic breast cancer who have received no more than 3 prior chemotherapies and no more than 2 regimens for advanced disease. However, patients had received prior anthracyclines and taxanes in the neoadjuvant or adjuvant setting or for locally advanced or metastatic disease. Patients had to have documented progression during or after their last anticancer therapy. As in the EMBRACE study, enrollment included patients with preexisting neuropathy up to grade 2, and all patients had an ECOG performance status of 0–2. The primary endpoints in this trial are OS and PFS, with secondary endpoints including quality-of-life (European Organisation for Research and Treatment of Cancer assessment); overall response rate; duration of response; survival rates at 1, 2, and 3 years; pain intensity and analgesic consumption; adverse events; and pharmacokinetics/pharmacodynamics.

Overall, both eribulin and ixabepilone have demonstrated activity in women with heavily pretreated metastatic breast cancer. Grade 3/4 peripheral neuropathy appears to occur much less frequently with eribulin (8%) than with ixabepilone administered as a single agent (up to 20%) or in combination with capecitabine (23%). A trial comparing the incidence of neuropathy with the 2 agents recently completed accrual. With regard to survival improvements, single-agent eribulin is associated with a significant improvement in OS versus TPC. The addition of ixabepilone to capecitabine is not associated with a significant improvement in OS, although there may be a benefit in patients with a lower performance status.

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# Case Discussion

Hope S. Rugo, MD

A 43-year-old woman is diagnosed with an intermediate-grade, 6-cm T3 invasive ductal breast cancer. It is ER/PR-positive and HER2-normal, with 5 of 12 nodes testing positive. Staging studies show no evidence of distant disease. She receives dose-dense doxorubicin, cyclophosphamide, and paclitaxel followed by tamoxifen. Her menses return 6 months after completing chemotherapy. She notes persistent mild peripheral neuropathy. One year later, she develops lower back pain. A bone scan shows uptake at T8 and L1. A computed tomography (CT) scan shows no visceral disease. Magnetic resonance imaging (MRI) of the spine confirms disease recurrence with lytic lesions at T5, T8, and L1. A biopsy at L1 reveals that the disease is ER-positive, PR-negative, and HER2-negative. The patient receives radiation to the L1 lesion followed by a laparoscopic oophorectomy. She is then enrolled on a placebo-controlled clinical trial of exemestane plus an insulin-like growth factor receptor monoclonal antibody, and she also starts zoledronic acid. Her pain resolves, and she feels well for 8 months. However, she then develops rib and back pain, and staging studies reveal several new bony metastases. A CT scan again shows no evidence of visceral disease. She would like to avoid chemotherapy to maintain her quality of life. What is the recommended treatment at this point: fulvestrant, a nonsteroidal aromatase inhibitor (AI), estrogen, capecitabine, paclitaxel and bevacizumab, or another option?

**Edith A. Perez, MD:** There are several factors that I would take into consideration. The patient seems to be in pretty good overall condition, and she would like to maintain her current quality of life. I would think several of these options could work, including fulvestrant, a nonsteroidal AI, and capecitabine alone. I would probably reserve paclitaxel and bevacizumab for a later time.

**Christopher Twelves, MD:** Given that she is relatively well, with only bony disease and no evidence of rapidly progressing visceral disease, I would opt for endocrine therapy and see how she does after 2–3 months.

**Hope S. Rugo, MD:** I agree; although she has relatively resistant disease, she has relatively mild symptoms, with no areas of pathologic fracture and a good performance status. Therefore, I would also favor endocrine therapy.

Dr. Twelves, what are your thoughts on the use of fulvestrant, given the recent data from the randomized, phase II FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatments)[1] trial and the randomized, phase III CONFIRM[2] (Comparison of Faslodex in Recurrent or Metastatic Breast Cancer) trial, which demonstrated the superiority of a higher dose of fulvestrant? In the CONFIRM trial, fulvestrant administered at 500 mg intramuscularly on days 0, 14, and 28, and every 28 days thereafter was associated with a significant PFS improvement over fulvestrant administered at 250 mg every 28 days.

**Christopher Twelves, MD:** Now that the correct dose has apparently been identified, fulvestrant seems to be a decent drug. The main drawback of fulvestrant is the mode of administration. However, fulvestrant would be my preference for this patient. Another benefit of endocrine therapy for this patient is that it will allow her to prepare for the time when chemotherapy is needed.

**Hope S. Rugo, MD:** Returning to our case study, the patient does receive fulvestrant. Her pain improves, but 6 months later, staging studies reveal several new liver lesions. Liver function tests are normal. A bone scan is stable with sclerotic lesions. Her performance status is good, but she notes increasing fatigue and mild anorexia. She would like to avoid frequent clinic visits for as long as possible. At this point, what treatment would you recommend: a nonsteroidal AI, estrogen, capecitabine, paclitaxel and bevacizumab, gemcitabine and carboplatin, or another option?

**Christopher Twelves, MD:** Although she has liver metastases, there is not high-volume disease in the liver. She still feels well, and her biochemistry tests are reasonable. If she were a "serial responder" to endocrine therapy, I would probably consider switching her to an AI at this point. However, she appears instead to be slowly progressing on endocrine therapy, and switching to an AI would be risky. I would therefore look toward chemotherapy. Capecitabine would be an appropriate option, given that she wishes to avoid frequent hospitalization. Because our patient does not have rapidly progressing disease, I would not feel obliged to introduce a taxane at this point.

**Hope S. Rugo, MD:** I agree; capecitabine is a reasonable option at this point. Although one could not be faulted for choosing paclitaxel and bevacizumab, there is generally a greater toxicity risk in this case. The patient does start capecitabine at a dose of 1,000 mg/m$^2$ twice daily for 14 of every 21 days. She requires several dose reductions due to pain and swelling in her hands and feet. A CT scan after 3 cycles (9 weeks) shows a near complete response in the liver with stable sclerotic bone lesions. Her disease remains in good control on capecitabine. She switches to a 1-week-on, 1-week-off schedule because of the neuropathy. Eight months later, a staging scan shows a significant increase in the size and number of liver lesions, although the bone remains stable. Bevacizumab is added, but 6 weeks later, a CT scan shows further progression. At this point, her liver enzymes are slightly elevated, and her bilirubin is normal. She is concerned about the time required for IV chemotherapy due to her home responsibilities and her neuropathy. What treatment do you recommend at this point: weekly paclitaxel, every-3-week docetaxel, gemcitabine and carboplatin, eribulin, or ixabepilone?

**Edith A. Perez, MD:** Weighing patients' desires and concerns is always a challenge for us as we try to select the best treatment in each situation. In some cases, we have agents that could really diminish the side effects of the disease. However, drug dosages must be managed carefully to minimize treatment-related toxicity. For this patient, I believe eribulin is now a very appropriate choice. Another option, although it has not been approved in the United States, is liposomal doxorubicin. This single-agent therapy is approved in Europe and is associated with no alopecia.

**Hope S. Rugo, MD:** The patient does go on to receive eribulin at a full dose (1.4 mg/m$^2$ IV on days 1 and 8 every 21 days), along with filgrastim on day 8 starting at cycle 2. After 3 cycles, she has a near complete response in the liver. After 5 cycles, she has increasing peripheral neuropathy. Her eribulin dose is reduced to 1.1 mg/m$^2$, after which she reports improved symptoms.

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