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Individualizing Treatment to Optimize Survival Outcomes in Breast Cancer

A Review of an Adjunct Symposium of the 2013 American Society of Clinical Oncology Annual Meeting

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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 field of oncology with a special interest in breast cancer.

Statement of Need/Program Overview

Although metastatic breast cancer remains incurable, there is evidence that patients are now living longer and with a higher quality of life. Patient characteristics, tumor characteristics, and prior adjuvant therapies are important components of the therapeutic decisions for recurrent disease. Recent years have brought new treatment approaches for patients with metastatic breast cancer. Patients with certain tumor subtypes may be especially likely to benefit from novel therapies. Eribulin mesylate, a microtubule-targeting agent, gained approval in 2010 after showing improved overall survival in a phase III clinical trial. Endocrine therapies and targeted agents, such as monoclonal antibodies, small molecules, and vaccines, have generated much interest. Platinums and other DNA-damaging agents are being explored in patients with *BRCA*-induced or sporadic triple-negative metastatic breast cancer. Oncologists must be able to tailor management based on patient and tumor characteristics, and incorporate novel agents into the sequencing algorithm.

Educational Objectives

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

- Discuss the importance of new clinical trial data in the treatment of patients with metastatic breast cancer
- Identify patient-related and tumor-related characteristics that can be used to guide treatment decisions in metastatic breast cancer
- Incorporate novel agents into the sequencing algorithm for treating patients with metastatic breast cancer
- Integrate strategies to implement the latest knowledge on emerging therapies and methods for treating breast cancer that improve patient outcomes

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This monograph was authored by an independent medical writer, Lisa Cockrell, PhD, based on presentations given at "Individualizing Treatment to Optimize Survival Outcomes in Breast Cancer," an adjunct symposium of the 2013 American Society of Clinical Oncology Annual Meeting, held on June 2, 2013.

A Landscape Update on Metastatic Breast Cancer—What Works? What Doesn't? Strategies for Optimizing Survival: An Evidence-to-Practice Road Map for Individualizing Therapy for Metastatic Breast Cancer

Edith A. Perez, MD

The current treatment of metastatic breast cancer is based upon standards of care that are determined to be the best for the average population, not the individual patient. Mounting evidence, however, shows that the application of systems biology, such as molecular profiling technologies, enables clinicians to tailor and individualize medical care. In the future, it is likely that the application of these technologies will vastly improve individual patient outcomes.

There are several challenges in the development of novel approaches based on systems biology. Foremost is the identification and validation of molecular markers. Although several molecular markers have been proposed in the literature, many have not undergone the rigorous testing required to validate their utility and robustness. Validation studies often require considerable resources and time, as well as large numbers of patients and tissue specimens. In addition, it will be necessary to successfully integrate an understanding of the molecular crosstalk and bypass mechanisms present in the individual tumor, to allow optimal application of combinatorial treatment strategies. Finally, there is a need to more fully identify early predictors of clinical outcome, thereby minimizing a patient's exposure to therapies not active against her particular breast tumor.

A number of strategies have been established to maximize therapeutic benefits—that is, to improve efficacy while minimizing toxicity. For example, there is a focus on the clinical development of more effective agents directed against appropriate targets. In addition, the recognition of pretreatment determinants of efficacy may help to identify those patients who will most likely derive the best clinical benefit from a specific treatment. Such factors may also double as early markers of response. Determinants may include characteristics derived from the tumor, serum, and molecular imaging. Currently, techniques such as molecular imaging are still nascent and not yet readily available for widespread adoption into routine clinical practice.

What Is "Clinically Meaningful?"

In a presentation at the 2010 Seventh European Breast Cancer Conference, investigators discussed findings from a study that compared patient and doctor views on the goal of therapy for metastatic breast cancer.[1] A total of 28 breast medical oncologists were asked what they thought was the most important endpoint in the first-line metastatic setting. Of these, 52% reported that overall survival was the most important endpoint, whereas 48% said that it was

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progression-free survival (PFS). The oncologists were then asked to state what they believed to be the minimal meaningful incremental improvement in overall survival. Nearly half (48%) responded that a 4–6 month improvement was the minimum they would accept as meaningful, and 44% believed that a 2–4 month improvement was the minimum.

When metastatic breast cancer patients (n=52) were asked what they thought was the most important endpoint in the first-line metastatic setting, overall survival was the most frequent response, reported by 52%. Response was most important to 17% of patients. It is possible that the concept of PFS is not well understood by patients, although oncologists often refer to this endpoint in discussions with colleagues. When the patients were asked what they accepted as the minimum meaningful incremental improvement in overall survival, the difference in their expectations from those of the physicians was stark. Nearly half (46%) responded that more than a 12-month improvement in overall survival was the minimum they would accept as meaningful, 17% responded that a 10–12 month improvement would be meaningful, and 10% responded that a 1–2 month improvement would be meaningful.

One interpretation of these data is that oncologists have become more realistic in terms of considering what can be achieved with current therapies. At the same time, physicians must be considerate of what patients want to be accomplished. Therefore, it is imperative that patients and physicians work together and participate in clinical trials to help advance clinical development as well as improve understanding of the biology underlying metastatic breast cancer.

Targeting Tumor Biology

Characterization of breast cancers by tumor biology is based primarily on the presence or absence of both hormone receptors (either the estrogen receptor and/or the progesterone receptor) and the human epidermal growth factor receptor 2 (HER2). Approximately 75% of metastatic breast cancer cases are classified as hormone-sensitive and are either estrogen receptor–positive and/or progesterone receptor–positive. Multiple endocrine therapies targeting these hormone receptors are now available and are a preferred choice for these patients because they are associated with a favorable toxicity profile. An estimated 20% of metastatic breast cancers are HER2-positive.[2] Standard therapy for these patients incorporates agents that target and inhibit the HER2 receptor in these tumors.[2]

Between 10% and 15% of metastatic breast cancer patients are negative for both of these criteria and are classified as having triple-negative disease.[3] These patients are not considered candidates for currently approved targeted therapies. Instead, they are typically treated with cytotoxic chemotherapeutic agents. The aggressive phenotype associated with triple-negative metastatic breast cancer, coupled with the limited treatment options for this subtype, results in a poor prognosis for these patients.[3-5]

The Future Landscape

Many of the novel agents under investigation for future treatment of metastatic breast cancer have mechanisms of action that target hallmark characteristics identified as critical components of the underlying tumor biology (Figure 1).[6] For example, several abstracts recently presented at international meetings have reported on promising developments with cyclin-dependent kinase (CDK) inhibitors. Other studies have demonstrated success with novel inhibitors of vascular endothelial growth factor signaling, as well as inhibitors of the poly (adenosine diphosphate–ribose) polymerase protein.

Currently, much of the emphasis in the field of targeted treatment of metastatic breast cancer is placed upon targeting the tumor itself. However, the future landscape will likely include agents that target the tumor microenvironment as well. The tumor microenvironment is being increasingly recognized as an important determinant of metastasis. It can also impact gene expression and protein activity in the tumor cells. It will be critical for clinical studies evaluating biopsy specimens to include not only the tumor but tissue that extends beyond the margins of the tumor.

The current era in the management of breast cancer patients emphasizes prevention as well as treatment of metastatic disease. Novel "omic" approaches can be applied to allow early detection of metastasis-prone tumors, identify residual metastatic cancers, and reveal molecular characteristics unique to metastatic disease. These unique molecular features could be assayed for in routine blood screenings or tumor biopsies, thereby identifying patients at high risk for metastasis. This high-risk subgroup could then undergo more rigorous screening with sensitive anatomic, histopathologic, and other omic assays.[7] These genomic and proteomic assays not only evaluate expression of genes and proteins but also monitor their role in signal transduction pathways. Thus, it is important to understand the static changes in gene and protein expression and how this expression is altered in the tumor cell.

Several issues will be important to consider when applying new and emerging genomic information to treatment decisions for metastatic breast cancer patients. Chief among these issues is the need to determine which tests are most appropriate for which patients. It is necessary to prioritize tests to avoid wasting time and resources. Additionally, clinicians must be able to knowledgeably interpret the results provided by each of the tests, especially in the context of constantly emerging information regarding these genes and proteins.

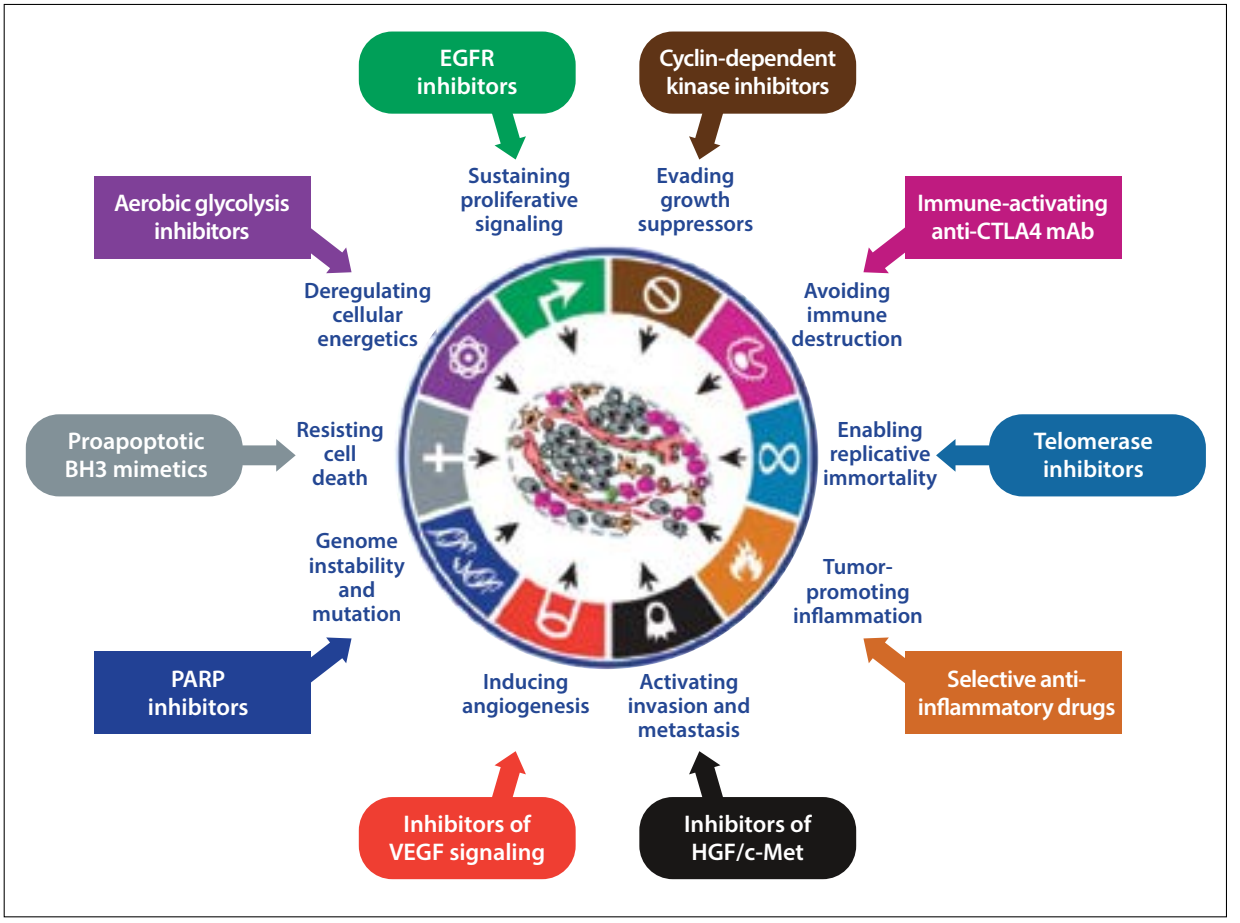

Figure 1. In metastatic breast cancer, many of the novel agents under investigation have mechanisms of action that target hallmark characteristics identified as critical components of the underlying tumor biology. EGFR=epidermal growth factor receptor; mAb=monoclonal antibody; PARP=poly (ADP-ribose) polymerase; VEGF=vascular endothelial growth factor. Adapted from Hanahan D, Weinberg RA. *Cell.* 2011;144(5):646-674.[6]

Despite all of the advancements in the management of metastatic breast cancer, it is important to remember that chemotherapy remains a backbone of therapy. Chemotherapy is a backbone for patients with triple-negative disease; patients with hormone receptor–positive breast cancer, who will eventually exhaust the available endocrine therapies; and patients with HER2-positive breast cancer, who typically require chemotherapy in combination with HER2-targeted therapy.

Surrogate Markers in Metastatic Breast Cancer

Circulating tumor DNA has been proposed as a novel surrogate marker to monitor patients with metastatic breast cancer. Dawson and colleagues compared the sensitivity of an assay for circulating tumor DNA in the plasma of breast cancer patients with 3 other approaches typically used in clinical trials: detection of cancer antigen 15-3 (CA 15-3), detection of circulating tumor cells, and radiographic imaging.[8] A total of 52 women with metastatic breast cancer who were actively undergoing treatment were enrolled in this prospective, single-center study. Thirty patients were found to have somatic genomic aberrations in archived tumor tissue samples. Serial blood samples were collected in these patients at intervals of 3 or more weeks.

Circulating tumor DNA was quantified in 141 serial plasma samples from the 30 patients using 1 of 2 methods: digit=al polymerase chain reaction (PCR) assay or tagged-amplicon deep sequencing. Circulating tumor DNA was detected in 18 of the 19 patients (80 of 97 plasma samples) analyzed by digital PCR, and in all 11 of the remaining patients (35 of 44 plasma samples) analyzed by tagged-amplicon deep sequencing. Overall, circulating tumor DNA was detected in 29 of the 30 patients (97%) and in 115 of the 141 plasma samples (82%). The single patient who had no detectable circulating tumor DNA had a comparably low burden of metastatic disease and no evidence of disease progression during the study.

Importantly, multiple specific point mutations and structural variants were concurrently monitored in the serial blood samples. Genomic alterations identified in the circulating tumor DNA were also identified by tumor biopsy. Furthermore, in patients whose tumor biopsy samples showed evidence of gene amplification, these same genetic alterations were detected at higher levels within the plasma, suggesting that the assay of circulating tumor DNA is quantitative. Overall, these findings confirmed that measurement of circulating tumor DNA can detect somatic genomic aberrations as effectively as existing methods, and that this approach offers a potentially simpler and less invasive alternative to repeated tumor biopsy. In the future, it may be possible to easily detect the presence of potential targets and monitor changes in their expression.

In the study by Dawson and colleagues, data comparing CA 15-3 levels with circulating tumor DNA levels were available in 27 patients (114 serial plasma samples).[8] CA 15-3 levels were elevated (>32.4 U/mL) in 21 of the 27 patients (78%) and in 71 of the 114 samples (62%). In comparison, circulating tumor DNA was detected in 26 of the 27 patients (96%) and in 94 of the 114 samples (82%; Figure 2). Circulating tumor DNA was detectable in nearly two-thirds (63%) of the samples that did not have elevated CA 15-3 levels. A modified bootstrapping method was applied to the data, resulting in a median difference in sensitivity of 26% between the 2 detection methods (95% confidence interval [CI], 11–37; *P*<.002).

Circulating tumor cells were also quantified in all 30 patients (126 serial plasma samples; positive detection was considered to be ≥1 cell per 7.5 mL of blood). Circulating tumor cells were detected at 1 or more time points in 26 of the 30 patients (87%), and 18 patients (60%) showed high circulating tumor cell levels (≥5 cells per 7.5 mL of blood). Of the 126 samples, 76 (60%) were positive for circulating tumor cells, and 46 (37%) had high circulating tumor cell levels. In comparison, circulating tumor DNA was detected in 29 of the 30 patients (97%) and in 106 of the 126 samples (84%). Two-thirds (66%) of the samples that were negative for circulating tumor cells were found to be positive for detectable levels of circulating tumor DNA. The modified bootstrapping method showed that detection of circulating tumor DNA had superior sensitivity to detection of circulating tumor cells (median difference in sensitivity of 27%; 95% CI, 13–37; *P*<.002).

Detection of circulating tumor DNA (in ≥3 time points over a period of more than 100 days of follow-up) was compared with computed tomography (CT) scans in 20 patients with measurable disease. Circulating tumor DNA was detected and showed fluctuations in 19 of the 20 patients (95%). In general, the changes in circulating tumor DNA levels correlated well with

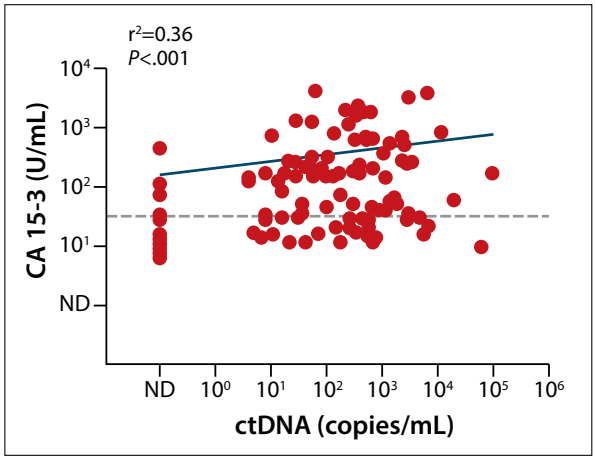

Figure 2. In a study analyzing circulating tumor DNA to monitor metastatic breast cancer, the number of amplifiable copies of circulating tumor DNA was 133 times the number of circulating tumor cells and had a greater dynamic range. CA 15-3=Cancer antigen 15-3; ND=not detected. Reprinted from Dawson SJ et al. *N Engl J Med*. 2013;368(13):1199-1209.[8]

treatment responses observed by CT scan. All but 1 of the 20 patients showed evidence of progressive disease by CT scan. Increases in circulating tumor DNA levels were noted in 17 of these 19 patients (89%). However, CA 15-3 levels were found to increase in 9 of 18 patients (50%), and the number of circulating tumor cells increased in only 7 of the 19 patients (37%).

A Cox proportional-hazards model showed that an increase in levels of circulating tumor DNA was associated with significantly worse overall survival (*P*<.001). Furthermore, patients in the lowest quartile of circulating tumor DNA experienced the best rates of survival compared with patients in the highest quartile, who had the worst survival rates. Circulating tumor cells were also shown to be prognostically significant (*P*=.03), but CA 15-3 levels were not.

This proof-of-concept analysis demonstrated that circulating tumor DNA is an informative and inherently specific methodology that offers potential as a highly sensitive surrogate biomarker of metastatic breast cancer. The results of this analysis will likely be incorporated in many of the metastatic breast cancer clinical studies that will be conducted in the near future.

Role of Clinical Trials

The many advancements made in recent years that have deepened our understanding of the biology underlying metastatic breast cancer are a direct result of the effort and resources that have been devoted to basic research in this field. Clinical trial research, however, remains critical to address the growing global cancer burden and to improve the lives of patients with metastatic breast cancer world-

wide. Clinical trials enable investigators and clinicians to determine if findings in the basic research setting translate into improved outcomes for patients.

The 2 general types of clinical cancer research trials—publicly supported studies and industry-supported studies—have slightly different but complementary objectives. Publicly supported studies have the overall goal of identifying optimal therapies for cancer patients. Industry-supported studies may have multiple goals, including rapid evaluation of an innovative product or agent, evaluation of efficacy, and approval from the US Food and Drug Administration (FDA). Global research is also necessary. Many of the metastatic breast cancer clinical trials currently under way are global, which acknowledges the differences among populations in the incidence and biology of this cancer type. Global trials help to elucidate differences in drug metabolism and pharmacogenomics that may affect tolerability and responsiveness. Additionally, worldwide there is a clear difference in access to healthcare services, which remains an extremely important consideration in treatment decisions as well as in the rationale for conducting clinical trials.

Acknowledgment

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Assessing the Current Endocrine- and Chemotherapy-Focused Landscape for Metastatic Breast Cancer: The Role of Receptor Status for Individualizing Clinical Decisions in Metastatic Breast Cancer

William J. Gradishar, MD

The primary aim of management for patients with metastatic breast cancer is simple—prolonging survival. However, it is important to consider the impact of this goal on the patient's quality of life.[1] Because metastatic breast cancer is currently considered an incurable disease, treatment strategies should offer an acceptable, if not favorable, trade-off in terms of toxicity, convenience, and cost. Symptom palliation, disease control, and delay of disease progression are also important endpoints for treatment.

Metastatic breast cancer remains incurable, but there have been modest gains in the survival of patients over the past several decades. Although the vast majority of metastatic breast cancer patients ultimately succumb to the disease, there is evidence that they are now living longer and better. These gains are especially notable for particular patient subsets, such as those with HER2-positive or hormone receptor–positive disease. The introduction of agents that target these proteins has dramatically changed the natural history of these subtypes. Significant challenges remain for patients with triple-negative metastatic breast cancer.

One study assessed survival in 834 women who had developed recurrent breast cancer between 1974 and 2000 and had been treated with adjuvant anthracycline-based protocols.[2] The patients were divided into 5 consecutive cohorts according to their year of breast cancer recurrence. An unadjusted analysis found that overall survival was incrementally and significantly improved across the 5 cohorts, with patients in the most recent cohorts having the longest survival times ($P<.001$). Several prognostic variables predicted longer survival times, including smaller

Table 1. Factors to Consider When Developing an Individualized Treatment Strategy for Metastatic Breast Cancer

Patient-Related Factors		Preferences Scheduling needs Symptoms Comorbidities
Disease-Related Factors	Prior Adjuvant Therapy	Endocrine vs biologic vs chemotherapy Combined regimens
	Feasibility of Multidisciplinary Treatments	Oligometastatic disease Surgery vs radiofrequency ablation vs stereotactic radiotherapy
Tumor-Related Factors	Tumor Biology	Hormone receptor status (protein) HER2 status (protein or gene)
	Tumor Aggressiveness	Duration of relapse-free interval after primary diagnosis Location of metastases (visceral vs nonvisceral) Extent of metastatic spread (oligometastatic vs polymetastatic)

Table 2. Potential Treatment Scenarios for Patients Previously Diagnosed With Early-Stage Breast Cancer Who Subsequently Developed Recurrent Metastatic Disease

Adjuvant	First-Line	Second-Line	Third-Line	Fourth-Line and Later
Anthracycline/taxane	Decision point	NA	NA	NA
Anthracycline	Taxane	Decision point	NA	NA
Taxane	Anthracycline	Decision point	NA	NA
No chemotherapy or nonanthracycline/nontaxane regimen, such as cyclophosphamide/methotrexate/5-fluorouracil; capecitabine; or vinorelbine	Anthracycline/taxane	Decision point	NA	NA
	Taxane	Anthracycline	Decision point	NA
	Anthracycline	Taxane	Decision point	NA
	No chemotherapy or nonanthracycline/nontaxane regimen, such as cyclophosphamide/methotrexate/5-fluorouracil; capecitabine; or vinorelbine	Anthracycline or taxane	Anthracycline or taxane	Decision point

Adapted from Murphy CG, Seidman AD. *Clin Breast Cancer*. 2009;9(suppl 2):S58-S65.[4]

initial tumor size, lower stage of disease, fewer involved lymph nodes, longer disease-free survival, estrogen receptor–positive status, and nonvisceral dominant site of disease recurrence. Because these prognostic variables were not evenly distributed across the patient cohorts, a multivariate analysis was performed to adjust for these factors. The multivariate analysis found that year of recurrence remained associated with a trend toward improved survival, with a 1% reduction in risk for each increasing year.

A systematic review of recent clinical trials for metastatic breast cancer described typical (lower and upper ranges), best-case, and worst-case scenarios that could be used to help estimate patient survival.[3] A total of 36 randomized first-line chemotherapy trials were identified, which included a total of 13,083 metastatic breast cancer patients. The mean for median PFS was 7.6 months (interquartile range [IQR], 6.0–9.0), and the mean for median overall survival was 21.7 months (IQR, 18.2–24.0). The mean for median overall survival increased with better scenarios; it was 6.3 months (IQR, 4.8–7.5) for the worst case scenario, 11.9 months (IQR, 9.9–13.2) for the lower-typical scenario, 36.2 months (IQR, 31.1–41.3) for the upper-typical scenario, and 55.8 months (IQR, 47.5–60.2) for the best case scenario. As expected, overall survival was longest in studies that contained higher proportions of patients with tumors that were hormone receptor–positive (P=.001) or higher proportions of patients with HER2-positive tumors who were treated with trastuzumab (P=.001).

Individualizing Treatment Strategies

The management plan of patients with metastatic breast cancer is determined according to a number of parameters, which can be categorized as patient-related, disease-related, or tumor-related (Table 1). An especially important factor is the patient's treatment history.

Table 3. Recommended Chemotherapeutic Agents for Treatment of Metastatic Breast Cancer

Single Agents				
Preferred	Anthracyclines Doxorubicin Pegylated liposomal doxorubicin	Taxanes Paclitaxel	Antimetabolites Capecitabine Gemcitabine	Other Microtubule Inhibitors Vinorelbine Eribulin
Other	Cyclophosphamide Carboplatin Docetaxel Albumin-bound paclitaxel	Cisplatin Epirubicin Ixabepilone		
Combination Regimens				
CAF/FAC	Cyclophosphamide/doxorubicin/fluorouracil			
FEC	Fluorouracil/epirubicin/cyclophosphamide			
AC	Doxorubicin/cyclophosphamide			
EC	Epirubicin/cyclophosphamide			
CMF	Cyclophosphamide/methotrexate/fluorouracil			
	Docetaxel/capecitabine			
GT	Gemcitabine/paclitaxel			
	Gemcitabine/carboplatin			
	Paclitaxel/bevacizumab			

Data from the National Comprehensive Cancer Network. Breast cancer. Clinical Practice Guidelines in Oncology. Version 3.2013.[7]

Impact of Adjuvant Therapy on Treatment Decisions

In recent years, the patient's prior adjuvant therapies have had an increased influence on therapeutic decisions for recurrent disease. The vast majority of patients do not present with de novo metastatic disease. Most patients had been previously diagnosed with early-stage breast cancer and typically had received adjuvant therapy. They develop metastatic disease after this initial presentation. Therefore, several scenarios are possible for the successive courses of therapy in these patients (Table 2).[4]

A retrospective assessment of changes in adjuvant chemotherapy choices was recently presented.[5] It included data for 26,095 patients (many of whom were treated in community practice) diagnosed between 2007 and 2010 with stage I–III breast cancer. For patients with HER2-positive disease, there was a marked movement toward greater use of taxane-based nonanthracycline-containing regimens, especially the combination of docetaxel, carboplatin, and trastuzumab, increasing from 26% in 2007 to 62% in 2010. Simultaneously, use of anthracycline-based regimens decreased from 33% to 15%. The potential for cardiotoxicity when trastuzumab is combined with anthracyclines provides a potential explanation for the decreased use of anthracyclines in HER2-positive patients.[6] In HER2-negative patients with hormone receptor–positive disease, the most widely used regimen from 2007–2010 was docetaxel plus carboplatin. It was used in 41% of patients. This combination is becoming more widely adopted by clinicians, especially for lower-risk patients such as those with node-negative or low nodal burden disease. Anthracycline-plus-taxane regimens were more often used in HER2-negative patients with hormone receptor–negative disease (32%). Overall, these data suggest that in the adjuvant setting, patients are increasingly less likely to receive an anthracycline.

Treatment Guidelines

Guidelines from the National Comprehensive Cancer Network (NCCN) provide recommendations for chemotherapeutic agents used as monotherapy or in combination in the metastatic setting (Table 3).[7] The guidelines note that combination regimens are not considered superior to sequential single agents.

Regardless of which chemotherapeutic agent is chosen, the probability of achieving a response to treatment declines with greater drug exposure. Likewise, the duration of response to chemotherapy decreases with increasing lines of therapy. Overall, metastatic breast cancer patients treated with single-agent chemotherapy in the first-line setting have a response rate between 25% and 45%, and a time to progression of 5–8 months.[8] In the second-line setting, the response rate declines to 15–30%, and the time to progression is 2–5 months. In the third-

line setting, the response rate is as low as 0% to 20%, and the time to progression is 1–4 months. There are very few data available to determine outcomes for patients treated in the fourth-line setting and beyond.

The First International Consensus Conference for Advanced Breast Cancer (ABC 1), held in November 2011, produced consensus guidelines specifically for metastatic breast cancer.[9] In these guidelines, sequential monotherapy is considered a preferred choice for treatment of metastatic disease in the absence of rapid clinical progression, life-threatening visceral metastases, and a need for rapid symptom and/or disease control. Additionally, it is recommended that each chemotherapy regimen be administered until disease progression or unacceptable toxicity (which can be defined with the patient).

In early-stage breast cancer, there is high-level evidence supporting the use of multiple treatment options. In contrast, as noted in the ABC 1 guidelines, there are few agents considered to be therapeutic standards in metastatic breast cancer, especially beyond the first-line setting. Furthermore, there are insufficient data to support recommendation of a particular sequence of chemotherapeutic agents, with few studies demonstrating a benefit in overall survival. Importantly, the ABC 1 guidelines recognize that adjuvant breast cancer regimens have changed significantly over time, resulting in a current population of metastatic breast cancer patients with untested treatment-exposure histories and unique mechanisms of drug resistance. Thus, even relatively recent clinical trial data may be difficult to apply to these patients.

Chemotherapeutic Agents—New and Revisited

Amidst the enthusiasm that has developed for targeted therapies in metastatic breast cancer—such as monoclonal antibodies, small molecules, and vaccines—there have been significant developments in novel chemotherapeutic agents that have resulted in new approvals. One of these agents, eribulin mesylate, gained FDA approval in 2010 for the treatment of metastatic breast cancer following treatment with at least 2 chemotherapeutic regimens for metastatic disease. Prior therapy must have included an anthracycline and a taxane in the adjuvant or metastatic setting. FDA approval was based on results of the phase III EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) study, which is described in greater detail below.[10] The EMBRACE study was unique in several aspects of design. For example, the comparator arm was broadly defined to be a treatment of the physician's choice, resulting in the inclusion of a broad spectrum of regimens as control. Additionally, unlike many other metastatic breast cancer studies that employ a primary efficacy endpoint of PFS, the primary endpoint of the EMBRACE trial was overall survival.

Eribulin was also evaluated in comparison with capecitabine in heavily pretreated metastatic breast cancer patients.[11] This trial, known as Study 301, is described in greater detail below. Eribulin showed similar efficacy to capecitabine in both PFS and overall survival, but had a very different toxicity profile, with more grade 3/4 hematologic toxicities, a higher rate of grade 3/4 peripheral neuropathy, and fewer instances of hand-foot syndrome. A subset analysis of this study suggested that eribulin may be of particular benefit in patients with triple-negative disease.

Platinums and other DNA-damaging agents are being re-explored in patients with *BRCA*-induced or sporadic triple-negative metastatic breast cancer. Recent clinical trials of patients with stage IV triple-negative metastatic breast cancer have reported response rates as high as 30% with different regimens containing either cisplatin or carboplatin.[12-15] Further research is needed to confirm these data and to provide a better understanding of the mechanism of action of platinum agents in breast tumors with impaired DNA repair mechanisms.

Subset analyses of previously conducted trials evaluating bevacizumab, such as ECOG (Eastern Cooperative Oncology Group) 2100, AVADO (Avastin and Docetaxel), and RIBBON-2 (A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy for Second-Line Treatment of HER2-Negative Metastatic Breast Cancer), suggest a consistent advantage associated with the addition of bevacizumab to chemotherapy for patients with triple-negative metastatic breast cancer.[16-19] For example, in the subset of pretreated triple-negative patients in the RIBBON-2 study, median PFS improved from 2.7 months with chemotherapy alone to 6.0 months with chemotherapy plus bevacizumab (hazard ratio [HR], 0.494; 95% CI, 0.33–0.74; P=.0006).[20] The median overall survival was 12.6 months versus 17.9 months (HR, 0.624; 95% CI, 0.39–1.007; P=.0534).

Etirinotecan pegol is a novel conjugate that combines a topoisomerase I inhibitor with a polymer. It is currently under investigation in the phase III BEACON (Breast Cancer Outcomes With NKTR-102) trial, which includes more than 800 patients with metastatic breast cancer who had previously been treated with an anthracycline, a taxane, and capecitabine.[21] Notably, the design of this clinical trial is similar to the EMBRACE study in that the comparator arm is defined as treatment of physician's choice, and the primary study endpoint is overall survival.

Choice of Endocrine Therapy

There has been a paucity of data regarding endocrine therapy in recent years. According to NCCN guidelines, endocrine therapy should be continued in patients with

metastatic breast cancer until the occurrence of either disease progression or unacceptable toxicity.[7] It is recommended that premenopausal women with estrogen receptor–positive metastatic breast cancer first undergo ovarian ablation/suppression and then follow the guidelines for postmenopausal women. Several endocrine therapies are recommended for postmenopausal women (Table 4).

Endocrine therapy in the metastatic setting may be discontinued for several reasons, such as if the patient has exhausted the available agents, the patient has become refractory to endocrine therapy (as evidenced by lack of response or a progressively shortened interval of response), or the patient has developed bulky, rapidly progressive disease.

Table 4. Recommended Endocrine Therapy for Treatment of Postmenopausal Women With Metastatic Breast Cancer

Nonsteroidal Aromatase Inhibitors Anastrozole Letrozole
Steroidal Aromatase Inhibitors Exemestane
Fulvestrant
Tamoxifen or toremifene
Megestrol acetate
Fluoxymesterone
Ethinyl estradiol

Data from the National Comprehensive Cancer Network. Breast cancer. Clinical Practice Guidelines in Oncology. Version 3.2013.[7]

Novel Treatment Strategies Involving Endocrine Therapy

Several lines of evidence indicate that the signaling network controlled by the mammalian target of rapamycin (mTOR) is an important factor in overcoming resistance to currently available endocrine therapies. Preclinical studies have shown that estrogen-dependent cells become dependent on mTOR signaling when they are cultured in an estrogen-depleted medium, conditions that mimic resistance to aromatase inhibitors.[22,23] These cells are particularly sensitive to agents that inhibit mTOR.[22,23] Further, endocrine-resistant breast cancer cells regain sensitivity to endocrine therapy agents when treated with mTOR inhibitors.[24-26] Strategies targeting mTOR for inhibition in combination with endocrine therapy have been met with success in the clinic, with several trials demonstrating that the addition of an mTOR inhibitor to endocrine therapy results in an enhanced response compared with endocrine therapy alone.

The TAMRAD (Tamoxifen and RAD001) study was an open-label, randomized, phase II trial that evaluated everolimus in combination with tamoxifen in 111 patients with hormone receptor–positive, HER2-negative metastatic breast cancer.[27] Patients with aromatase inhibitor–resistant disease were randomized to receive either tamoxifen plus everolimus or tamoxifen alone. The clinical benefit rate was higher in the combination arm than with tamoxifen alone (61% vs 42%). Furthermore, there was a 46% reduction in the risk of progression associated with tamoxifen plus everolimus (HR, 0.54; 95% CI, 0.36–0.81; *P*=.002), corresponding to an increase in time to progression from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus. Interestingly, an exploratory subgroup analysis found that the benefit associated with the addition of everolimus occurred mainly in patients with secondary hormone resistance. Patients with secondary hormone resistance showed a 54% reduction in the risk of progression with the addition of everolimus compared with tamoxifen alone (median time to progression, 14.8 months vs 5.5 months; HR, 0.46; 95% CI, 0.26–0.83), whereas patients with primary resistance showed a lesser magnitude of benefit (median time to progression, 5.4 months vs 3.8 months; HR, 0.70; 95% CI, 0.40–1.21). There was a 55% reduction in the risk of death for patients treated with the tamoxifen plus everolimus combination (HR, 0.45; 95% CI, 0.24–0.81; *P*=.007).

BOLERO-2 (Breast Cancer Trials of Oral Everolimus-2) was an international, double-blind, randomized phase III trial designed to assess the efficacy and safety of the combination of everolimus and exemestane in patients with hormone receptor–positive advanced breast cancer that was refractory to nonsteroidal aromatase inhibitor therapy (letrozole or anastrozole).[28] It included 724 patients who were randomized in a 2:1 fashion to receive either everolimus plus exemestane or exemestane plus placebo. Notably, more than half of the patients in each treatment arm had received 3 or more prior therapies. An interim analysis of this study reported that the trial met its primary endpoint of PFS, with both investigator and central assessment analyses crossing the prespecified thresholds for significance. The median investigator-assessed PFS was 6.9 months in the everolimus plus exemestane combination therapy arm versus 2.8 months for the exemestane plus placebo arm (HR, 0.43; 95% CI, 0.35–0.54; *P*<.001). The benefit in median centrally assessed PFS was even greater, at 10.6 months versus 4.1 months (HR, 0.36; 95% CI, 0.27–0.47; *P*<.001). Based upon the results of the BOLERO-2 trial, everolimus in combination with exemestane received FDA approval for the treatment of hormone receptor–positive, HER2-negative advanced breast cancer following failure of treatment with letrozole or anastrozole. Everolimus is now widely viewed in the clinic as the preferred treatment strategy for patients who experience disease progression with aromatase inhibitor therapy. The NCCN guidelines recommend that the addition of everolimus to exemestane be considered in patients who fulfill the eligibility criteria of the BOLERO-2 study.[7]

In addition to mTOR inhibition, other targets have been examined for their potential to augment endocrine therapy in

metastatic breast cancer. An agent that has garnered much interest is PD 0332991, an oral CDK 4/6 inhibitor previously tested in combination with letrozole in a phase I study.[29,30] Recently, the second interim analysis of TRIO-18 (A Randomized Phase 2 Study of PD 0332991, a Cyclin-Dependent Kinase [CDK] 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+, HER2– Advanced Breast Cancer), a 2-part randomized phase II trial of PD 0332991, was reported.[31] This study compared PD 0332991 in combination with letrozole versus letrozole alone as first-line therapy in postmenopausal women with estrogen receptor–positive, HER2-negative advanced breast cancer. This study had 2 parts. In part 1, in which 66 patients were randomized to treatment, the PD 0332991 combination with letrozole was associated with a significant improvement in PFS (P=.006).[32] Biomarkers for *p16* gene loss and *CCND1* (the gene encoding the cyclin D1 protein) gains did not provide improved patient selection over estrogen receptor positivity alone in an exploratory analysis of these patients. In part 2 of this study, which included 99 patients, *CCND1* amplification and/or *p16* loss were applied as additional eligibility criteria. The second interim analysis combined efficacy and safety data from the cohorts in part 1 and part 2. Median PFS was dramatically and significantly prolonged with the combination of PD 0332991 plus letrozole versus letrozole alone (26.1 vs 7.5 months; HR, 0.37; 95% CI, 0.21–0.63; P<.001). Based on these promising phase II results, a phase III trial evaluating PD 0332991 is planned.

Targeting HER2 in Metastatic Disease

Several agents that target HER2-positive breast tumors are now FDA-approved or in the investigational setting. These agents form 2 primary classes of drugs: monoclonal antibodies or small molecules. The primary challenge regarding these agents is how they should best be incorporated into therapy; that is, what combination and sequence of agents will result in optimal patient outcomes.

CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) was a double-blind, placebo-controlled phase III trial that randomized 808 patients with HER2-positive metastatic breast cancer to receive trastuzumab plus docetaxel, plus either pertuzumab or placebo, as first-line therapy.[33] Median PFS was significantly increased in the pertuzumab arm compared with the placebo arm (18.5 vs 12.4 months; HR, 0.62; 95% CI, 0.51–0.75; P<.001). At a median follow-up of 30 months, the median overall survival had not yet been reached in the pertuzumab arm, and it was 37.6 months in the placebo arm (HR, 0.66; 95% CI, 0.52–0.84; P=.0008).[34] These results have been practice-changing, and the pertuzumab, trastuzumab, and docetaxel triplet is now considered a preferred first-line option for patients with HER2-positive breast cancer.[7]

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) was an open-label, international phase III trial that randomized 991 patients with HER2-positive advanced breast cancer to treatment with either trastuzumab emtansine (T-DM1) or the combination of lapatinib plus capecitabine.[35] All patients had previously been treated with trastuzumab and a taxane. The median PFS was 9.6 months for T-DM1 versus 6.4 months for lapatinib plus capecitabine (HR, 0.65; 95% CI, 0.55–0.77; P<.001). In a second interim analysis, the median overall survival crossed the stopping boundary for efficacy (30.9 months for T-DM1 versus 25.1 months for lapatinib plus capecitabine; HR, 0.68; 95% CI, 0.55–0.85; P<.001). The objective response rate was also greater in the T-DM1 arm compared with the lapatinib plus capecitabine arm (43.6% vs 30.8%; P<.001). T-DM1 recently gained FDA approval, and it is considered a preferred agent for trastuzumab-exposed HER2-positive disease.[7]

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Microtubule-Targeting Agents for Metastatic Breast Cancer: A Comparative Mechanistic and Trial-Based Analysis of the Current Armamentarium

Edith A. Perez, MD

Microtubules are essential to many of the normal functions in cells. They provide cell shape and structure, and are involved with cell motility, intracellular trafficking and transport, secretion, signal transduction, and cellular division. The role of microtubules in mitosis is especially well characterized; they are known to control the precise separation of chromosomes to daughter cells during cell division.

The structure of microtubules is composed of heterodimers of α-tubulin and β-tubulin, which polymerize in a head-to-tail array to form parallel linear protofilaments that assemble around a hollow core.[1] They have polar ends—a fast-growing plus end with a β-tubulin subunit exposed and a slow-growing minus end with an α-tubulin subunit exposed—that are important determinants in the direction of movement along the microtubule.

Microtubules undergo rapid cycles of assembly and disassembly, during which the tubulin dimers polymerize and depolymerize. There are alternate cycles of growth and shrinkage at the plus end, as well as a behavior referred to as *dynamic instability*, which is responsible for the rapid turnover of microtubules. The β-tubulin subunit contains a guanosine 5'-triphosphate (GTP) binding site, which must be bound to GTP for assembly into microtubules.

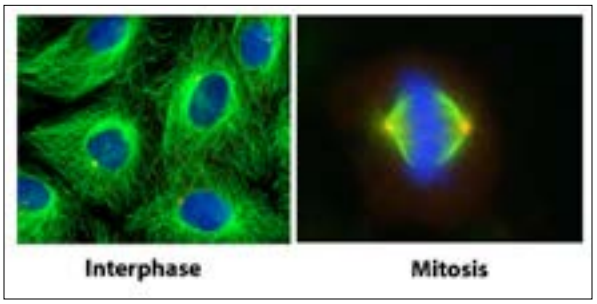

Figure 1. When cells enter mitosis, the intracellular microtubule network is reorganized from a lattice-like structure into the mitotic spindle.

Afterward, GTP is hydrolyzed to GDP. The microtubule is stabilized with a "cap" of GTP-bound β-tubulin at the plus end. When the GTP is hydrolyzed to GDP before another GTP-bound β-tubulin subunit is incorporated, rapid depolymerization of the microtubule ensues (a process known as *microtubule catastrophe*). In contrast, a more controlled loss of tubulin subunits from the minus end with simultaneous gain of subunits at the plus end results in no net change in microtubule mass (referred to as *microtubule treadmilling*).

Dynamic instability is critical for several microtubule functions, including remodeling of the cytoskeleton during mitosis (Figure 1). Specifically, when cells enter mitosis, the intracellular microtubule network is reorganized from a lattice-like structure into the mitotic spindle. Precise and responsive microtubule dynamics are critical for this reorganization, as well as for finding, attaching, and separating the chromosomes during division. Consequently, alteration of microtubule dynamics provides a target in rapidly dividing cells, such as tumor cells, that can be leveraged for cancer therapy. Both microtubule-associated proteins and microtubule-interacting drugs can promote or inhibit microtubule dynamics and affect the rate of microtubule growth and shortening.

Microtubules as Anticancer Targets

Microtubule-targeting agents differ from each other in several ways. They bind to different locations on microtubules and within the tubulin subunits, and they show different sensitivities to the tubulin isotypes. Their pharmacokinetic and pharmacodynamic properties are diverse, with different tissue and tumor susceptibilities, unique mechanisms of resistance, and different degrees of reversibility and cellular persistence. Microtubule-targeting agents can be classified as microtubule stabilizers or destabilizers. Microtubule stabilizers stimulate polymerization of the tubulin subunits, creating an increase in the density of cellular microtubules. In contrast, microtubule destabilizers inhibit microtubule polymerization, resulting in a loss of cellular microtubules.

Table 1. Microtubule-Stabilizing and -Destabilizing Agents Used in Metastatic Breast Cancer Chemotherapy

Microtubule-Stabilizing Agents	Microtubule-Destabilizing Agents
Taxanes	Vinca alkaloids
Paclitaxel	Vinblastine
Docetaxel	Vincristine
Nab-paclitaxel	Vinorelbine
Epothilones	Halichondrins
Ixabepilone	Eribulin

Microtubules play a critical role during mitosis and are therefore an important target for anticancer drugs. A large group of chemically diverse agents have been found to target microtubules via various tubulin-binding sites. Although the use of many of these agents is largely limited to the laboratory, several have gained approval for the treatment of a wide variety of cancers, including metastatic breast cancer (Table 1).

At high concentrations, microtubule-targeting agents have dramatic effects on interphase microtubules. Even at very low concentrations, these drugs inhibit mitosis and are thus classified as antimitotic agents. The highly dynamic nature of the mitotic spindle causes it to be especially susceptible to the effects of microtubule-targeting agents. During mitosis, microtubule dynamics increase 4-fold to 100-fold.[2] Suppression of these dynamics causes the development of aberrant mitotic spindles and abnormal DNA alignment, both triggers of mitotic arrest and subsequent cell death.

Recently, there has been a paradigm shift regarding the mechanism of microtubule-targeting agents in cancer. It has been proposed that inhibition of interphase microtubule dynamics is the primary mechanism contributing to the efficacy of these agents in tumors.[3] This effect would lead to interference with cell signaling and trafficking, slowing of cell cycle progression, alterations in cell migration and invasiveness, and vascular disruption. One of the primary arguments supporting this notion is that mitosis-specific agents that inhibit targets other than microtubules have not achieved similar clinical success.

Eribulin: A Novel Microtubule-Disrupting Agent

Despite their marked and durable success in the clinic, microtubule-targeting agents are not without their limits. These drugs can be toxic to noncancerous cells, resulting in peripheral neuropathy. The cause of this neuropathy may be related to drug-induced microtubule inhibition within neurons, which rely heavily upon microtubules for trafficking.[2] Another limitation of currently available microtubule-targeting agents is the development of resistance. The clear clinical importance of microtubule-targeting agents, however, has paved the way for the development of novel agents that target the microtubules with better toxicity and resistance profiles.

One of the most successful next-generation microtubule-targeting agents is eribulin mesylate, which is now FDA-approved for the treatment of patients with metastatic breast cancer who have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting as well as at least 2 chemotherapeutic regimens for the treatment of metastatic disease. A synthetic analog of halichondrin B—a natural product isolated from the marine sponge *Halichondria okadai*—eribulin is classified as a nontaxane microtubule dynamics inhibitor. Halichondrin B was initially shown to inhibit tumor cell proliferation, potentially by inhibiting cell cycle progression.[4] In vitro studies demonstrated that halichondrin B binds to tubulin near the vinca alkaloid binding site, which is located on β-tubulin near the GTP-binding site, and inhibits the polymerization of tubulin into microtubules.[5-7]

Multiple ecologic and environmental issues are related to obtaining sufficient quantities of natural products such as halichondrin B. Therefore, a chemical synthesis process was created to develop the synthetic analogue eribulin, which has a simpler structure but retains a similar potency.[8] Like halichondrin B, eribulin binds to tubulin and inhibits microtubule polymerization at the plus ends. Eribulin is thought to act through an "end-poisoning mechanism," in which microtubule growth is inhibited—although not shortened—and thus suppresses dynamic instability.[9,10] This mechanism makes eribulin unique among the other characterized microtubule-targeting agents, such as vinblastine and paclitaxel, which decrease both the shortening and growth phases of microtubule dynamic instability. Studies in cells have demonstrated that eribulin suppresses the rate of microtubule growth, length, duration, and overall dynamicity by 27%, 50%, 28%, and 28%, respectively.[9] Eribulin contributes to microtubule inhibition, and it induces sequestration of the tubulin subunits into globular aggregates. The cumulative effects of eribulin in tumor cells result in cell cycle inhibition and disruption of mitotic spindle formation, which lead to subsequent mitotic arrest, inhibition of proliferation, and apoptosis.[11,12]

A recently published study has provided further insight into the cellular pharmacodynamics and in vivo pharmacokinetics of eribulin, suggesting an explanation for the high potency of the drug in tumors.[13] This study investigated the mitotic blockade induced by eribulin using flow cytometry and cell viability assays of cultured cancer cell lines. According to these findings, the mitotic arrest induced by eribulin appears to be irreversible, owing to both persistent drug retention as well as sustained phosphorylation-dependent inactivation of the anti-apoptotic protein Bcl-2. The reversibility ratio for eribulin was calculated by dividing the minimum drug concentration required to maintain a complete mitotic block 10 hours following drug washout by the minimum concentration required to initially induce complete mitotic block. The result was 1, meaning that the complete mitotic block initially induced by 10 nmol/L eribulin remained intact 10 hours after the washout. This finding supports the conclusion that eribulin-induced mitotic arrest is irreversible. In contrast, the reversibility ratio of a structurally similar but less potent synthetic analogue of halichondrin B, ER-076349, showed it was moderately reversible. Reversibility ratios were also calculated for several other microtubule-targeting agents, leading the study investigators to conclude that their mitotic arrest reversibility profiles were unique and quantifiable (Table 2). Interestingly, even small structural changes in microtubule-targeting agents affect whether the drug reversibly or irreversibly causes mitotic arrest, which can have a marked impact on the potency of the drug in vivo.

Table 2. Mitotic Arrest Reversibility Ratios of Microtubule-Targeting Agents

Microtubule-Targeting Agent	Reversibility Ratio	Reversibility Behavior
Eribulin*	1	Irreversible
Vincristine*	1	Irreversible
Colchicine	1.7	Nearly irreversible
ER-076349	12	Moderately reversible
Paclitaxel*	14	Moderately reversible
Vinblastine*	65	Highly reversible
Colcemid	>100	Highly reversible
Nocodazole	>100	Highly reversible

*Approved by the US Food and Drug Administration for an anticancer indication.

Data from Towle MJ et al. *Cancer Res.* 2011;71(2):496-505.[13]

Interestingly, in clinical trials, eribulin was associated with a relatively low incidence and severity of neuropathy. In contrast, other microtubule-targeting agents induce significant neurotoxicity. Using mice as a surrogate model, the neuropathy-inducing propensity of eribulin was compared with that of paclitaxel and the epothilone ixabepilone.[14] Paclitaxel and ixabepilone were both associated with significant deficits in caudal nerve conduction velocity, caudal amplitude, and digital nerve amplitudes, as well as moderate-to-severe degenerative pathologic changes in the dorsal root ganglia and the sciatic nerve. In contrast, eribulin was not associated with any significant negative effects on nerve conduction, and it caused only mild and infrequent morphologic changes.

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Increasing Overall Survival Prolongation in Metastatic Breast Cancer: The Foundational Role of Nontaxane Microtubule Dynamics Inhibitors Based on Tumor Burden and Receptor Status

Christopher Twelves, MD

Anthracyclines and taxanes play an important part in the treatment of breast cancer. Where and how these drugs are incorporated into treatment regimens can vary from the adjuvant setting to the first-line, second-line, or later lines of therapy in patients with metastatic disease. Unlike 10–15 years ago, when these drugs were reserved mainly for metastatic breast cancer, patients are now increasingly receiving anthracyclines and taxanes in adjuvant therapy. Clinicians are therefore faced with the question of how to manage patients with metastatic breast cancer who had received anthracycline and/or taxanes in earlier treatment courses.

Despite the importance of determining how best to treat metastatic breast cancer patients who have progressed following anthracycline-based and taxane-based therapy, few clinical trials have addressed this issue. To comprehensively assess the current evidence, a systematic review of 22 trials (totaling 2,046 patients) was conducted.[1] Studies in this analysis met several criteria: they were phase II or III clinical trials; at least 80% of enrolled patients had advanced breast cancer pretreated with anthracyclines and taxanes; and they evaluated palliative chemotherapy with capecitabine (10 studies), vinorelbine (9 studies), gemcitabine (3 studies), or liposomal doxorubicin monotherapy (1 study). The weighted mean disease control rates were 57% for capecitabine, 49% for vinorelbine, 35% for gemcitabine, and 38% for liposomal doxorubicin (P=.031). There were no significant differences in other efficacy outcomes, including median time-to-progression, PFS, and overall survival (Table 1).

Clinical Development of Eribulin Mesylate: Early Studies

In preclinical studies, eribulin mesylate had potent anticancer activity both in vitro and in vivo.[2,3] Additionally, eribulin was active in cell lines possessing paclitaxel-resistant β-tubulin mutations, likely due to its unique mechanism of action inhibiting microtubule dynamics.[4-7] In animal studies, eribulin was associated with a wide therapeutic window and dramatically less neurotoxicity compared with paclitaxel.[8] Based on this preclinical rationale, eribulin was evaluated in phase I and phase II clinical trials for metastatic breast cancer.

In an initial phase I trial, Synold and colleagues used a rapid titration design, with dose-escalation guided by real-time pharmacokinetics.[9] Eribulin was administered weekly for 3 of 4 weeks per treatment cycle. A total of 40 patients with advanced or refractory solid tumors were enrolled, including 4 patients with breast tumors. Eribu-

Table 1. Comparison of Treatment Outcomes With Single-Agent Chemotherapy in Metastatic Breast Cancer Patients Pretreated With Anthracyclines and Taxanes

Agent	Number of Trials	Number of Patients	Treatment Outcomes (Weighted Mean Values)			
			Response Rate (%)	Median Time-to-Progression (months)	Median Progression-Free Survival (months)	Median Overall Survival (months)
Capecitabine	10 8 phase II 2 phase III	1,404	18	3.9	4.2	13.5
Vinorelbine	9 7 phase II 2 phase III	406	24	3.6	3.8	12.6
Gemcitabine	3 3 phase II 0 phase III	86	13	1.9	4.5	9.8
Liposomal Doxorubicin	1 1 phase II 0 phase III	150	10	Not calculated	2.9	10.4

Data from Oostendorp LJ et al. *Lancet Oncol.* 2011;12(11):1053-1061.[1]

lin was initiated at a dosage of 0.125 mg/m^2 and escalated on a standard 3 × 3 schedule until a grade 2 or higher toxicity occurred. The occurrence of 2 dose-limiting toxicities—1 grade 3 febrile neutropenia and 1 grade 4 neutropenia—led to the maximum tolerated dose being set at 1.4 mg/m^2. A minor response was observed in 1 of the breast cancer patients.

A phase I study by Goel and colleagues enrolled 32 patients with advanced solid malignancies (including 2 with breast cancer) who were treated with eribulin on days 1, 8, and 15 of a 28-day cycle.[10] Dosing was initiated at 0.25 mg/m^2, with dose-escalation guided by the emergence of dose-limiting toxicities. The primary dose-limiting toxicity, neutropenia, led to the maximum tolerated dose being set at 1 mg/m^2. The most frequent adverse events included fatigue (53%), nausea (41%), and anorexia (38%). Eight patients reported neuropathy, which occurred only at grades 1 or 2. One of the 2 breast cancer patients achieved stable disease during the study.

A third phase I trial, by Tan and coworkers, included 21 patients with advanced solid malignancies (none with breast cancer).[11] The maximum tolerated dose, identified by using an accelerated titration design, was 2 mg/m^2. Febrile neutropenia was the primary dose-limiting toxicity.

Subsequently, eribulin was evaluated in several phase II clinical trials. Two trials focused on patients with metastatic breast cancer. Vahdat and associates reported results from an open-label, single-arm, phase II trial of 103 heavily pretreated metastatic breast cancer patients who had previously received an anthracycline and a taxane.[12] The median number of prior chemotherapy regimens was 4 (range, 1–110). Eribulin was initially administered at a dosage of 1.4 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. The occurrence of neutropenia led to an alternative regimen, in which eribulin was administered on days 1 and 8 of a 21-day cycle. The objective response rate was 11.5%; all responses were partial. The clinical benefit rate, which included partial responses and patients with stable disease for at least 6 months, was 17.2%. The median duration of response was 5.6 months (171 days; range, 44–363 days). The median PFS was 2.6 months (79 days; range, 1–453 days), and the median overall survival was 9.0 months (275 days; range, 15–826 days). The most frequent drug-related grade 3/4 adverse events included neutropenia (64%), leukopenia (18%), fatigue (5%), peripheral neuropathy (5%; grade 3 only), and febrile neutropenia (4%). No grade 4 neuropathy was reported.

Cortes and colleagues published data from an open-label, single-arm, phase II trial of 299 patients with locally advanced or metastatic breast cancer who had previously been treated with an anthracycline, a taxane, and capecitabine.[13] Patients were heavily pretreated, with a median of 4 prior chemotherapy regimens. The objective response rate was 9.3%; all responses were partial. The clinical benefit rate was 17.1%. The median duration of response was 4.1 months, the median PFS was 2.6 months, and the median overall survival was 10.4 months. The most frequent grade 3/4 adverse event was neutropenia (54%), followed by leukopenia (14%), asthenia/fatigue (10%), peripheral neuropathy (6.9%; grade 3 only), and febrile neutropenia (5.5%). No grade 4 neuropathy was reported.

Clinical Development of Eribulin: The EMBRACE Trial

EMBRACE was a phase III, global, multicenter, open-label, randomized trial that compared eribulin with a treat-

ment of the physician's choice in 762 women with heavily pretreated locally recurrent or metastatic breast cancer.[14] The size of this trial is significant, dwarfing the studies previously conducted in similar patient populations.[1]

Inclusion criteria for this trial included (1) age 18 years or older; (2) histologically or cytologically confirmed measureable or evaluable breast cancer; (3) treatment with 2–5 prior chemotherapy regimens, including an anthracycline and a taxane, and with at least 2 of these regimens used for locally recurrent or metastatic disease; (4) progression within 6 months on the most recent chemotherapy; (5) adequate organ function; (6) ECOG performance status of 0–2; and (7) life expectancy of at least 3 months. Exclusion criteria included pre-existing grade 3 or higher neuropathy, untreated or unstable brain metastases, or treatment that was administered within 3 weeks of study entry.

The baseline patient characteristics were well balanced between the treatment arms. The median age was 55.0 years (range, 27–85 years). The vast majority of patients were white (92%), and nearly two-thirds were recruited from North America, western Europe, or Australia (64%). Most patients had a performance status of either 0 or 1 (42% and 49%, respectively), and 8% had a performance status of 2. Three-quarters of the patients were HER2-negative (74%), but two-thirds 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), and the most common chemotherapeutic agent was capecitabine (73%).

Patients were stratified according to geographic region, previous capecitabine treatment, and HER2 status prior to randomization in a 2:1 fashion to receive either eribulin (n=508; 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle) or a treatment of the physician's choice (n=254), defined as (1) any single-agent chemotherapy, endocrine therapy, or biological therapy approved for the treatment of cancer; (2) radiotherapy; or (3) symptomatic treatment alone. Treatment was continued until disease progression or unacceptable toxicity. The primary study endpoint was overall survival, which is notable because few prior studies in this setting had shown an improvement in overall survival. Secondary endpoints included PFS, objective response, and duration of response.

The median duration of eribulin therapy was 3.9 months (range, 0.7–16.3 months), with 59% of patients receiving 5 or more cycles of treatment (range, 1–23 cycles). The median duration of chemotherapy in the treatment of physician's choice arm was 2.1 months (range, 0.03–21.2 months). In the treatment of physician's choice arm, nearly all patients received chemotherapy (96%)—specifically, vinorelbine (25%), gemcitabine (19%), capecitabine (18%), taxanes (15%), anthracyclines (10%), and other chemotherapies (10%). The remaining patients in this arm were treated with endocrine therapy.

The EMBRACE study met its primary endpoint. Patients in the eribulin arm demonstrated a significantly improved median overall survival compared with patients in the treatment of physician's choice arm (13.1 vs 10.6 months; HR, 0.81; 95% CI, 0.66–0.99; *P*=.041).

An updated analysis of overall survival, which was not specified in the protocol design, was conducted at the request of European and US regulatory authorities. This analysis included 589 deaths, compared with 422 deaths in the primary analysis. The increase in median overall survival observed in the eribulin arm compared with the treatment of physician's choice arm remained significant (13.2 vs 10.6 months; HR, 0.81; 95% CI, 0.68–0.96; *P*=.014; Figure 1). The rate of 1-year survival was 54.5% in the eribulin group and 42.8% in the treatment of physician's choice group.

In an exploratory subgroup analysis that analyzed overall survival according to patient stratification factors, overall survival was significantly prolonged with eribulin versus treatment of physician's choice in patients from North America, western Europe, and Australia (HR, 0.72; 95% CI, 0.57–0.92; *P*=.009). Eribulin also prolonged overall survival in patients from Latin America and South Africa (HR, 0.91; 95% CI, 0.47-1.78). It did not appear to improve overall survival in patients from Eastern Europe, Russia, and Turkey (HR, 1.09; 95% CI, 0.70–1.71).

Not surprisingly, when overall survival was analyzed according to the patients' treatment histories, those with 3 or fewer prior chemotherapy regimens achieved a significantly prolonged median overall survival compared with those who received more than 3 prior chemotherapy regimens (13.5 vs 11.7 months; *P*=.04).[15]

Although there was a trend toward improved median PFS with eribulin compared with treatment of physician's choice, this difference did not reach statistical significance (3.7 vs 2.2 months; HR, 0.87; 95% CI, 0.71–1.05; *P*=.0137) in the independent review assessment. This difference was statistically significant in the investigator review assessment (HR, 0.76; 95% CI, 0.64–0.90; *P*=.002).

The objective response rate was significantly improved with eribulin versus treatment of physician's choice (12% vs 5%; *P*=.002). This objective response rate included 3 complete responses in the eribulin arm and no complete responses in the treatment of physician's choice arm. Similarly, the rate of clinical benefit was 23% in the eribulin arm and 17% in the treatment of physician's choice arm. The median duration of response was 4.2 months for eribulin and 6.7 months for treatment of physician's choice (*P*=.159).

The rates of serious adverse events were 25% in the eribulin arm and 26% in the treatment of physician's choice arm. Adverse events led to discontinuation

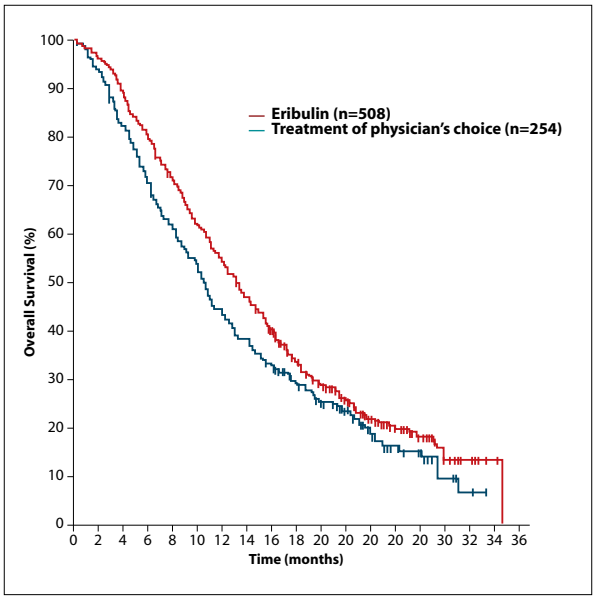

Figure 1. In an updated analysis of overall survival in the EMBRACE trial, the increase in median overall survival observed in the eribulin mesylate arm as compared with the treatment of physician's choice arm remained significant (*P*=.014).

EMBRACE=Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. Adapted from Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2012.[20]

in 13% of eribulin patients and 15% of patients who received treatment of physician's choice. Most of the adverse events reported in both groups were grade 1 or 2 in severity; of these, the most frequently reported were asthenia or fatigue, and neutropenia. Grade 3 or 4 adverse events that were reported more frequently with eribulin compared with treatment of physician's choice included neutropenia, leukopenia, and peripheral neuropathy. In the eribulin arm, grade 3 neutropenia occurred in 21% and grade 4 neutropenia occurred in 24%. Neutropenia was effectively managed with dose delays, reductions, and granulocyte colony-stimulating factor.

Peripheral neuropathy occurred in the eribulin arm at rates of 8% for grade 3 and less than 1% for grade 4. Peripheral neuropathy was the adverse event that most frequently resulted in discontinuation from eribulin (5%). For patients who continued eribulin despite grade 3/4 neuropathy, it improved to grade 2 or better with dose reductions or delays.

Eribulin was approved for the treatment of metastatic breast cancer on the basis of the significant improvement in overall survival reported in the EMBRACE trial. The study was well-designed, in that it was a large randomized trial with the robust clinical endpoint of overall survival, and it compared eribulin to a control arm that largely represented real-world clinical practice because there is not a standard of care chemotherapy regimen for heavily pretreated metastatic breast cancer. However, the EMBRACE trial was limited in that it was not powered for comparison of eribulin against the individual drugs used in the treatment of physician's choice arm. In addition, it did not include quality of life analyses.

Clinical Development of Eribulin: Study 301

Study 301 was designed to be complementary to the EMBRACE trial.[16] It addressed the limitations of the EMBRACE trial and was conducted simultaneously. Because the clinical data required a longer time to mature, the study was reported after results from the EMBRACE trial were published. In Study 301, capecitabine was chosen as the treatment in the comparator arm because it is so widely used for metastatic breast cancer in the first-line, second-line, and third-line settings for patients who had previously received an anthracycline and a taxane. The use of this more conventional control arm allowed the collection of quality of life data.

Study 301 was a global, open-label, randomized, multicenter phase III trial in 1,102 women with locally advanced or metastatic breast cancer.[16] Prior to randomization, patients were stratified by geographic region and HER2 status. Patients were randomized 1:1 to receive either eribulin (n=554; 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle) or capecitabine (n=548; 1,250 mg/m^2 on days 1–14 of a 21-day cycle). All patients included in this study had 3 or fewer prior chemotherapy regimens, up to 2 of which were used for advanced disease. All patients had received a prior anthracycline and a taxane, either in the adjuvant or neoadjuvant setting or for locally advanced or metastatic disease.

Baseline characteristics were well balanced between the treatment arms. The median age was 54.0 years (range, 24–80 years) in the eribulin group and 53.0 years (range, 26–80 years) in the capecitabine group. Most patients in both groups had a performance score of either 0 or 1. Prior use of chemotherapy was similar in both arms. Among the eribulin patients, 21% had not received prior chemotherapy, 50% had received 1 chemotherapy regimen, 28% had received 2, and 1% had received 3 or more. In the capecitabine arm, 19% had not received prior chemotherapy, 53% had received 1 chemotherapy regimen, 27% had received 2 regimens, and 1% had received 3 or more. Most patients were HER2-negative (68% in the eribulin group and 69% in the capecitabine group). Triple-negative disease was reported in 27% of the eribulin patients and 25% of the capecitabine patients.

The primary study endpoints were overall survival and PFS. Secondary endpoints included objective response; duration of response; quality of life; 1-year, 2-year, and 3-year survival; tumor-related symptom assessment; safety; and population pharmacokinetics (in the eribulin

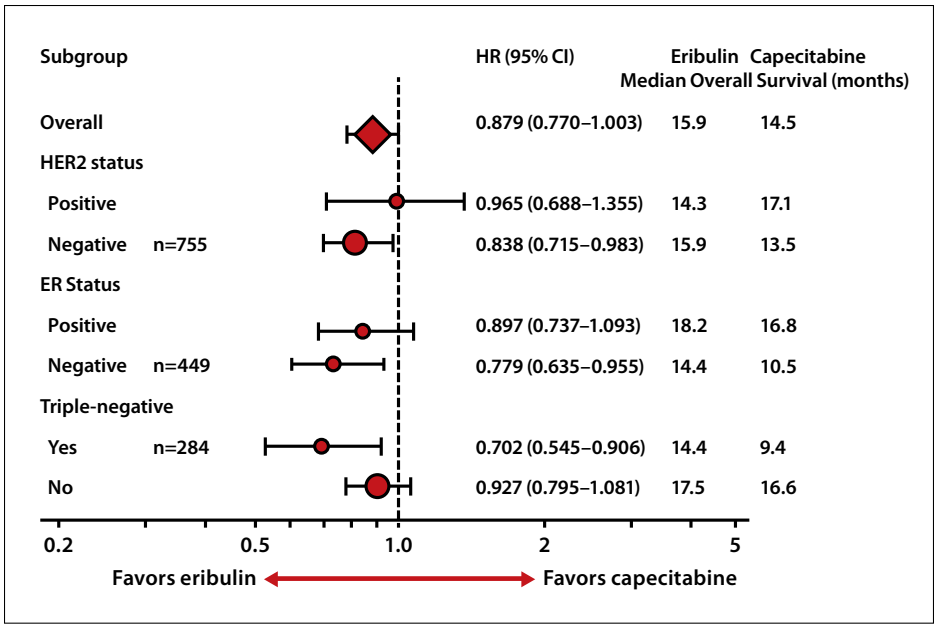

Figure 2. In a phase III trial of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes, prespecified subgroup analyses suggested that eribulin was favored in patients with HER2-negative disease, ER-negative disease, and triple-negative breast cancer.

CI=confidence interval; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; HR=hazard ratio. Adapted from Kaufman PA et al. Paper presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S6-6.[16]

arm only). A positive final analysis was planned if at least 1 of the following 2 criteria were met: overall survival with eribulin was significantly better compared with capecitabine ($P \leq .0372$), or PFS by independent review was significantly better with eribulin versus capecitabine ($P \leq .01$) and the HR for overall survival was less than 1.

In this study, there was no statistically significant improvement in overall survival with eribulin versus capecitabine (15.9 vs 14.5 months; HR, 0.879; 95% CI, 0.770–1.003; $P=.056$). The yearly overall survival rates for eribulin versus capecitabine were as follows: 1-year, 64.4% versus 58.0% ($P=.035$); 2-year, 32.8% versus 29.8% ($P=.324$); and 3-year, 17.8% versus 14.5% ($P=.175$). A subgroup analysis suggested that patients with certain tumor subtypes may show increased survival benefit with eribulin than capecitabine (Figure 2). These subgroups included HER2-negative patients (15.9 months vs 13.5 months; HR, 0.838; 95% CI, 0.715–0.983), estrogen receptor–negative patients (14.4 months vs 10.5 months; HR, 0.779; 95% CI, 0.635–0.955), and patients with triple-negative tumors (14.4 months vs 9.4 months; HR, 0.702; 95% CI, 0.545–0.906).

Similarly, median PFS was not significantly different between the eribulin and capecitabine groups. This observation was true regardless of whether the analysis was conducted by investigator review (4.2 vs 4.1 months; HR, 0.977; 95% CI, 0.857–1.114; $P=.736$) or independent review (4.1 vs 4.2 months, HR, 1.079; 95% CI, 0.932–1.250; $P=.305$). The objective response rate remained similar between the eribulin and capecitabine arms (11% vs 12%; $P=.849$), as did the rate of clinical benefit (26% vs 27%).

Grade 3/4 hematologic toxicities occurred at a far greater frequency with eribulin than capecitabine. Rates of grade 3/4 neutropenia and leukopenia were 46% and 15%, respectively, with eribulin, as compared with 4% and 2%, respectively, with capecitabine. Eribulin was also associated with a higher rate of grade 3/4 peripheral neuropathy: 4% versus less than 1%. Not surprisingly, hand-foot syndrome and diarrhea occurred at a greater frequency in the capecitabine arm than the eribulin arm (14% vs <6%, respectively).

Using the quality of life data gathered in this study, the global health status was pooled for patients in both treatment arms. There was a clear stepwise difference in quality of life according to treatment response, with patients who attained a complete or partial response achieving the best global health status. When the global health status data were analyzed by treatment group, they were found to improve more with eribulin than with capecitabine, suggesting some subjective patient benefit ($P=.048$). Differences in quality of life included eribulin-associated improvements in parameters linked to gastrointestinal effects, such as diarrhea, nausea, and

vomiting. Interestingly, quality of life questions regarding body image favored capecitabine, presumably due to the greater rate of alopecia associated with eribulin.

Incorporating Eribulin Into Treatment Strategies

The EMBRACE study was the first to show overall survival with a novel therapeutic agent in a heavily pretreated population of metastatic breast cancer patients. Eribulin was the first drug to receive FDA approval for the treatment of refractory metastatic breast cancer on the basis of improved overall survival. Importantly, this study demonstrated the feasibility of improving overall survival with novel agents and therefore supported the use of overall survival as a primary endpoint in clinical trials of refractory metastatic breast cancer.[17] This difference represents a change in the paradigm, which had previously supported the notion that improved overall survival was an unachievable goal in metastatic breast cancer.

The positive results achieved with the design of the EMBRACE trial will likely influence the design of future studies in metastatic breast cancer. This effect can already be observed with trials of NKTR-102, an investigational novel polymer conjugate of irinotecan with a biodegradable spacer. Preclinical studies show that NKTR-102 is more active than irinotecan in xenograft models and is also better tolerated. A phase II trial of NKTR-102 in metastatic breast cancer reported a response rate of 29%, including 2 patients with a complete response and 2 other patients showing complete resolution of target lesions.[18] The median PFS was 4.6 months, and the median overall survival was 10.3 months. These promising results led to the design of the ongoing BEACON study, in which patients with metastatic breast cancer are being randomized to treatment with either NKTR-102 or a treatment of physician's choice.[19] The primary study endpoint is overall survival.

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Individualizing Treatment to Optimize Survival Outcomes in Breast Cancer: Case Discussion

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Lee Schwartzberg, MD The patient is a 64-year-old woman with stage IIB, T2N1 breast cancer. She was strongly positive for the estrogen receptor, slightly positive for the progesterone receptor, and HER2-negative. She had been treated with a mastectomy and docetaxel/cyclophosphamide. She received letrozole for 14 months. She presented with pain in her right flank, moderate fatigue, and nausea. CT scan and bone scan showed evidence of metastatic lesions to her liver and ribs. She had an ECOG performance status of 1.

William J. Gradishar, MD Because this patient is symptomatic and has liver metastases, as a first step I would give her chemotherapy, such as capecitabine. Although I am an advocate for using endocrine therapy as frequently as possible and for as long as possible, this patient is symptomatic. If she were able to achieve a response to chemotherapy, down the line, I might consider endocrine therapy.

Christopher Twelves, MD A liver biopsy might be appropriate if it is thought that the patient's HER2 status has changed. I would lean toward chemotherapy if the patient has a single superficial lesion that is causing some irritation on the liver surface and a liver biochemistry is normal. If the patient has bulky disease, and the liver biochemistry starts to deteriorate, then clearly we would move toward chemotherapy.

Lee Schwartzberg, MD The point being that visceral disease in and of itself is not a contraindication to endocrine therapy. The patient is switched to exemestane, and she has progression of disease on the first scan at 8 weeks. Her ECOG performance status is 1. She now has increasing pain in the right upper quadrant, which is thought to be caused by progressive liver metastasis.

Edith A. Perez, MD This patient has primary endocrine-resistant breast cancer. She developed progressive disease within 2 years of adjuvant hormonal therapy.

Lee Schwartzberg, MD She has visceral disease, a short disease-free interval, relatively quick progression on adjuvant hormonal therapy, and moderate disease burden. Recently, I have become much more aggressive at checking the phenotype in these types of patients, who do not follow the traditional path of strongly endocrine-positive disease. If you are not sure of the quality control of the original immunohistochemistry and/or fluorescence in situ hybridization (FISH) testing on HER2, it might make sense to retest, so as not to miss an opportunity to treat a patient who is HER2-positive.

The liver was biopsied, and it showed adenocarcinoma consistent with breast origin. Interestingly, the phenotype was somewhat different now. The patient was still HER2-negative, but the estrogen receptor was just very mildly positive and the progesterone receptor was negative. The patient did indeed have progression in her bones as well as the liver. Because she did not wish to lose her hair, she chose to receive capecitabine. She had stable disease for 4 months. She developed moderate hand-foot syndrome but then had mild progression in the liver. Her performance score remained 1, and she continued to work. Her liver function was 3 times the upper limit of normal.

She began treatment with eribulin. She experienced a partial response in her liver. She developed grade 1 neuropathy but, gratifyingly, she was able to continue to work. After 6 months, she progressed asymptomatically in the liver.

William J. Gradishar, MD At this point, I would most likely give her either liposomal doxorubicin or nab-paclitaxel.

Christopher Twelves, MD She has had a period of a decent duration of response on this last line of therapy, although she ultimately progressed. Liposomal doxorubicin would be very reasonable.

Lee Schwartzberg, MD Yes. In third-line treatment, the goal is to balance toxicity with relief of symptoms, by using agents with different mechanisms of action and differing toxicity profiles, while maintaining quality of life. As you go through clinical decision-making, both from the neoadjuvant to the adjuvant to the metastatic setting at each line of therapy, those principles must be kept in mind for every patient.

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Individualizing Treatment to Optimize Survival Outcomes in Breast Cancer

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

1. In a survey that compared patient and doctor views of the goals of therapy for metastatic breast cancer, how many patients reported that a 12-month improvement in overall survival was the minimum they would accept as meaningful?

   a. 18%
   b. 24%
   c. 37%
   d. 46%

2. Approximately ___ of metastatic breast cancer cases are classified as hormone-sensitive and are either estrogen receptor–positive and/or progesterone receptor–positive.

   a. 55%
   b. 65%
   c. 75%
   d. 85%

3. In a retrospective assessment of changes in adjuvant chemotherapy from 2007–2010, what was the most commonly used regimen in HER2-negative patients with hormone receptor–positive disease?

   a. Anthracycline plus a taxane
   b. Docetaxel plus carboplatin
   c. Eribulin mesylate plus trastuzumab
   d. Gemcitabine plus cisplatin

4. Among metastatic breast cancer patients treated with single-agent chemotherapy in the second-line setting, the time to progression is:

   a. 1–4 months
   b. 2–5 months
   c. 6–8 months
   d. 9–12 months

5. Recent clinical trials of patients with stage IV triple-negative metastatic breast cancer have reported response rates as high as ___ with different regimens containing either cisplatin or carboplatin.

   a. 30%
   b. 40%
   c. 50%
   d. 60%

6. In the BOLERO-2 trial, what was the median investigator-assessed progression-free survival in the everolimus plus exemestane combination therapy arm?

   a. 2.8 months
   b. 4.1 months
   c. 6.9 months
   d. 7.8 months

7. In a second interim analysis of the EMILIA trial, which treatment arm achieved a median overall survival crossing the stopping boundary for efficacy of 30.9 months?

   a. Eribulin
   b. Gemcitabine
   c. Lapatinib plus capecitabine
   d. TDM-1

8. Studies in cells have demonstrated that eribulin mesylate suppresses the rate of microtubule growth by:

   a. 27%
   b. 28%
   c. 50%
   d. 51%

9. In a systematic review of 22 trials that assessed how best to treat metastatic breast cancer patients who have progressed following anthracycline-based and taxane-based therapy, which agent had the highest weighted mean disease control rate?

   a. Capecitabine
   b. Gemcitabine
   c. Liposomal doxorubicin
   d. Vinorelbine

10. In Study 301, patients with tumors that were HER2-negative, estrogen receptor–negative, or triple-negative were found to have increased benefit from:

    a. Capecitabine
    b. Eribulin
    c. Gemcitabine
    d. TDM-1

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Evaluation Form: Individualizing Treatment to Optimize Survival Outcomes in Breast Cancer

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 9471**. 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 importance of new clinical trial data in the treatment of patients with metastatic breast cancer
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Identify patient-related and tumor-related characteristics that can be used to guide treatment decisions in metastatic breast cancer
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Incorporate novel agents into the sequencing algorithm for treating patients with metastatic breast cancer
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Integrate strategies to implement the latest knowledge on emerging therapies and methods for treating breast cancer that improve patient outcomes
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

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

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

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

❒ I do plan to implement changes in my practice based on the information presented
❒ My current practice has been reinforced by the information presented
❒ I need more information before I will change my practice

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

Please use a number (for example, 250):

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

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

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

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

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

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

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

❒ Yes ❒ No, please explain:

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

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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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