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Evidence-Driven, Patient-Specific Approaches for Optimizing Survival Prolongation in Breast Cancer

A Review of an Adjunct Symposium of the 2014 American Society of Clinical Oncology Annual Meeting

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Target Audience

This activity has been designed to meet the educational needs of physicians, nurses, academicians, researchers, investigators, support staff, and program directors from the field of oncology involved in the care of patients with breast cancer.

Statement of Need/Program Overview

Despite significant advances in the treatment of breast cancer, metastatic disease remains incurable. There are few therapeutic standards for metastatic breast cancer, and the most effective sequence of agents has not been defined. Outcomes can be optimized by individualizing management based on multiple factors, including tumor biology, tumor aggressiveness, treatment history, presence of symptoms, patient preferences, and comorbidities. The heterogeneity of breast cancer is being recognized in current trials, which are evaluating the optimal approaches for various patient subgroups. Eribulin mesylate is a microtubule-targeting agent that gained approval in 2010 after showing improved overall survival in a phase 3 clinical trial. A subsequent study has shown that eribulin may have particular benefit in patients with triple-negative breast cancer. A greater understanding of the genetic events associated with cancer biology is providing new insight into potential therapeutic targets. Novel therapies under investigation include poly (ADP-ribose) polymerase inhibitors and agents targeting the PI3K/Akt/mammalian target of rapamycin pathway, the androgen receptor, and the epidermal growth factor receptor. Oncologists must be able to identify patients who are likely to benefit from novel strategies and sequence these agents into the management plan.

Educational Objectives

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

- Prolong survival in patients with metastatic breast cancer who have received multiple chemotherapeutic treatment courses with documented remissions
- Compare the safety, efficacy, and survival prolongation profiles associated with novel treatments for metastatic breast cancer
- Individualize therapy in patients with metastatic breast cancer based on factors such as receptor status (ER, PR, and HER-2), clinical tumor burden, treatment history, comorbidities, and patient preferences
- Sequence or combine chemotherapeutic agents to prolong overall survival in patients with metastatic breast cancer

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This monograph was authored by an independent medical writer, Mindy Tanzola, PhD, based on presentations given at "Evidence-Driven, Patient-Specific Approaches for Optimizing Survival Prolongation in Breast Cancer," an adjunct symposium of the 2014 American Society of Clinical Oncology Annual Meeting, held on May 31, 2014.

Optimizing Survival in Patients With Advanced and Metastatic Breast Cancer: Individualizing Therapy

William J. Gradishar, MD

Across disease types, the field of cancer therapy is moving from a standard-of-care model, in which the optimal treatment approach has been defined for average populations, to a strategy of individualized medicine, in which treatment is tailored to each patient's individual circumstances. The movement toward personalized medicine is being aided by the application of systems biology, in which molecular profiling technologies are used to help guide medical care. There are challenges, however, in implementing personalized medicine in breast cancer, including the need to identify and validate relevant markers, account for molecular crosstalk and bypass mechanisms, and establish early predictors of outcome.

An important aspect in implementing individualized therapy is the identification of treatment goals. Studies have suggested that clinicians and patients may differ in their expectations for treatment. In a survey of 28 medical oncologists and 52 breast cancer patients, both groups reported that survival is the most important endpoint in the first-line treatment setting.[1] The groups differed, however, in their perception of the minimal length of time that constitutes a meaningful improvement in survival; most clinicians identified 4 to 6 months (48%) or 2 to 4 months (44%), whereas most patients identified more than 12 months (46%) or 10 to 12 months (17%).

Despite the treatment advances seen in recent decades, metastatic breast cancer (MBC) remains incurable.[2] Outcomes can be optimized by individualizing management based on multiple factors, including tumor biology, tumor aggressiveness, prior adjuvant therapy, prior local and systemic treatments, and the patient's symptoms, comorbidities, and preferences.

In general, treatment approaches for breast cancer can be categorized based on the tumor expression of the hormone receptors—the estrogen receptor (ER) and the progesterone receptor (PR)—and the human epidermal growth factor receptor 2 (HER2). For the approximately 65% of patients with hormone receptor–positive breast cancers, endocrine therapy is a component of treatment. Approximately 15% to 20% of patients have HER2-positive tumors,[3-5] and the development of HER2-targeted therapy has led to substantial progress in the treatment of these patients.[6,7] For the 10% to 15% of patients with triple-negative breast cancer (TNBC),[8] treatment is largely based on chemotherapy. However, novel therapies are currently under evaluation. The hope is that the progress attained for HER2-positive tumors can also be reached for other subsets.

Within these broad categories, numerous agents and combinations are currently used in the treatment of advanced MBC and, depending on individual circumstances, patients will often progress through many different types of therapies. In the setting of advanced disease, there are few therapeutic standards, and the optimal sequence of agents has not been defined.[9] In general, advanced breast cancer is treated with single-agent therapy, although combinations may be preferred in some circumstances.

Adjuvant breast cancer therapy has changed substantially in the past few decades. These advances have implications for treatment in the metastatic setting, as patients can present with resistance to certain agents.[10] Such factors can complicate the applicability of clinical trial findings.

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Table 1. Genetic Lesions and Potentially Active Targeted Drugs

Gene	Aberration	Frequency	Targeted Drug(s)
PI3K	Activating mutations	36%	PI3K, Akt, mTOR inhibitors (BKM120, MK-2206, everolimus)
HER2	Amplification	20%	Trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib, afatinib
HER2	Activating mutations	1%-2%	HER2 inhibitors (lapatinib, neratinib, afatinib)
FGFR1, FGFR2	Amplification	10%	FGFR inhibitors (dovitinib)
c-MET	Amplification/mutation	15%	Foretinib, tivantinib
Akt	Activating mutations	2%	Akt, mTOR inhibitors (MK-2206, everolimus, temsirolimus)
JAK2	Activating mutations	2%	Tofacitinib, ruxolitinib
ESR1	Activating mutations	2%-5%	Fulvestrant
PTEN	Inactivating mutations or methylation	20%	PI3K, Akt, mTOR inhibitors
CCND1	Amplification	36%	Cyclin-dependent kinase inhibitors
CDK4	Amplification	16%	
RB1	Inactivating mutations	2%	
CDKN1B	Inactivating mutations	1%	
CDH1	Inactivating mutations	7%	Wnt inhibitors
BRCA1/BRCA2	Inactivating mutations	5%	PARP inhibitors

FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase.

Identifying Targets for Cancer Therapy

Cancer therapy has evolved significantly over recent years with the advent of treatments that target characteristics that are central to the development and progression of the malignancy. For example, epidermal growth factor receptor (EGFR) inhibitors block sustained proliferative signaling associated with cancer cells, immunomodulating agents target immune evasion, proapoptotic agents overcome cell death resistance, and vascular endothelial growth factor (VEGF) signaling inhibitors target angiogenesis.[11] Further elucidation of these key mediators and pathways, and the development of agents that disrupt these pathways, may lead to new ways of targeting cancer biology.

Progress Toward Precision Medicine

A greater understanding of the genetic events associated with cancer biology is providing new insight into potential therapeutic targets. Genetic studies have elucidated numerous genetic aberrations, including active or inactive mutations, amplifications, and epigenetic modifications, that are recurrent in breast cancer (Table 1).[12] The observation that PI3 kinase (PI3K) mutations are some of the most commonly occurring mutations in breast cancer has led to the development of multiple agents that target the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway (Figure 1). These therapies remain an active area of research in multiple cancer types.

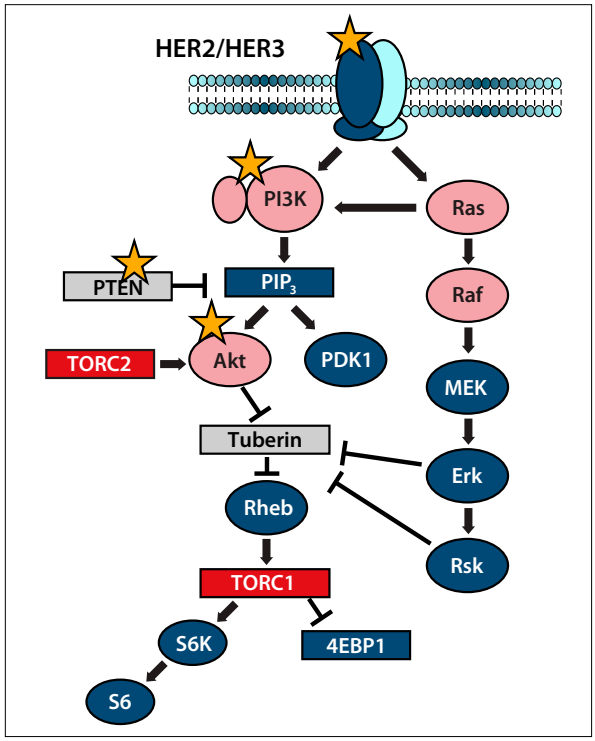

Figure 1. The PI3K/Akt/mTOR pathway and breast cancer.

mTOR, mammalian target of rapamycin; PTEN, phosphatase and tensin homolog; Rheb, Ras homolog enriched in brain.

In addition to revealing potential therapeutic targets, molecular assessments may also reveal potential biomarkers, such as gene mutations and circulating tumor DNA. These

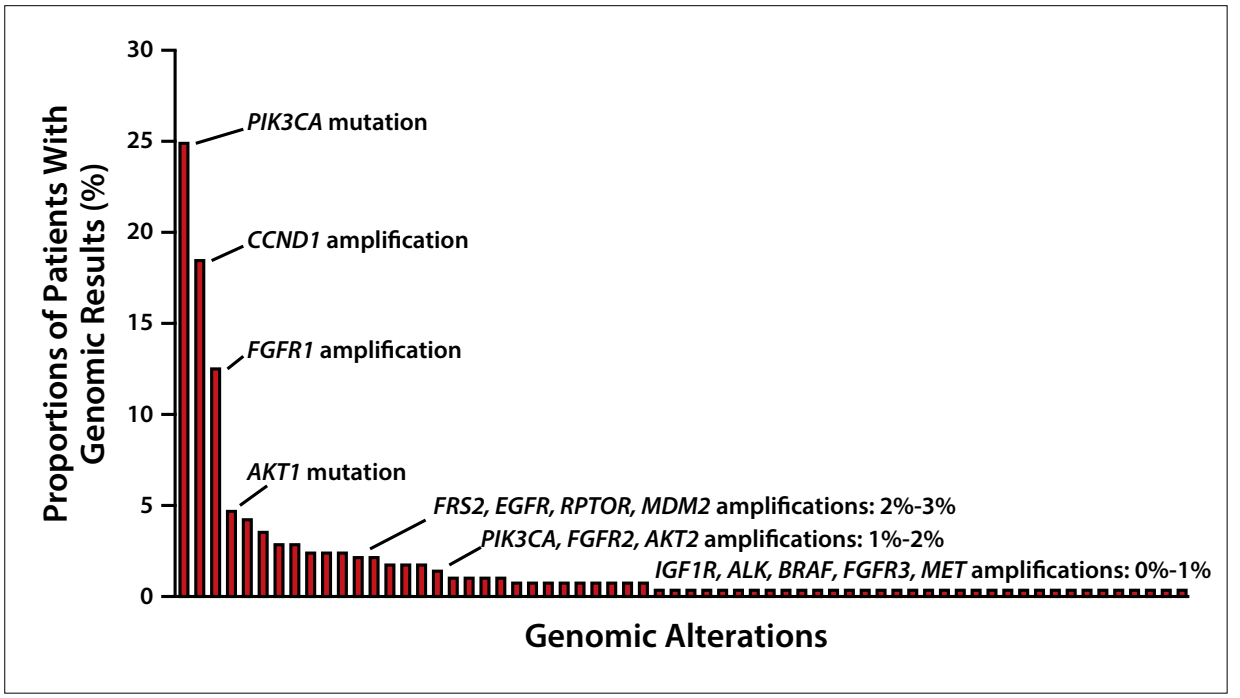

Figure 2. Mutations in breast cancer as identified in the SAFIR 01 analysis.

SAFIR, High Throughput Technologies to Drive Breast Cancer Patients to Specific Phase I/II Trials of Targeted Agents. Adapted from André F et al. *Lancet Oncol.* 2014;15(3):267-274.[16]

biomarkers may provide prognostic information and help predict which therapies could be most active. For example, the amount of circulating tumor cells detectable at baseline is significantly associated with overall survival in patients with MBC.[13] However, results from the randomized, phase 3 SWOG S0500 trial indicate that circulating tumor cells are not an adequate marker for deciding when to switch therapies.[14] Compared with patients who switched therapy upon progression, patients who switched therapy earlier based on elevated circulating tumor cells had no significant difference in overall survival or progression-free survival (PFS).

Although blood assessments have been evaluated in clinical trials, the optimal method of deriving specimens for biomarker assessments—whether from the blood or using serial biopsies—has not yet been identified for MBC. Assessing the tumor over time may provide information on how the tumor biology evolves.

At the 2013 San Antonio Breast Cancer Symposium, Balko and colleagues presented results of a study evaluating the genetic characteristics of 68 cases of residual TNBC after neoadjuvant chemotherapy.[15] Among these patients with residual disease, the development of new amplifications in Janus kinase 2 (JAK2) was associated with significantly worse outcomes. These tumors may be targetable with available JAK2 or pan-JAK inhibitors.

The feasibility of genomic-driven medicine was also tested in SAFIR (High Throughput Technologies to Drive Breast Cancer Patients to Specific Phase I/II Trials of Targeted Agents) 01, a prospective trial in which French researchers conducted genomic analyses from biopsies of metastatic lesions and attempted to match the genetic alterations present in individual patients with available targeted agents. Among the 407 patients with available biopsy samples, genomic analysis was successful in approximately 70% and yielded targetable genomic alterations in 195 patients.[16] The analysis identified a few recurring mutations, most commonly in PI3KCA (25% of identified mutations), *CCND1* (19%), and FGFR1 (13%; Figure 2). However, 39% of patients had rare genomic alterations that occurred in less than 5% of the population. Genomic analysis led to the identification of a potential personalized treatment option in 13% of patients. Among patients who received personalized therapy, 9% achieved an objective response. The overall response rate (ORR) across the entire patient population was only 1%.

The findings from the SAFIR 01 trial represent an early attempt at precision medicine for MBC. The development of additional targeted agents for patients with druggable lesions may further improve outcomes. Looking forward, clinical trials will likely attempt to enrich patient populations for tumors expressing relevant mutations. These trials, and the application of systems biology to research, will continue the movement toward individualized care for breast cancer.

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

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The Unmet Need for Effective Treatment of Triple–Receptor Negative Breast Cancer

William J. Gradishar, MD

TNBC is a heterogeneous group of breast cancers that do not express hormone receptors or HER2.[1] Typically, TNBC has a poor histologic grade, presents with a larger tumor size (although nodal metastases are less common), is associated with *BRCA* mutations, and reflects a basal genotype in gene expression profiling (Figure 3).[1] Relapses typically occur early—within 5 years of diagnosis—and develop in visceral sites, including the central nervous system.[2] The prognosis of patients with TNBC is usually poor, as nearly all women with metastatic TNBC die of the disease.[3]

Population-based data indicate that the basal-like phenotype, which is frequently associated with TNBC, occurs more frequently in African American women, particularly those who are premenopausal.[4] Conversely, the more favorable luminal A type occurs less frequently in African American women and is more common in older white women.

Current Treatment of TNBC

TNBC presents a particular therapeutic challenge. It lacks approved targeted therapies and does not respond to HER2-targeted agents or hormonal treatments. Chemotherapy remains the standard treatment, but no optimal approach has been identified.[3] Efforts are underway using genetic analysis to identify pathways that might be important to the biology of TNBC; these studies have revealed new ways of classifying breast cancer into biologically and clinically distinct entities based on gene expression patterns. Most patients with TNBC have the basal-like molecular subtype, which is characterized by high expression of proliferation genes and greater genomic instability.[5] A minority of TNBC patients have the claudin-low subtype, which is characterized by relatively low expression of proliferation genes and greater genomic stability.

Therefore, although TNBC is classified as ER-negative, PR-negative, and HER2-negative by clinicopathologic markers, it has greater heterogeneity at the molecular level compared with other breast cancer subtypes.[1] Cheang and colleagues evaluated a cohort of borderline TNBC cases, which were HER2-negative and had ER or PR expression ranging from 1% to 10%.[6] Of 48 borderline tumors, 46% displayed a luminal phenotype, 29% were HER2-enriched, and 17% were basal-like. These findings suggest that for patients with any hormone-receptor positivity, endocrine therapy should be considered.

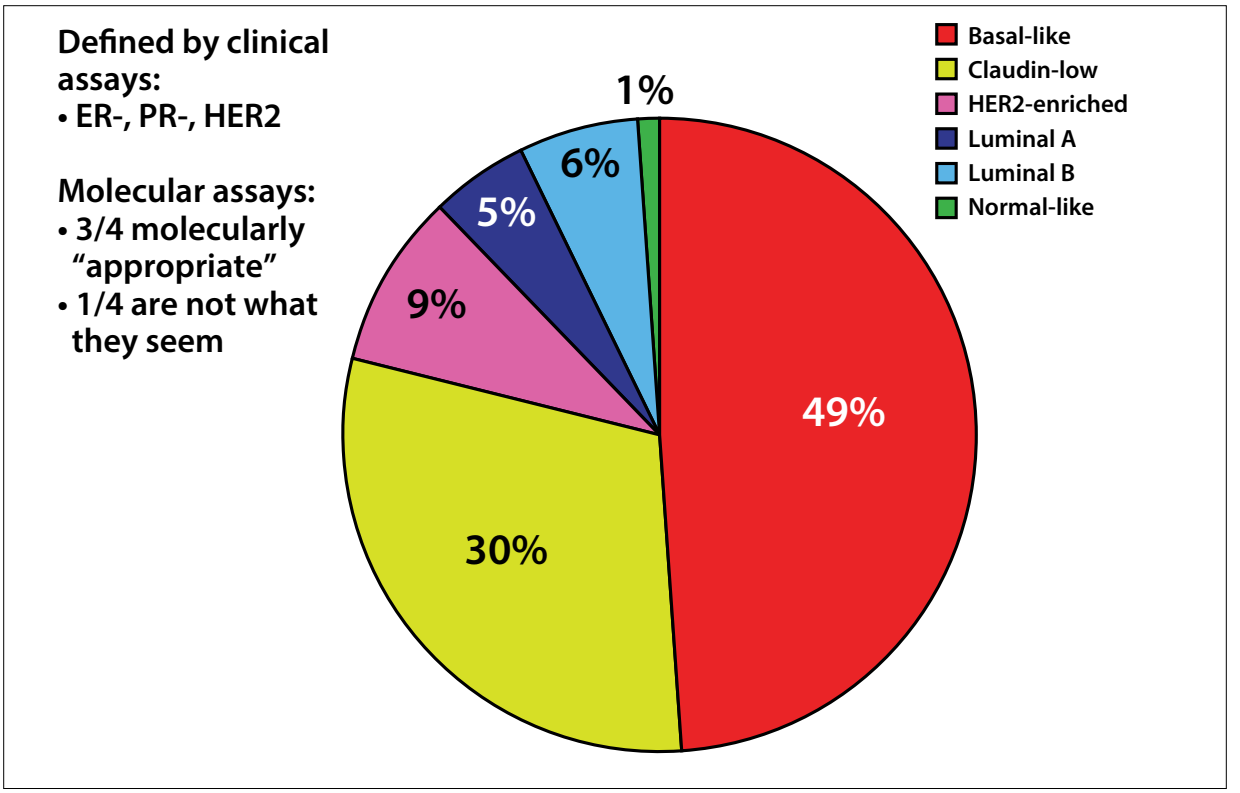

Figure 3. Nearly half of triple-negative breast cancers are basal-like.

Adapted from Prat A, Perou CM. *Mol Oncol.* 2011;5(1):5-23.[1]

Gene expression profiling studies revealed that TNBC can be categorized into 6 subtypes: basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor.[7] Each has a discrete gene expression pattern.

The ultimate goal of this type of molecular characterization is to identify potential therapeutic targets. Thus far, this information has not led to the development of effective therapies. Currently, chemotherapy is the only known treatment for TNBC. Data suggest that intrinsic breast cancer subtypes may differ in their responsiveness to specific chemotherapy regimens.[8] Cheang and colleagues evaluated the significance of intrinsic subtype on outcomes in 476 patients with node-positive disease enrolled in the National Cancer Institute of Canada Clinical Trials Group MA.5 trial of cyclophosphamide, epirubicin, and fluorouracil vs cyclophosphamide, methotrexate, and fluorouracil.[9] The intrinsic subtype was significantly associated with relapse-free survival (P=.0005) and overall survival (P<.0001).[9] Patients with HER2-enriched disease had the greatest benefit from cyclophosphamide/epirubicin/fluorouracil vs cyclophosphamide/methotrexate/fluorouracil, with an absolute difference between the arms exceeding 20% for both 5-year relapse-free survival and 5-year overall survival. Conversely, the difference between arms among patients with non–HER2-enriched disease was less than 2%.

Table 2. Characteristics of *BRCA*-Associated Breast Cancers

High grade	EGFR expression
ER-negative	TP53 mutations
HER2-negative	X-chromosome inactivation pattern
Medullary	Aneuploidy
Pushing margins	Sensitivity to DNA damage
Associated with lymphocytic infiltrate	Less frequently ductal carcinoma in situ
C-Myc–amplified	

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

Data from Chappuis PO et al. *Semin Surg Oncol.* 2000;18(4):287-295[10] and Garber JE. *Cancer Prev Res (Phila).* 2009;2(2):100-103.[11]

Significance of *BRCA1* in Breast Cancer Therapy

There has been a suggestion that TNBC may share characteristics with *BRCA1*-associated breast cancer (Table 2).[10,11] Approximately 80% of *BRCA1*-associated breast cancers are basal-like.[12,13]

There are also important differences between TNBC and *BRCA*-induced breast cancer. *BRCA*-induced tumors have impaired DNA repair mechanisms, which make them sensitive to DNA-damaging chemotherapy, such as platinum

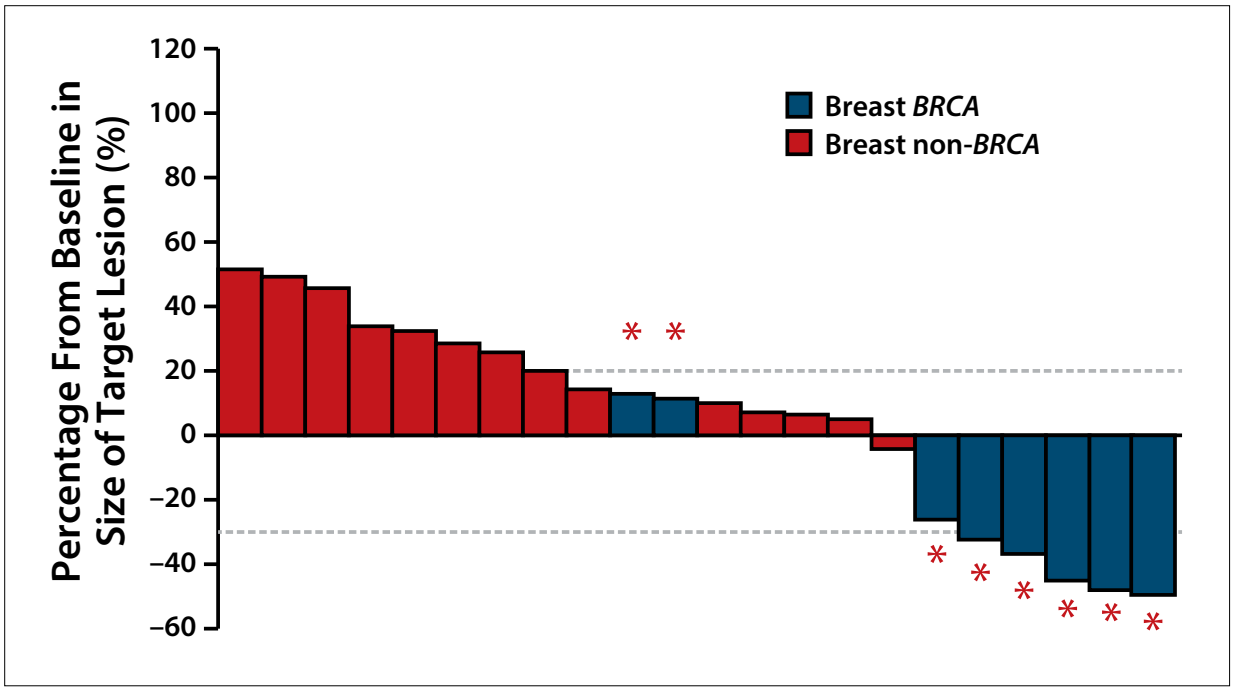

Figure 4. In a phase 2 study, single-agent olaparib showed antitumor activity in TNBC patients with *BRCA1* or *BRCA2* mutations.

*BRCA1/2-associated. TNBC, triple-negative breast cancer. Adapted from Gelmon KA et al. *Lancet Oncol.* 2011;12(9):852-861.[18]

agents. In a study of patients with *BRCA1* mutations who received neoadjuvant chemotherapy, cisplatin was associated with a pathologic complete response rate of 83% (10 of 12 patients).[14] In other studies, neoadjuvant platinum-based therapy has yielded pathologic complete response rates of approximately 20% to 30%.[15,16] The role of platinum-based therapy in patients with non-*BRCA* TNBC is unclear.

PARP Inhibitors

The impaired DNA repair mechanisms observed in *BRCA*-associated tumors led to a hypothesis that outcome could be improved if an additional DNA-damaging agent were added to standard treatment. This strategy of synthetic lethality led to the evaluation of poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of *BRCA*-induced breast cancer.[17] PARP inhibition has demonstrated some activity in patients with *BRCA*-associated tumors. In a phase 2 study of patients with advanced TNBC or high-grade serious or poorly differentiated ovarian cancer, single-agent therapy with the PARP inhibitor olaparib did not induce any objective responses in patients with breast cancer but showed antitumor activity in patients with *BRCA1* or *BRCA2* mutations (Figure 4).[18] In another phase 2 study, combination therapy with the PARP inhibitor veliparib and the chemotherapy agent temozolomide also showed antitumor activity in patients with *BRCA1/2*-associated MBC.[19]

The potential utility of PARP inhibitors in breast cancer was evaluated in the context of the I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis) program, which was designed to rapidly identify potentially active agents and evaluate them in the most appropriate patient populations.[20] I-SPY 2 was a multicenter, phase 2 screening trial in which a series of novel agents and combinations were added to standard chemotherapy in the neoadjuvant setting in women with high-risk stage II/III breast cancer. Adaptive randomization was used within biomarker subtypes to identify therapies that might be effective in specific breast cancer subtypes.

The first I-SPY 2 efficacy results were presented in 2013.[21] Patients with high-risk breast cancer (n=116) received standard neoadjuvant therapy with or without the PARP inhibitor veliparib plus carboplatin. In the subset of patients with TNBC, the estimated pathologic complete response rate was 52% in the veliparib/carboplatin arm and 26% in the control arm. A statistical analysis indicated that there was a 99% probability that the veliparib/carboplatin regimen would be superior to the control arm in a larger trial. Conversely, in patients with hormone receptor–positive, HER2-negative breast cancer, veliparib/carboplatin was associated with an estimated pathologic complete response rate of 14% vs 19% in the control arm. These findings provide additional evidence supporting the evaluation of PARP inhibitors in patients with TNBC.

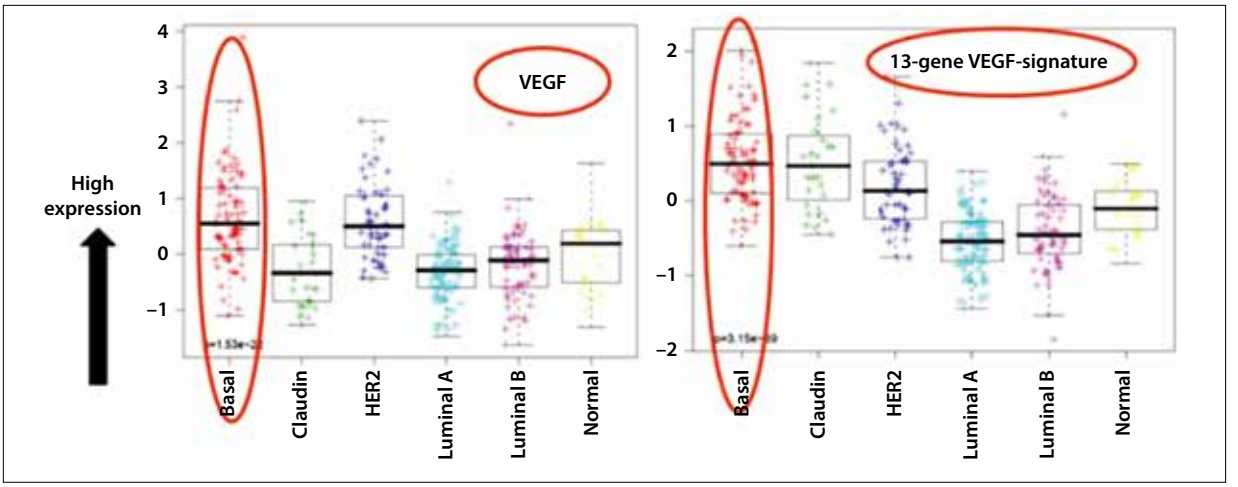

Figure 5. In a microarray analysis of multiple tumor subtypes, basal-like breast cancer was associated with a VEGF signature.

VEGF, vascular endothelial growth factor. Adapted from Hu Z et al. *BMC Med*. 2009;7(1):9.[22]

There are several unanswered questions and potential concerns regarding the use of PARP inhibitors. It is necessary to identify the most appropriate patient populations (both in breast cancer and, potentially, in other types of cancer). It will be important to define the optimal cytotoxic partner to administer with the PARP inhibitor. In addition, there are toxicity issues, including the potential for secondary malignancies, which are a particular concern in adjuvant or prevention studies.

Other Investigational Approaches

Antiangiogenic Therapy

Preclinical data have indicated that TNBC may be particularly sensitive to antiangiogenic therapy. In a microarray analysis of multiple tumor subtypes, basal-like breast cancer was associated with a VEGF signature, indicating that VEGF-targeted therapy might be an appropriate treatment (Figure 5).[22] The VEGF inhibitor bevacizumab initially demonstrated a significant efficacy benefit in patients with MBC,[23,24] leading to approval from the US Food and Drug Administration (FDA). Subsequent analyses, however, failed to show an improvement in survival,[25,26] and the breast cancer indication was removed.

Despite the negative findings in the overall breast cancer population, it has been proposed that antiangiogenic therapy might have benefit in the subset of patients with TNBC. Among patients with measurable TNBC in the Eastern Cooperative Oncology Group (ECOG) 2100 trial, response rates were 41% in the bevacizumab arm vs 17% in the control arm.[23] The potential role of bevacizumab remains under debate.

Androgen Receptor–Targeted Therapy

Although hormone receptor–negative cancer is not responsive to endocrine therapy, there is a subset of patients with hormone receptor–negative disease that expresses the androgen receptor. These cancers may be sensitive to androgen receptor–targeted therapy. In an analysis of 424 patients with ER-negative/PR-negative MBC, 12% of patients (n=51) tested positive for the androgen receptor. Twenty-six patients went on to receive the androgen-receptor antagonist bicalutamide, which yielded a clinical benefit rate of 21%.[27] This study supported the feasibility of androgen receptor–targeted therapy in this subset of patients. A phase 2 study is evaluating the androgen-receptor antagonist enzalutamide in patients with advanced, androgen receptor–positive TNBC.[28]

EGFR-Targeted Therapy

EGFR-targeted therapy has also been evaluated in the treatment of TNBC. In a phase 2 study of patients with metastatic TNBC, the combination of the anti-EGFR monoclonal antibody cetuximab plus cisplatin was associated with an ORR of 20.0%, compared with 10.3% among patients receiving cisplatin alone.[29] The median clinical PFS was 3.1 months for cetuximab/cisplatin vs 1.5 months for cisplatin alone. Although these findings represent some improvement with the addition of cetuximab, this strategy is not likely to change the standard of care.

Eribulin in TNBC

A treatment that did result in a substantial improvement in outcomes is the nontaxane microtubule inhibitor eribulin. In the phase 3, open-label, randomized EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin) trial of patients with locally recurrent breast cancer or MBC, eribulin was associated with a significant survival benefit over physician's choice of treatment. The median overall survival was 13.1 months

with eribulin vs 10.7 months with the treatment of physician's choice (hazard ratio [HR], 0.81; 95% CI, 0.66-0.99; *P*=.041).[30] Subset analysis suggested a trend toward a survival benefit with eribulin in patients with TNBC.

Study 301 was a phase 3, open-label, randomized, multicenter trial comparing eribulin with capecitabine in patients with locally advanced or MBC previously treated with anthracyclines and taxanes.[31] The trial did not show a significant difference between the 2 arms in the overall patient population. Among the 284 patients with TNBC, however, eribulin was associated with a significant improvement in overall survival over capecitabine, with a median overall survival of 14.4 months vs 9.4 months (HR, 0.70; 95% CI, 0.55-0.91). Therefore, eribulin may have particular benefit in specific breast cancer subsets, including TNBC.

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Nontaxane Microtubule Inhibitors in Breast Cancer

Christopher Twelves, MD

Substantial advances have been made in the treatment of some breast cancer subtypes. However, chemotherapy remains at the core of management for nearly all patients with MBC (Figure 6). Patients with hormone receptor–positive breast cancer often receive chemotherapy after developing resistance to hormonal therapy, and patients with HER2-positive breast cancer often receive HER2-targeted therapy in combination with chemotherapy. Chemotherapy is also a component of treatment for patients with TNBC.

When evaluating therapeutic options for patients with MBC, one should consider the treatment goals, which include controlling symptoms, preventing serious complications, and maintaining quality of life.[1] As patients progress through multiple lines of treatment, quality of life gains greater importance. For many years, extending survival was not a focus in MBC, as relatively few trials had demonstrated an improvement in overall survival, particularly among the subset of patients already treated with an anthracycline. The potential to improve survival in MBC was shown in 1999, when Nabholtz and colleagues reported superior survival with docetaxel over mitomycin plus vinblastine.[2] Three years later, O'Shaughnessy and coworkers reported superior survival with the combination of capecitabine plus docetaxel over docetaxel alone.[3]

These 2 studies demonstrated that extension of survival could be considered a treatment goal in MBC and a reasonable expectation for the first and second lines of therapy. However, there have been relatively few randomized trials evaluating therapies for the many patients already treated with an anthracycline and a taxane. In 2011, an analysis of the existing trials showed that survival rates with conventional chemotherapeutic agents were relatively low, and there was no clear superior option, findings that added to the difficulty in making clinical decisions for these patients.[4]

Eribulin Mesylate: Overview

Eribulin mesylate is a synthetic analogue of halichondrin B, a natural marine sponge product that exhibits potent anticancer activity. As a synthetic compound, eribulin mesylate is more easily produced than the relatively scarce halichondrin B, but it is structurally similar and retains the potency of its parent compound.[5]

Eribulin is a microtubule dynamics inhibitor with a mode of action that differs from those of vinca alkaloids or taxanes. Vinblastine binds to the positive ends of microtubules and along the sides, and taxanes bind along the inside surface of microtubules. In contrast, eribulin suppresses dynamic instability by inhibiting microtubule growth only at the positive ends.[6] Eribulin shows minimal or no effect on microtubule shortening.[6] The binding of eribulin to microtubules is a high-affinity interaction, as 1 molecule of eribulin is bound per 2 microtubules.[7]

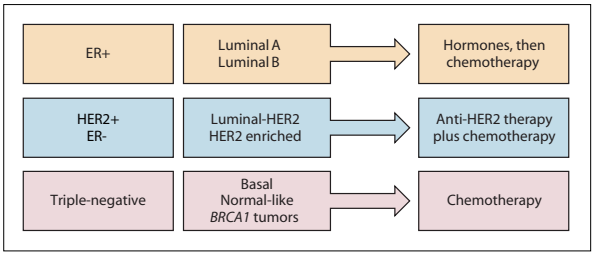

Figure 6. Chemotherapy remains at the core of treating women with metastatic breast cancer.

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

Eribulin demonstrates potent antiproliferative effects in vitro and in vivo.[5] Activity is retained in β-tubulin–mutated cell lines that are resistant to paclitaxel.[8] Moreover, eribulin exhibited a wide therapeutic window in preclinical studies,[5] and induced less neuropathy than paclitaxel in animal studies.[9,10]

Eribulin was first evaluated in phase 1 studies in patients with advanced solid tumors.[11-13] Subsequent phase 2 studies evaluated patients with MBC.[14,15] Based on the demonstrated activity and safety profile observed in these phase 2 studies, the phase 3 EMBRACE trial was undertaken.

The EMBRACE Trial

The EMBRACE trial was a global, multicenter, open-label, randomized phase 3 study evaluating the efficacy and safety of eribulin in 762 women with heavily pretreated locally recurrent breast cancer or MBC.[16] Eligible patients had received between 2 and 5 prior chemotherapy regimens for advanced disease, including an anthracycline and a taxane. Progression within 6 months of the last chemotherapy cycle was required for enrollment. Patients with grade 3 or higher neuropathy at baseline were excluded, as were patients with an ECOG score greater than 2.

Patients were stratified by geographic region, use of prior capecitabine, and HER2/neu status. They were randomly assigned 2:1 to eribulin mesylate, administered intravenously

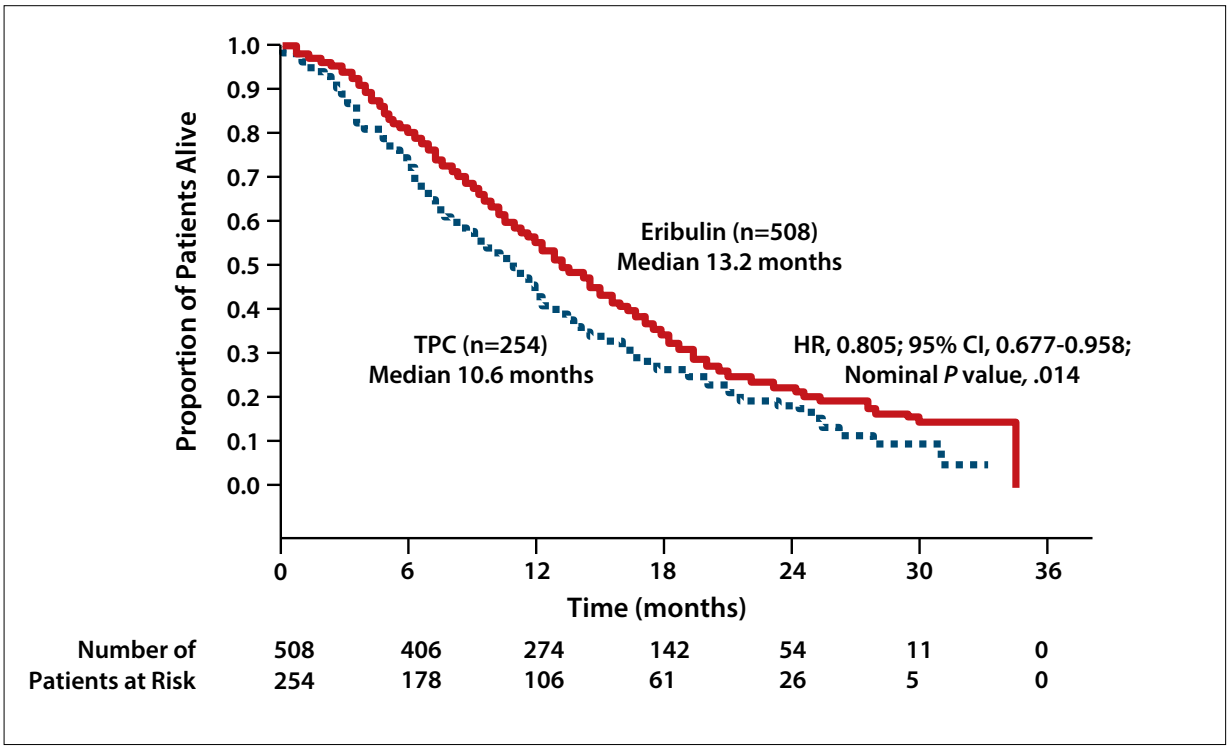

Figure 7. Updated overall survival in the intent-to-treat population of the EMBRACE trial. This survival analysis was requested by regulatory authorities to provide updated outcomes.

EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin; HR, hazard ratio; TPC, treatment of physician's choice. Adapted from Cortes J et al. *Lancet*. 2011;377(9769):914-923.[16]

at 1.4 mg/m^2 throughout 2 to 5 minutes on days 1 and 8 every 21 days (n=508) or to a treatment of the physician's choice (n=254).[16] Physicians could choose any approved monotherapy (chemotherapy, hormonal therapy, or biologic therapy) or supportive care only. The selection of physician's choice as the control arm reflects the lack of standard treatment for these patients at the time the trial was designed.

The primary endpoint was overall survival, an uncommon trial endpoint for MBC at the time the trial was designed. Secondary endpoints included PFS, ORR, and safety. Quality of life was not assessed in the EMBRACE study, given that the variability of treatment schedules and regimens would complicate data interpretation.

In the primary analysis, eribulin was associated with a significant improvement in survival. Median overall survival was 13.1 months with eribulin vs 10.7 months with treatment of physician's choice (HR, 0.81; 95% CI, 0.66-0.99; *P*=.041), which represented a median improvement in survival of approximately 2.5 months.[16] The estimated 1-year survival rates were 53.9% for eribulin and 43.7% for treatment of physician's choice. In an independent review, eribulin was associated with an improvement in PFS that did not reach statistical significance (3.7 vs 2.2 months; HR, 0.87; 95% CI, 0.71-1.05; *P*=.137). This improvement in PFS did reach statistical significance in the investigator review (HR, 0.76; 95% CI, 0.64-0.90; *P*=.002). The objective response rate was significantly improved with eribulin vs the control (12% vs 5%; *P*=.002).

Subset analyses, although not powered to show statistical significance for any individual subsets, suggested a benefit with eribulin across receptor status subsets. There appeared to be a trend toward a greater benefit with eribulin in less heavily pretreated patients. Among women who had received up to 3 prior chemotherapy regimens, the median overall survival was 13.3 months with eribulin and 10.7 months with treatment of physician's choice (HR, 0.774; 95% CI, 0.606-0.988; *P*=.039), a median difference of 2.6 months. Conversely, among women who had received more than 3 prior regimens, the median overall survival with eribulin and treatment of physician's choice was not significantly different (11.7 months vs 10.0 months, respectively; HR, 0.899; 95% CI, 0.666-1.348).

A subsequent survival analysis was requested by regulatory authorities to provide updated outcomes after more events had occurred. The unplanned analysis, which was completed after 77% of patients had died, confirmed the survival benefit initially observed with eribulin and showed nearly identical outcomes as the primary analysis, with a median overall survival of 13.2 months with eribulin and 10.6 months with treatment of physician's choice.

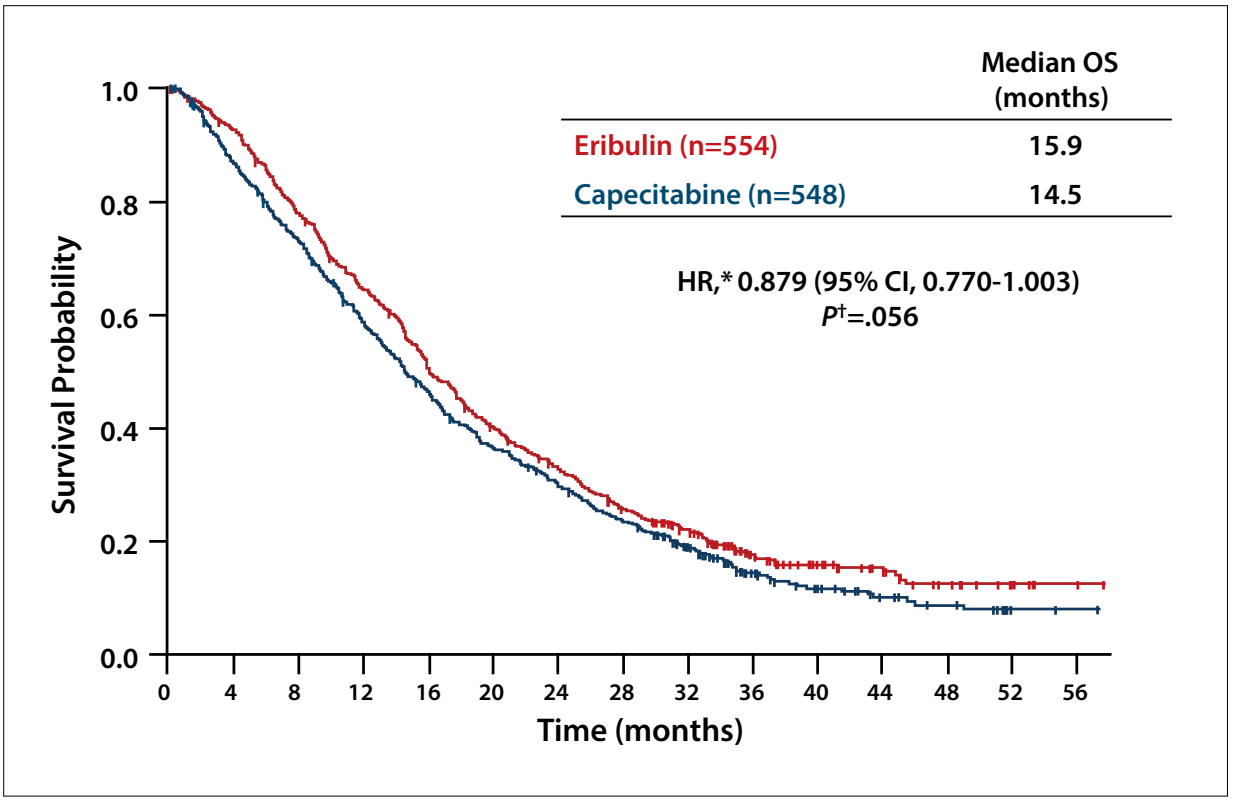

Figure 8. Overall survival among the intent-to-treat population in Study 301.

*HR Cox model including geographic region and HER2 status as strata. †*P* value from stratified log-rank test based on clinical database. HER2, human epidermal growth factor receptor 2. Adapted from Kaufman P et al. SABCS abstract S6-6. *Cancer Res.* 2012;72(suppl 3).[20]

The difference observed in this analysis showed a stronger statistical significance (HR, 0.805; 95% CI, 0.677-0.958; *P*=.014) than in the first analysis (Figure 7).[16]

The EMBRACE trial was the first phase 3 single-agent trial in patients with heavily pretreated MBC to meet a primary endpoint of overall survival. Eribulin demonstrated a significant 2.5-month improvement in median overall survival over the control arm. Response rates and PFS also favored eribulin. Although quality of life was not assessed, the toxicity associated with eribulin, including increased myelosuppression, was manageable. The results of the EMBRACE trial have resulted in a shift in the treatment goals for patients with MBC, as extending survival has now been reported in the third-line setting.

The efficacy and safety demonstrated in the EMBRACE trial led to the approval of eribulin by multiple regulatory authorities worldwide. Eribulin was the first drug to receive initial approval in refractory MBC based on an improvement in overall survival, which the FDA described as "clinically and statistically meaningful."[17] The EMBRACE trial also demonstrated the utility of using treatment of physician's choice as a control arm in the absence of a single standard of care, a strategy that has been incorporated into other ongoing trials in breast cancer.[18,19] Finally, the EMBRACE trial set a new standard for studies in MBC, showing the feasibility of overall survival as a primary endpoint in late-stage disease.

Study 301

Study 301 was a global, randomized, open-label phase 3 trial comparing eribulin vs capecitabine in 1102 patients with locally advanced or MBC.[20] Patients in Study 301 were less heavily pretreated than patients in EMBRACE. They had received up to 3 prior chemotherapy regimens (up to 2 for advanced disease) and had received prior anthracycline and taxane in the neoadjuvant or adjuvant setting or for locally advanced breast cancer or MBC. Capecitabine was selected as the control arm based on its approval for use in this patient population and its status as a standard of care in this setting.

After stratification by geographic region and HER2 status, patients were randomly assigned to eribulin administered intravenously at 1.4 mg/m^2 throughout 2 to 5 minutes on days 1 and 8 every 21 days (n=554) or capecitabine administered orally at 1250 mg/m^2 twice daily on days 1 to 14 every 21 days (n=548). The co–pri-

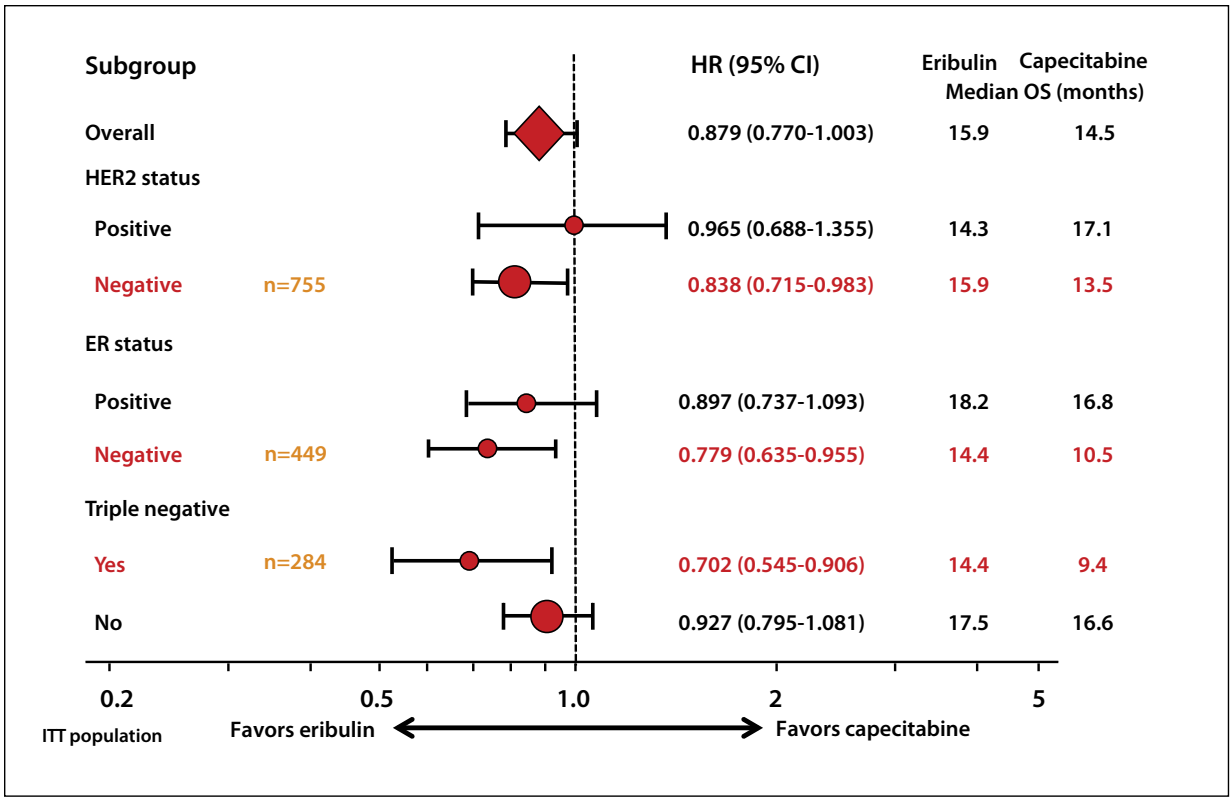

Figure 9. In Study 301, an exploratory subset analysis showed some differences in the relative OS with eribulin vs capecitabine in preplanned subgroups.

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OS, overall survival; ITT, intent-to-treat. Adapted from Kaufman P et al. SABCS abstract S6-6. *Cancer Res.* 2012;72(suppl 3).[20]

mary endpoints of the trial were overall survival and PFS; the selection of these 2 primary endpoints influenced the final analysis. The study employed more stringent criteria to identify statistical significance than the usual *P* value of .05 or less. To meet the primary endpoint of overall survival, the study required that eribulin show a benefit over capecitabine with a *P* value of 0.0372 or lower. To meet the primary endpoint of PFS, the benefit would need to be associated with a *P* value of 0.01 or lower, and an HR for overall survival of less than 1.0.[20]

Patient characteristics were well balanced between the arms. Approximately 20% of patients in each arm had not received prior chemotherapy for advanced disease, and approximately half of patients had received 1 prior therapy. Approximately 26% of patients had TNBC.[20]

Study 301 did not meet its primary endpoint. Median overall survival was 15.9 months with eribulin and 14.5 months with capecitabine, a difference that was not statistically significant (HR, 0.879; 95% CI, 0.770-1.003; *P*=.056; Figure 8).[20] Although the trial was not designed as a noninferiority study, the agents did appear to have similar survival outcomes. Overall survival outcomes were similar across all lines of therapy.

Similarly, there was no significant difference in PFS. Median PFS was 4.1 months with eribulin and 4.2 months with capecitabine (HR, 1.079; 95% CI, 0.932-1.250; *P*=.305), per independent review. The ORR was 11% for eribulin and 12% for capecitabine. The clinical benefit rate, which included patients with stable disease for at least 6 months, was 26% and 27%, respectively.

Hypotheses have been made as to why treatment with eribulin suggested an improvement in overall survival but not PFS. Differences in poststudy treatment may have contributed; a lower proportion of patients in the eribulin arm received subsequent therapies.

An exploratory subset analysis showed some differences in the relative overall survival with eribulin vs capecitabine in preplanned subgroups (Figure 9). In the 755 patients with HER2-negative disease, the median overall survival was 15.9 months with eribulin and 13.5 months with capecitabine (HR, 0.838; 95% CI, 0.715-0.983). In the 449 patients with ER-negative disease, the median overall survival was 14.4 months with eribulin and 10.5 months with capecitabine (HR, 0.779; 95% CI, 0.635-0.955). The strongest difference was observed in the 284 patients with TNBC, in whom the median overall survival was 14.4

Table 3. Overall Survival in a Pooled Analysis of Eribulin Phase 3 Trials

	Overall		HER2-		HER2+		TNBC	
	Eribulin	Control	Eribulin	Control	Eribulin	Control	Eribulin	Control
n	1062	802	748	572	169	123	243	185
Overall Survival (months)	15.2	12.8	15.2	12.3	13.5	12.2	12.9	8.2
HR (95% CI)	0.85 (0.77-0.95)		0.84 (0.72-0.93)		0.82 (0.62-1.06)		0.74 (0.60-0.92)	
P Value	.003		.002		.135		.006	

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; TNBC, triple-negative breast cancer.

Data from Twelves C et al. ASCO abstract 631^. *J Clin Oncol*. 2014;32:5(suppl).[22]

months with eribulin and 9.4 months with capecitabine (HR, 0.702; 95% CI, 0.545-0.906).[20]

The rates of serious AEs were fairly similar with both treatments, at 17.5% for eribulin and 21.1% for capecitabine, as were the proportions of patients who discontinued treatment owing to AEs, at 5.7% and 6.2%, respectively. Treatment-related fatal AEs were infrequent, occurring in 0.9% of the eribulin arm and 0.7% of the capecitabine arm.[20]

Eribulin was associated with more hematologic adverse events (AEs) than capecitabine. Grade 3/4 neutropenia was reported in 46% of eribulin patients vs 4% of capecitabine patients. Febrile neutropenia was infrequent, occurring in 2% of eribulin patients and less than 1% of capecitabine patients. Other AEs that were increased with eribulin included alopecia (35% vs 4%, respectively) and peripheral sensory neuropathy (13% vs 7%). Eribulin was associated with less hand-foot syndrome (<1% vs 45%) and diarrhea (14% vs 29%) than capecitabine.[20]

In summary, Study 301 did not show a statistically significant superiority of eribulin over capecitabine for overall survival or PFS. Prespecified subgroup analyses, however, suggested a particular benefit with eribulin in patients with TNBC. Eribulin and capecitabine showed similar overall activity across the first-line, second-line, and third-line settings with no unexpected toxicities.

Selecting Patients for Eribulin

Clinicians and their patients with MBC can choose from a variety of agents. Several factors that may contribute to treatment decisions have been explored in studies of eribulin.

Age

Age may be a factor in the treatment selection process. A pooled analysis from 2 large phase 2 studies of eribulin and the 2 phase 3 trials indicated that eribulin monotherapy is associated with similar outcomes in younger patients vs older patients, including those ages 70 years and older.[21] However, it is important to keep in mind that the patients enrolled in these studies had good baseline performance status. These findings indicate that the benefits of eribulin are similar across age groups in a reasonably fit patient population.

Treatment History

Prior treatment status is also a consideration for selecting treatment. The EMBRACE trial suggested that benefits from eribulin were more pronounced in less heavily pretreated patients.[16] In contrast, Study 301 showed similar activity with eribulin and capecitabine in the first-line, second-line, and third-line settings.[20] Regardless of the latter finding, it seems likely that therapy is better tolerated in less heavily pretreated patients.

Another consideration is the number of lines of therapy that a patient is likely to receive. Although trends vary by practice, the likelihood that a patient will receive an additional line of treatment declines as she progresses through therapies. This observation argues in favor of using the most active agents sooner rather than later, so that patients have the potential to benefit from these agents before they become too unwell to receive additional therapy.

ER/HER2 Receptor Status

The effect of ER/HER2-receptor status on eribulin efficacy was evaluated in a pooled analysis of the EMBRACE trial and Study 301. Results were presented at the 2014 ASCO meeting.[22] The analysis, which was proposed by regulatory authorities, assessed efficacy in a total of 1864 patients with a median age of 54 years who received eribulin or the control (treatment of physician's choice in EMBRACE or capecitabine in Study 301). Because the EMBRACE trial included a 2:1 randomization and enrolled more heavily pretreated patients than Study 301, statistical adjustments were made.

In the overall pooled analysis, eribulin was associated with a significant improvement in overall survival. The median overall survival was 15.2 months with eribulin vs 12.8 months with capecitabine (HR, 0.85; 95% CI, 0.77-0.95; *P*=.003; Table 3).[22] A similar benefit was observed in the HER2-negative population; the median overall survival was 15.2 months with eribulin vs 12.3

months with the control treatment (HR, 0.82; 95% CI, 0.72-0.93; *P*=.002). In the HER2-positive population, the difference in survival with eribulin vs the control was not significantly different. The median overall survival was 13.5 months with eribulin vs 12.2 months with the control (HR, 0.82; 95% CI, 0.62-1.06). For this patient population, a combination of eribulin and HER2-targeted therapy may be an appropriate strategy.

This pooled analysis confirmed the Study 301 data showing that patients with TNBC preferentially benefited from eribulin. In the 428 patients with TNBC across both trials, the median overall survival was 12.9 months with eribulin and 8.2 months with the control treatment (HR, 0.74; 95% CI, 0.60-0.92; *P*=.006). Similar trends were observed for PFS.

The use of eribulin as first-line therapy was evaluated in a phase 2 trial of locally recurrent or metastatic HER2-negative breast cancer.[23] Eribulin was administered at a standard dose in 56 patients. Among the 38 patients (68%) who had received prior neoadjuvant or adjuvant therapy, 33 had received an anthracycline and/or a taxane-containing chemotherapy. Forty-one patients (73%) had ER-positive disease, and 12 patients (21%) had TNBC. Eribulin was associated with an ORR of 29% in the overall population and 17% in the TNBC population. The clinical benefit rates were 52% and 25%, respectively.[23] Grade 3/4 treatment-related AEs were reported in 64% of patients and primarily included neutropenia (50%), leukopenia (21%), and peripheral neuropathy (21%).

The role of eribulin in HER2-negative MBC is being evaluated in Study 303, from the Academic and Community Cancer Research United (ACCRU).[24] In this randomized, open-label, phase 3 trial, patients with locally recurrent or metastatic HER2-negative breast cancer are receiving first-line or second-line therapy with eribulin or standard weekly paclitaxel, which can be considered an optimal control arm. The trial is being conducted at multiple centers in the United States.

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Current Strategies and Future Directions in MBC Therapy

Hope S. Rugo, MD

The past 60 years, particularly the 1980s and 1990s, have witnessed a dramatic increase in the number of therapies available for breast cancer treatment, leading to a substantial increase in survival.[1] Survival rates remained relatively stable from 2000 to 2010, but they may increase again in the current decade with the introduction of new chemotherapeutic agents, novel HER2-targeted therapies, and, perhaps, the forthcoming introduction of new hormone-targeted therapies.

Although treatment for advanced breast cancer is evolving, there are therapeutic barriers that must be addressed to improve outcomes. First, breast cancer is a heterogeneous disease. Greater understanding is needed regarding the differences among tumors that are currently grouped together based on hormone receptor and HER2 expression. In the setting of recurrent breast cancer and MBC, there is a growing body of evidence suggesting that tumors may change characteristics, including positivity for the hormone receptor and HER2 receptor.[2] For example, a HER2-negative cancer may recur as HER2-positive disease or may change from ER-negative to ER-positive. In some cases, ER positivity may not have been detected in the initial sample owing to a variety of technical issues. Because of this potential for characteristics to evolve, metastatic tumors should be biopsied to evaluate the hormone receptor status and HER2 status. Although there is growing interest among both patients and clinicians in the use of genomic analyses to personalize breast cancer therapy, this technology is not yet ready for use as a guide to treatment decisions, particularly in the context of intratumor heterogeneity.

Drug resistance is also an important issue that is not well understood. In general, it is easier to increase the responsiveness of tumors that are somewhat responsive than to induce responsiveness in an unresponsive tumor.

Goals of Therapy

The patient's goals for therapy may differ from the endpoints and outcomes used in clinical trials. Patients' goals generally include extending survival, minimizing toxicity, and improving or maintaining quality of life. Other patient concerns include hair loss, intravenous access, frequency of office visits, and fatigue. Clinical trials tend to evaluate PFS and other time-to-event endpoints, response rate and duration, overall survival, safety, and quality of life as assessed by a clinician. In the last few years, clinical trials have evolved to include more patient-reported outcomes (PROs) to better ascertain the effects of treatment on patients. PROs are extremely important, particularly in the late-stage setting.

In order to optimize treatment goals, and help patients live as long as possible with the best quality of life, clinicians must consider the risk vs benefit of potential therapy. Today, the optimal sequence of therapy has not been defined. Therefore, it is important to provide patients with the best treatment that has the least toxicity.

Factors Influencing the Treatment Decision

Today, treatment is based largely on 3 main factors. First is the expression of biomarkers (eg, ER, HER2). Second is the tumor biology, which may be informed by various factors, including the extent of disease, location of disease, the disease-free interval, and response to prior therapy. Third are patient-related factors, such as preferences and comorbidities, including other diagnoses that could increase the toxicity of therapy. For some patients, any additional survival time a particular treatment could provide might not be worth the added toxicity.

Other factors that may influence therapeutic decisions include the need for intravenous access and a treatment's association with specific toxicities, such as hair loss or peripheral neuropathy. Preexisting neuropathy can be a factor, as neuropathy can progress to the point at which patients are unable to walk, which is clearly a detriment to quality of life. Patients with significant preexisting peripheral neuropathy will likely have issues with subsequent therapies. Bone marrow tolerance may also be a consideration; requirements for growth factors may add office visits or substantial costs. A logistical concern is the patient's geographic distance from the clinic. These factors must be considered at each step of the disease process.

Treatment of Recurrent or Metastatic Breast Cancer

The National Comprehensive Cancer Network (NCCN) management guidelines include a variety of single agents that are "preferred" for the treatment of recurrent breast

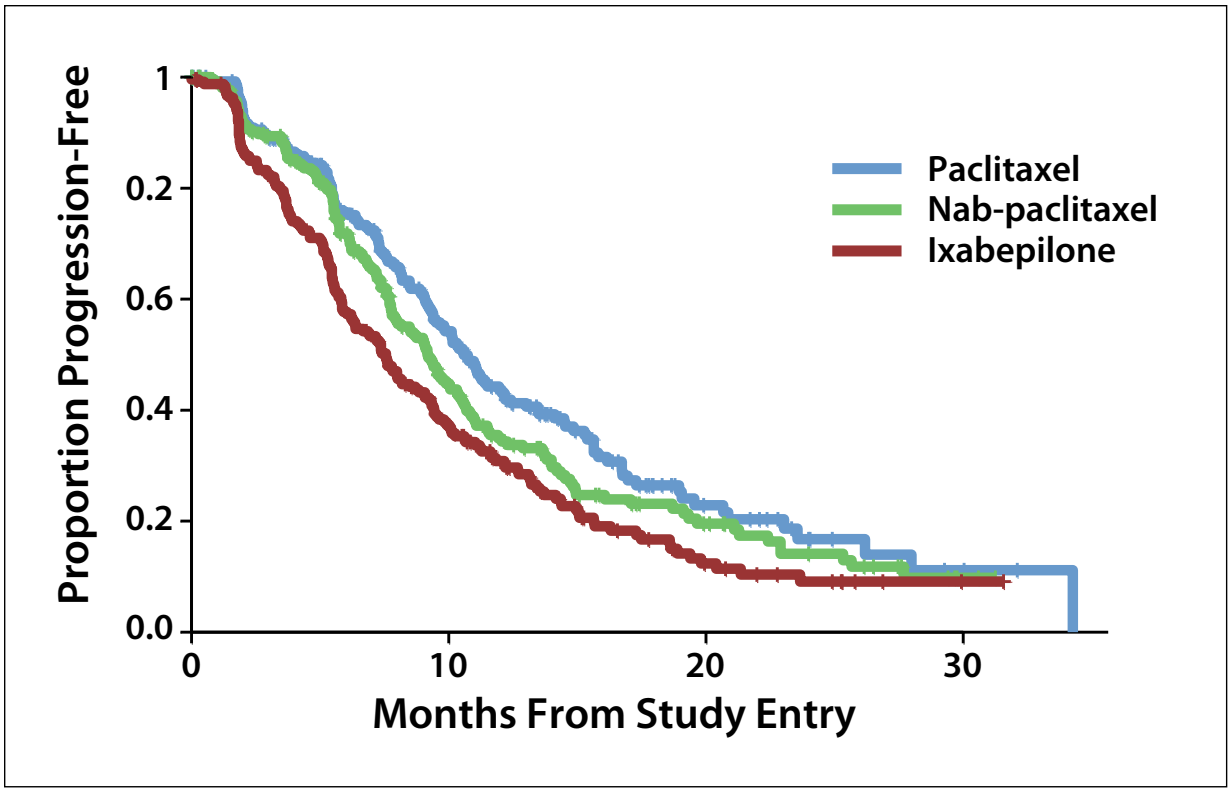

Figure 10. Progression-free survival in the CALGB 40502 trial.

CALGB, Cancer and Leukemia Group B. Adapted from Rugo HS et al. ASCO abstract CRA1002. *J Clin Oncol.* 2012;30(18 suppl).[6]

cancer or MBC. They include doxorubicin, pegylated liposomal doxorubicin, paclitaxel, capecitabine, gemcitabine, vinorelbine, and eribulin.[3] Aside from these preferred agents, other single agents to consider include cyclophosphamide, carboplatin, docetaxel, albumin-bound paclitaxel, cisplatin, epirubicin, and ixabepilone.

The use of combination therapy vs a single agent for patients with MBC continues to be a topic of debate. The NCCN guidelines include some combination therapies, including various chemotherapy regimens and combinations of HER2-targeted therapy and chemotherapy for patients with HER2-positive disease.[3] Although bevacizumab is still listed as a potential agent for use in combination with paclitaxel, support for bevacizumab continues to decline.

Combination regimens may be associated with higher response rates than single agents. In some cases, combination therapy may be associated with a longer PFS,[4,5] and, if patients are able to receive subsequent therapy, longer overall survival. The advantage of sequential single-agent therapy is that it is generally less toxic than combination therapy while conferring the same survival benefit. Thus, single agents are often preferred except in specific circumstances, such as patients with rapidly progressive, visceral-dominant disease or patients who are resistant to chemotherapy. When combination therapy is used, a strategy to reduce impact on quality of life is to eliminate 1 of the agents after a response is attained. This approach reduces the cumulative toxicity and potentially leaves another agent for future use.

Importance of Treatment Tolerability

In the setting of advanced breast cancer, tolerability determines treatability. The importance of tolerability was illustrated in the Cancer and Leukemia Group B (CALGB) 40502 study. This open-label, randomized, phase 3 trial compared 3 regimens for the initial treatment of HER2-negative MBC: nab-paclitaxel administered at 150 mg/m^2 weekly, paclitaxel at 90 mg/m^2 weekly, and ixabepilone at 16 mg/m^2 weekly (which is more frequent than the approved every-3-week dosing), each with bevacizumab at 10 mg/kg every 2 weeks.[6]

The trial was closed early based on futility. There was no difference in PFS with nab-paclitaxel vs paclitaxel, and the median PFS associated with ixabepilone was significantly worse than with paclitaxel (Figure 10).[6] These findings were confirmed in an unplanned subset analysis of patients with TNBC. A safety analysis showed that administration of nab-paclitaxel at 150 mg/m^2 weekly

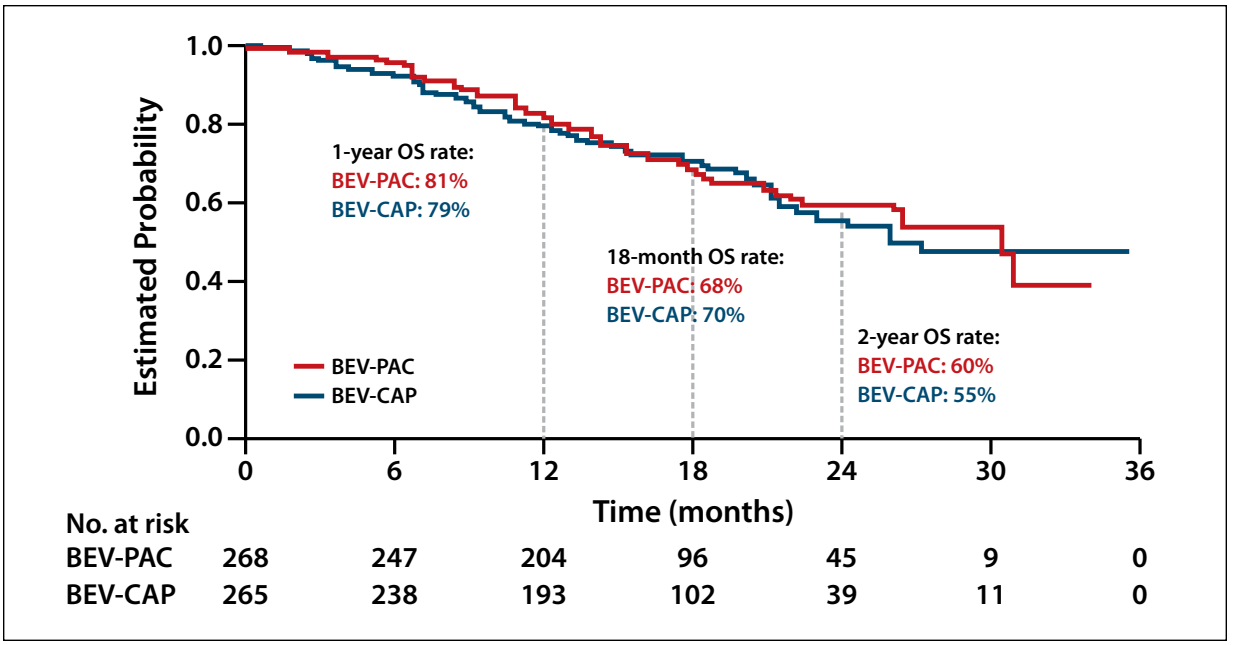

Figure 11. Overall survival in the TURANDOT trial. This analysis included all randomized patients who did not violate any inclusion criteria or meet any exclusion criteria.

BEV, bevacizumab; CAP, capecitabine; PAC, paclitaxel; TURANDOT, Capecitabine and Bevacizumab Randomised Against Avastin and Taxol Trial. Adapted from Lang I et al. *Lancet Oncol.* 2013;14(2):125-133.[9]

was associated with greater hematologic toxicity, and both nab-paclitaxel and ixabepilone were associated with more sensory neuropathy than paclitaxel. Therefore, at these doses and schedules, there was no advantage with either nab-paclitaxel or ixabepilone, and most toxicities were increased.

Current Issues and Future Directions in MBC Treatment

Current trials are evaluating the optimal approach for various groups of patients with advanced breast cancer. The multicenter, randomized, phase 3 ACCRU trial (Study 303) is comparing the efficacy and safety of eribulin vs paclitaxel in the first-line and second-line treatment of HER2-negative patients with locally recurrent breast cancer or MBC.[7]

The tnAcity (Triple-Negative Albumin-Bound Paclitaxel Combination International Treatment) study was designed to evaluate the role of nab-paclitaxel in the initial treatment of TNBC.[8] In the initial phase 2 portion, patients are being randomly assigned to nab-paclitaxel at 125 mg/m^2 plus carboplatin at an area under the curve (AUC) of 2 administered on days 1 and 8 every 3 weeks, nab-paclitaxel at 125 mg/m^2 plus gemcitabine at 1000 mg/m^2 on days 1 and 8, or gemcitabine at 1000 mg/m^2 plus carboplatin at an AUC of 2 on day 1 every 3 weeks. It has been suggested that these higher-dose combinations may be able to overcome some of the resistance seen in TNBC. The nab-paclitaxel arm with the better efficacy and safety will be compared to gemcitabine plus carboplatin in the phase 3 portion of the trial.

An ongoing issue in the treatment of MBC is the choice of initial chemotherapy. The TURANDOT (Capecitabine and Bevacizumab Randomised Against Avastin and Taxol Trial) study of paclitaxel plus bevacizumab vs capecitabine plus bevacizumab did not meet the noninferiority criteria for the study arm; the paclitaxel arm demonstrated superior PFS and ORR (Figure 11).[9] Subset differences were not presented, but this outcome is likely attributable to differential treatment effects in the 22% to 24% of enrolled patients with TNBC, in whom capecitabine is usually associated with benefit only when disease is indolent.

The optimal duration of chemotherapy is another important issue for MBC treatment. A meta-analysis of 11 randomized trials showed that longer first-line chemotherapy is associated with a significant improvement in PFS (HR, 0.64; 95% CI, 0.55-0.76; *P*<.001) and a slight improvement in overall survival (HR, 0.91; 95% CI, 0.84-0.99; *P*=.046).[10] The association between longer chemotherapy and survival improvement has been observed in other trials, including a randomized, phase 3 Korean study evaluating 2 different durations of gemcitabine/paclitaxel.[11] One caveat of this trial is that the 75% of patients with hormone receptor–positive disease did not receive hormonal therapy during the maintenance period.

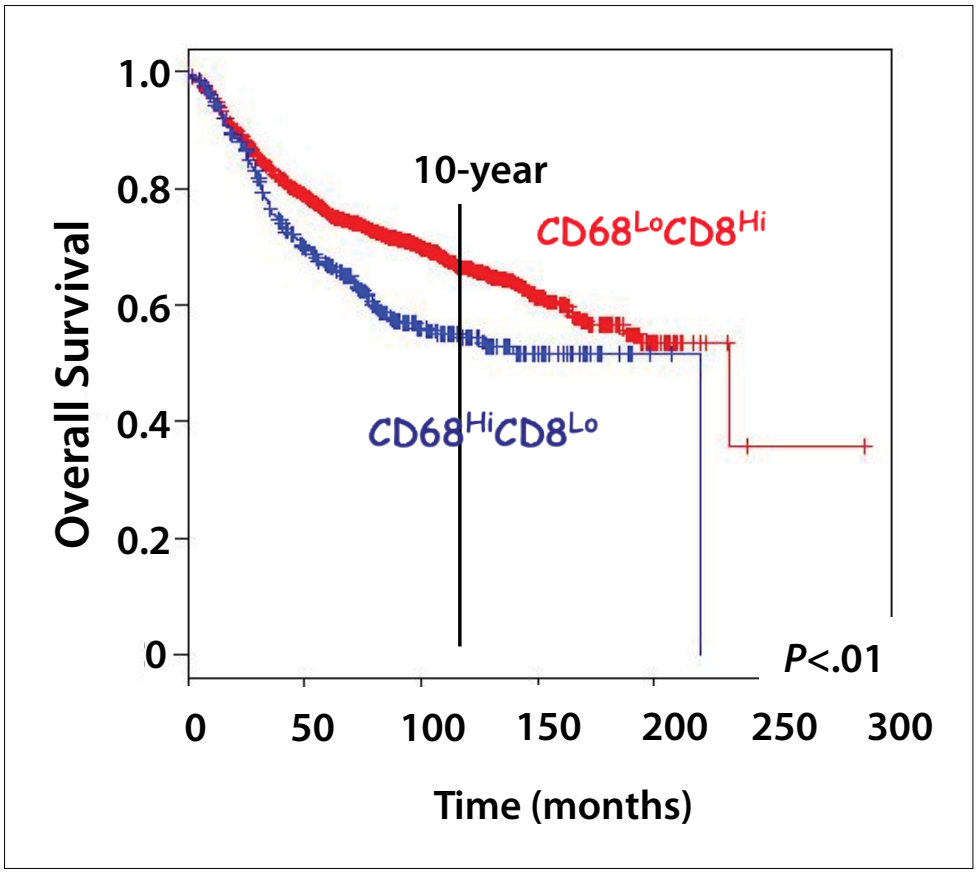

Figure 12. Gene expression studies have shown that the ratio of CD68-positive cells to CD8-positive cells is significantly associated with overall survival in breast cancer.

Adapted from DeNardo DG et al. *Cancer Discov*. 2011;1(1):54-67.[15]

Targeting Leukocytes in Breast Cancer

Among the new approaches being evaluated in the treatment of breast cancer are immune-based therapies that aim to modify the host antitumor response. One strategy involves inhibition of macrophages, which have been implicated in cancer biology. The composition of leukocytes in a tumor has been shown to correlate with responsiveness to chemotherapy.[12] Preclinical studies have indicated that increased macrophage presence correlates with higher vessel density and decreased survival; administration of a macrophage inhibitor slows tumor growth.[13,14]

Moreover, gene expression studies conducted on 22 data sets including more than 4000 patients have shown that the ratio of CD68-positive cells (a macrophage marker) to CD8-positive cells is significantly associated with overall survival in breast cancer (Figure 12).[15] Survival is significantly shorter in patients with more macrophages and fewer CD8-positive T cells compared with patients who have fewer macrophages. This trend holds true in both the basal phenotype and HER2-positive disease.[15]

Based on these preclinical findings, eribulin is being evaluated in combination with PLX3397, a novel oral small-molecule inhibitor of CSF1R, KIT, and oncogenic FLT3 kinases that inhibits macrophages.[16] The trial will consist of 2 phases: phase 1b will include the general breast cancer population, and phase 2 will enroll patients with metastatic TNBC. Serial tumor biopsies will be performed to assess the effect of the therapy on macrophages and other immune cells. Other macrophage inhibitors and immune-modifying agents have been developed, such as immune checkpoint inhibitors against PD-1 and PD-L1.

Conclusion

Many different approaches are being evaluated to optimize current therapies and develop new strategies to improve outcomes for patients with MBC. Looking forward, a challenge will be to understand the heterogeneity of breast cancer and apply this knowledge to individualize therapy for patients with MBC.

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Evidence-Driven, Patient-Specific Approaches for Optimizing Survival Prolongation in Breast Cancer

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

1. Characteristics of triple-negative breast cancer include all of the following EXCEPT:

   a. Commonly associated with CDH1 mutations
   b. Early relapse
   c. Usually poor histologic grade
   d. Presents with larger tumor size, but less commonly associated with nodal metastases

2. The most common metastases associated with triple-negative breast cancer are:

   a. Bone metastases
   b. Soft tissue metastases
   c. Visceral metastases
   d. Nodal metastases

3. True of False: A HER2-negative cancer may recur as HER2-positive disease.

   a. True
   b. False

4. Which of the following factors is the LEAST important consideration when selecting treatment for patients with metastatic breast cancer?

   a. Family history of disease and treatment
   b. Patient preferences
   c. HER2 status
   d. Previous adjuvant treatments

5. According to NCCN guidelines, all of the following are preferred single agents for recurrent or metastatic breast cancer, EXCEPT:

   a. Capecitabine
   b. Eribulin
   c. Docetaxel
   d. Doxorubicin

6. Which of the following statements regarding findings from the EMBRACE trial is FALSE?

   a. Treatment with eribulin demonstrated a clinically and statistically meaningful improvement in overall survival compared with treatment of physician's choice
   b. The study evaluated quality-of-life data
   c. Overall response rate and progression-free survival favored eribulin over treatment of physician's choice
   d. Patients receiving eribulin experienced more myelosuppression

7. In Study 301, capecitabine was associated with a median overall survival of:

   a. 13.2 months
   b. 14.5 months
   c. 15.9 months
   d. 16.8 months

8. Among the subgroup of patients with triple-negative breast cancer in Study 301, eribulin was associated with a median overall survival of:

   a. 12.9 months
   b. 13.4 months
   c. 14.4 months
   d. 15.1 months

9. The CALGB 40502 study showed that:

   a. Paclitaxel was associated with more sensory neuropathy than nab-paclitaxel and ixabepilone
   b. Progression-free survival was increased with nab-paclitaxel vs paclitaxel
   c. Progression-free survival was increased with ixabepilone vs paclitaxel
   d. There was no advantage with either nab-paclitaxel or ixabepilone

10. The TURANDOT study showed that:

    a. Capecitabine plus bevacizumab demonstrated superior progression-free survival and overall response
    b. Capecitabine plus bevacizumab demonstrated superior overall survival
    c. Paclitaxel and bevacizumab demonstrated superior progression-free survival and overall response
    d. Paclitaxel and bevacizumab demonstrated superior overall survival

Project ID: 10150

Evaluation Form: Evidence-Driven, Patient-Specific Approaches for Optimizing Survival Prolongation 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 10150**. 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:

Prolong survival in patients with metastatic breast cancer who have received multiple chemotherapeutic treatment courses with documented remissions

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

Compare the safety, efficacy, and survival prolongation profiles associated with novel treatments for metastatic breast cancer

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

Individualize therapy in patients with metastatic breast cancer based on factors such as receptor status (ER, PR, and HER-2), clinical tumor burden, treatment history, comorbidities, and patient preferences

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

Sequence or combine chemotherapeutic agents to prolong overall survival in patients with metastatic breast cancer

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

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

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

The content was evidence based

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

The educational material provided useful information for my practice

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

The activity enhanced my current knowledge base

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

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

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

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

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

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

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

❒ My current practice has been reinforced by the information presented

❒ I need more information before I will change my practice

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

Please use a number (for example, 250):

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

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

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

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

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

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

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

❒ Yes ❒ No, please explain:

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

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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

Project ID: **10150**