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Novel Treatment Options in the Management of Metastatic Breast Cancer

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Abstract: Few breast cancer patients present with metastatic disease at the initial diagnosis. However, approximately one-quarter of patients with lymph node–negative disease and one half of patients with lymph node–positive tumors will ultimately develop distant recurrent breast cancer. Standard treatment of metastatic breast cancer generally includes systemic treatment and surgery or radiation as needed and when indicated for palliation of localized symptomatic metastases. Extending survival and improving quality of life are the primary focus of patient management; thus, there is a preference for the use of minimally toxic treatments. Taxanes have played a significant role in improving outcomes, but many patients still experience disease progression. Many new and emerging agents have been developed for metastatic breast cancer, including both biologic therapies and chemotherapies. A common theme among these therapies is their ability to target specific molecules or processes unique to cancer cells, enhancing the potency and reducing many of the toxicities typically observed with standard cytotoxic chemotherapies. Such agents include poly(ADP)-ribose polymerase inhibitors (iniparib), trastuzumab-DM1, everolimus, the epothilones (ixabepilone), and eribulin. Although metastatic breast cancer remains incurable, the introduction of new agents and new treatment approaches has led to an incremental build-up in terms of survival benefits.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and other healthcare professionals who treat patients with breast cancer.

Statement of Need/Program Overview

Survival in patients with metastatic breast cancer (MBC) has improved over the past two decades, with the introduction of more effective therapies, including cytotoxic and targeted agents. Oncologists who treat MBC have a choice between using a combination of cytotoxic chemotherapies or sequential single agents. Treatment efficacy must be balanced against the risk of toxicities. Although taxanes have played a significant role in improving outcomes, many patients still experience disease progression. Clinical trials of novel non-taxane microtubule inhibiting agents have led to the approval of new therapies. Many new agents have either been recently approved or are in advanced clinical trials, increasing the treatment armamentarium for MBC.

Educational Objectives

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

- Explain the importance of new study findings and clinical trial data in the natural history of patients with metastatic breast cancer
- Describe the results of these new study findings, including current clinical trials
- Integrate into clinical practice the latest knowledge on emerging therapies—including PARP inhibition, TDM-1, and microtubule inhibition—and methods for treating metastatic breast cancer patients in an effort to improve current prognosis
- Identify future research directions for all therapies in metastatic breast cancer
- Recognize how emerging metastatic breast cancer therapies can improve patient outcomes

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Introduction

Christopher Twelves, MD

Over the past 10–15 years, the number and types of treatment for women with metastatic breast cancer (MBC) have greatly increased. There has also been an emerging emphasis on the molecular and genetic descriptions of breast cancer as compared to traditional histopathology. Nevertheless, despite the introduction of many "targeted" agents, the use of cytotoxic chemotherapy has neither been negated nor become less relevant.

In recent years, much of the focus on new advances has been on the development of new adjuvant treatments with the potential to improve survival for women with early breast cancer. However, the treatment of the large number of women with metastatic breast cancer remains an important aim in itself. Metastatic breast cancer remains essentially incurable, and treatment palliative, the goals being symptom control and prolongation of survival whilst maintaining or improving quality of life. In practice, however, whilst many clinical trials in women with MBC have shown higher response rates and/or progression-free survival (PFS), very few have demonstrated prolonged overall survival.

The treatment of women with MBC generally focuses primarily on systemic treatment, ie, chemotherapy, endocrine therapy, and/or biologic therapy, with surgery or radiation used as appropriate for palliation of localized, symptomatic metastases. Patients with MBC can be initially stratified according to the molecular characteristics (estrogen receptor [ER], progesterone receptor [PR], and HER2 status[1]) and the presence or absence of bone metastasis, and then further stratified. For patients with ER/PR-positive cancers, unless there has been a short disease-free interval or they have rapidly progressive visceral disease, endocrine therapy will be the first option, with the choice of agent based upon the patient's menopausal status and prior adjuvant therapy. If and when these women relapse, they may receive subsequent lines of endocrine therapy until they become refractory to such approaches or their disease becomes more aggressive; at that point they may be considered for chemotherapy. For those patients with HER2-positive cancers, the majority of which are ER/PR-negative, treatment choices include the HER2-targeted agents trastuzumab and lapatinib, usually in combination with cytotoxic chemotherapy. For all patients, other considerations include their performance status and comorbidities, as well as their personal preferences.

Anthracyclines (doxorubicin and epirubicin) were for many years a mainstay in the cytotoxic therapy of MBC, but they are now used principally in adjuvant combination chemotherapy regimens; cumulative cardiac toxicity is a specific issue limiting their use at relapse, although this may be mitigated by liposomal formulations (Myocet, Doxil/Caelyx). The taxanes (docetaxel, paclitaxel, and more recently *nab*-paclitaxel) are increasingly incorporated in adjuvant regimens but are still widely used in the metastatic setting. Capecitabine and ixabepilone are approved for patients with MBC previously treated with an anthracycline and a taxane. (Ixabepilone is approved in the United States, although not in Europe.) The vascular endothelial growth factor (VEGF)-targeted antibody bevacizumab also enhances the activity of chemotherapy in MBC, but its impact on overall survival remains unproven. Nevertheless, there are an increasing number of women with heavily pre-treated MBC who remain candidates for chemotherapy, but for whom there was until recently no treatment of proven benefit.

To meet the unmet need in women with heavily pretreated MBC, and also potentially for women with less advanced disease, many new endocrine, biologic therapies and chemotherapies are being evaluated. A common theme among these agents is their ability to target specific molecules or processes specific to cancer cells, with the aim of enhancing potency whilst reducing toxicity compared to standard cytotoxic chemotherapies. Some of these new agents are directed against conventional, "validated" molecular targets for anticancer drugs, such as the microtubule, while others take advantage of a more profound understanding of cancer biology, targeting, for example, molecules involved in DNA.

Today we can offer a woman with MBC an increasing range of treatment options tailored to her and her cancer, but the impact of recent advances has been modest. Although we have made progress down the route to offering personalized medicine for each woman with MBC, there remain many challenges.

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Survival in Metastatic Breast Cancer

Linda T. Vahdat, MD

Although both the incidence of breast cancer and the rate of breast cancer–related mortality are decreasing, metastatic breast cancer remains a significant issue, as many patients relapse after therapy and go on to develop metastatic disease. Fewer than 10% of breast cancer patients present with metastatic disease at the initial diagnosis.[1] In fact, data from 2001–2007 suggest that this proportion is closer to 5%.[2] However, approximately one-quarter of patients with lymph node–negative disease and one half of patients with lymph node–positive tumors will ultimately develop distant recurrent breast cancer.[3]

Trends in Survival of Metastatic Breast Cancer Patients

The rate of breast cancer–related deaths has steadily decreased over the past 2 decades, declining by 3.2% annually among women younger than 50 years, and by 2.0% annually in women ages 50 years or older.[4] The reasons for this decrease in mortality have remained uncertain, but they have been attributed to both trends in earlier diagnosis and an increasing availability of improved therapies and treatment strategies. However, while the benefit of adjuvant chemotherapy on improved survival of early-stage breast cancer has been well established in both randomized studies and meta-analyses,[5-9] the impact of improved therapies on the survival of patients with metastatic breast cancer has until recently been less clear. Improvements in metastatic breast cancer survival were first demonstrated in independent trials of newer chemotherapy regimens (eg, docetaxel, trastuzumab, and the combination of capecitabine with docetaxel, which have all been associated with significant prolongation of survival in metastatic breast cancer patients).[10-12]

In 2004, Giordano and colleagues reported a survival analysis of 834 patients who experienced recurrent breast cancer between 1974 and 2000 and who were treated at the University of Texas MD Anderson Cancer Center.[13] Prior to recurrence, all patients had received an anthracycline-based adjuvant chemotherapy protocol. The median follow-up for surviving patients after recurrence was 9.3 years, and recurrence was defined as both locally occurring disease as well as distant metastasis. For analysis, patients were divided into 5 groups, based on year of recurrence: 1974–1979 (n=93), 1980–1984 (n=216), 1985–1989 (n=235), 1990–1994 (n=185), and 1995–2000 (n=106). In an unadjusted comparison, survival from time of recurrence was prolonged among patients who developed that recurrence in more recent years; however, it should be noted that these more recent groups also tended to have more favorable prognostic factors. For the 5 groups, the median overall survival (OS) for patients in the increasing year groups was 15, 17, 22, 27, and 58 months, respectively, and the 5-year OS rates were 10%, 14%, 22%, 29%, and 44%, respectively. A multivariate analysis of the data found that the number of involved lymph nodes, the size of the primary tumor, and the site of disease recurrence were each independently associated with OS from time of recurrence. From their analysis, the investigators concluded that these patients with metastatic breast cancer experienced approximately a 1% reduction in the risk of death associated with every 1-year increase in the recurrence date. However, this change was not found to be statistically significant.

Also in 2004, Tai and colleagues published an analysis of long-term survival data of metastatic breast cancer patients registered in 2 separate Surveillance, Epidemiology, and End Results (SEER) databases.[14] This analysis included metastatic breast cancer patients from the Connecticut (n=782) and San Francisco-Oakland (n=580) SEER registries between the years 1981–1985, and from the same 2 registries (n=752 and n=632, respectively) between the years 1991–1995. In the Connecticut registry, the estimated 15-year cause-specific survival rate remained relatively steady between 1981–1985 (7.1%; 95% confidence interval [CI], 1.8–12.4) and 1991–1995 (9.1%; 95% CI, 3.8–14.4). Conversely, patients in the San Francisco-Oakland registry did demonstrate an improvement in the 15-year cause-specific survival rate from 1981–1985 (9.2%; 95% CI, 3.9–14.5) and 1991–1995 (14.7%; 95% CI, 9.8–19.6).

More recently, Cortesi and colleagues presented the results of a population-based study from Northern Italy, which investigated the outcomes of 8,654 patients with either de novo or relapsed metastatic breast cancer from 1988–2005.[15] OS was calculated from the date of first distant metastasis to the date of death or last follow-up. Patients were grouped into 4 time periods: 1988–1993, 1994–1997, 1998–2001, and 2002–2005. Among patients with de novo metastatic disease (median follow-up of 27 months), there was no significant change in the 5-year OS across each year group (12%, 14%, 9%, and 13%, respectively; P=.5). In contrast, patients with relapsed metastatic breast cancer (median follow-up of 29 months) did achieve a significant improvement in the 5-year OS from the first to the other 3 time periods (10%, 22%, 30%, and 25%, respectively; P=.001). Interestingly,

aromatase inhibitors conferred a significant survival benefit over the last 10 years among women with relapsed metastatic breast cancer ($P<.0001$). Among women with de novo metastatic breast cancer, however, this survival benefit was seen over the last 4 years ($P<.0001$).

In contrast, a retrospective review presented in 2008 by Pal and colleagues suggested that despite the introduction of several new therapeutic agents over the past decade, only minimal improvements in metastatic breast cancer patient survival have been made.[16] A total of 385 metastatic breast cancer patients were identified from the City of Hope Cancer Registry; all patients were diagnosed between 1985–2005. Patients were grouped into 2 time periods based on year of diagnosis: 1985–1994 and 1995–2005. OS was defined from the date of diagnosis of metastatic breast cancer to the date of death or last follow-up. The median OS was found to be statistically similar between the 2 groups (2.4 vs 3.1 years for 1985–1994 vs 1995–2005, respectively, hazard ratio [HR], 1.14; 95% CI, 0.87–1.50; $P=.26$). Although women with hormone receptor–positive metastatic breast cancer demonstrated improved survival compared with those with hormone receptor–negative disease, there was no significant difference in OS between the 2 time intervals. Notably, the investigators did demonstrate a significant improvement in OS among patients with metastatic colorectal cancer between the same 2 time periods (1.2 vs 2.0 years for 1985–1994 vs 1995–2005, respectively; HR, 1.69; 95% CI, 1.33–1.95; $P<.0001$).

Most recently, Sundquist and colleagues reported data from 557 consecutive metastatic breast cancer patients in Kalmar, Sweden who were diagnosed between 1985–2004.[17] In this study, patients were grouped into 5-year intervals: 1985–1989, 1990–1994, 1995–1999, and 2000–2004. It was determined that the median OS increased within each successive time period (10, 14, 16, and 22 months, respectively). OS improvements were noted between the first and last time periods (1985–1989 vs 2000–2004) among patients with either grade 3 tumors (3-year OS: from 14% to 34%, respectively) or grade 2 tumors (2-year OS: from 33% to 51%, respectively); however, no improvement was noted among patients with grade 1 tumors. Although the median OS among hormone receptor–positive patients did not change over time, the median OS improved from 14 to 21 months among HER2-positive patients diagnosed between 1985–1999 and 2000–2004, respectively.

Overall, growing evidence now suggests that survival is significantly improving among patients with metastatic breast cancer. A major shift towards improved survival among metastatic breast cancer patients began to be observed during the 1990s, a time that coincided with the introduction of a host of new agents demonstrated to be effective in the metastatic setting. These include the taxanes (paclitaxel and docetaxel), the aromatase inhibitors (anastrozole, exemestane, and letrozole), the HER2-targeted agent trastuzumab, the anthracyclines doxorubicin and epirubicin, and other chemotherapeutics (vinorelbine, gemcitabine, and capecitabine). More recently, other notable therapeutic introductions have included albumin-bound paclitaxel, the HER2-targeted agent lapatinib, and the epothilone B analog ixabepilone. The anti-VEGF targeted antibody bevacizumab is also an important addition to metastatic breast cancer treatment in recent years, although its ability to prolong OS has recently been called into question. Clearly, this ever-increasing availability of effective treatment agents for metastatic breast cancer has played an important role in controlling the spread of the disease and thus prolonging survival.

Traditional Treatment Approaches

The approach to treating a metastatic breast cancer patient can be highly complex. Physicians must consider a number of both patient-related and disease-related factors when choosing the optimal type and timing of therapy. Importantly, a careful balance between efficacy and toxicity must be aimed for. Patients with asymptomatic disease may not tolerate a great deal of toxicity and thus are less appropriate candidates for aggressive and highly toxic therapies; conversely, patients with symptomatic metastatic breast cancer may be better able and more willing to tolerate some drug-related adverse events (such as peripheral neuropathy) in an effort to relieve their tumor-related symptoms.

Further complicating the issue of metastatic breast cancer treatment is how molecular-based therapies may be used to target treatments to particular patients. Individualized therapeutic approaches have advanced to allow specific targeting of hormone receptor–positive disease as well as tumors expressing particular proteins (such as HER2 inhibition with trastuzumab or lapatinib, and more recently, VEGF inhibition with bevacizumab). In addition, sequencing of the human genome has enabled the identification of a genetic portrait of breast cancer that may increase therapeutic choices. Although these genetic classifications have primarily been used in the adjuvant therapy setting for breast cancer, their importance in the metastatic setting is becoming increasingly apparent. Now, in addition to tailoring treatment to the presence or absence of specific biomarkers—such as the ER, PR, or HER2—the genetic type of cancer may also be considered when choosing therapy. Four major molecular subtypes of breast cancer have been identified: luminal A, luminal B, triple negative/basal-like, and HER2 type. Each of these subtypes responds differently to treatment, and notably, the different molecular subtypes of breast cancer may be responsible for a large amount of the heterogeneity in

response rates and PFS that has been observed in chemotherapy clinical trials.

It is striking that none of the approaches used in the treatment of metastatic breast cancer (including cytotoxic chemotherapeutics, hormonal therapies, or molecularly targeted agents), appear to be superior when compared with each other from a standpoint of prolonging patient survival. Thus, a great deal of effort has been expended in recent years on the development of new cytotoxic and targeted therapies for metastatic breast cancer. The advanced clinical study and approval of a number of these agents has further expanded the treatment arsenal from which physicians may select therapies for their metastatic breast cancer patients. However, as patients continue to experience disease progression, new agents must continue to be investigated. Continued research will likely result in an ever-improving understanding of the underlying biology of this malignancy, and it is hoped that this increased understanding will translate to new targets and novel strategies to improve metastatic breast cancer patient outcomes.

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Emerging Treatment Options for Patients with Metastatic Breast Cancer

Christopher Twelves, MD

The number of new agents and approaches to treating MBC precludes evaluation of them all, but it is possible to select a limited number that illustrate the breadth of potential future treatment options.

PARP Inhibition

While most cytotoxic chemotherapies target cancer cells by inducing DNA damage, one of the most interesting emerging options for women with MBC is inhibition of a key enzyme in the DNA repair process. DNA repair pathways are upregulated in a number of cancer cell types, including breast cancer. Overactivation of these pathways provides a mechanism by which these cancer cells can repair chemotherapy-induced DNA damage, thus abrogating the effects of cytotoxic chemotherapeutic agents and contributing to resistance.[1]

Several major DNA repair pathways have been identified.[1,2] Of these, base excision repair can repair several types of DNA damage, including single-strand DNA breaks, DNA adducts and base damage, and replication

lesions. Poly(ADP)-ribose polymerase 1 (PARP-1), a nuclear enzyme that catalyzes the covalent post-translational modification of poly(ADP)-ribose from NAD+,[3] is a critical component of the base excision repair pathway. PARP-1 binds directly to regions of DNA damage, inducing the formation of large branched chains of poly(ADP)-ribose polymers on target proteins and recruiting other DNA repair enzymes.

In the presence of DNA-damaging cytotoxics and the resulting single-strand DNA breakage, tumor cells use the PARP-1-mediated base excision repair pathway to repair the DNA damage. If PARP-1 is inhibited, it cannot induce further recruitment of other DNA repair enzymes; this leads to the accumulation of single-strand DNA breaks.[4,5] Left unrepaired, these single-strand breaks impede DNA replication at the site of damage, resulting in the formation of double-strand DNA breaks. This type of DNA damage is repaired through a unique set of DNA repair pathways, including BRCA1/BRCA2-mediated homologous recombination. In cells unable to perform homologous recombination, most notably those with BRCA1 or BRCA2 mutations, double-strand DNA damage goes unrepaired and cell death occurs. This is the basis for PARP inhibitors being particularly potent in BRCA1/BRCA2-deficient cells,[6,7] a concept similar to synthetic lethality.[8,9]

The oral PARP inhibitor olaparib has been evaluated in a multicenter, nonrandomized, open-label, single-arm, phase II clinical trial for women with advanced/metastatic breast cancer confirmed as carrying a BRCA1 or BRCA2 mutation.[10] Two sequential cohorts, each comprising 27 patients with BRCA 1 or 2 mutations, who had received at least 1 prior chemotherapy regimen for advanced disease, were included in this study. The first received a higher dose of olaparib (400 mg twice daily), while the second received a lower dose (100 mg twice daily); patients in the later, lower dose cohort could cross-over to receive the higher dose. Although not powered to compare the efficacy of the 2 dose levels, twice as many patients in the 400 mg group than in the 100 mg group achieved an overall response (41% vs 22%); likewise, PFS in the 400 mg and 100 mg groups was 5.7 months (95% CI, 4.6–7.4 months) and 3.8 months (95% CI, 1.9–5.5 months), respectively. Both dose levels were well tolerated, but grade 3/4 adverse events were more common in the 400 mg group than the 100 mg group, including fatigue (15% vs 4%), nausea (15% vs 0%), and vomiting (11% vs 0%). This level of efficacy for an agent targeting DNA repair is remarkable in patients who had received a median of 3 prior chemotherapy regimens, albeit a group all carrying BRCA 1 or 2 mutations, a biomarker for potential sensitivity.

BRCA 1 and 2 mutations are, however, uncommon. A much higher proportion of women, between 15% and 20%, have triple-negative breast cancers (ie, ER, PR, and HER-2 negative). These triple-negative cancers share many of the characteristics of BRCA1-associated breast tumors, including hormone receptor-negative/HER2-negative status, p53 mutation, basal-like gene expression pattern, and high-grade.[11,12] Moreover, many triple-negative breast tumors exhibit PARP1 upregulation, whilst both BRCA1-associated breast tumors and triple-negative tumors have reduced BRCA1 activity, either due to mutational inactivation (in BRCA1-associated tumors) or diminished expression (in triple-negative tumors).

Results of an open-label, randomized, phase II trial of the most clinically advanced of the PARP inhibitors, the intravenous drug iniparib, in women with triple-negative breast cancer were recently published.[13] Patients (N=123) were randomized to receive gemcitabine plus carboplatin administered either with or without iniparib. Patients in the iniparib group achieved a significantly higher rate of clinical benefit (defined as objective response plus stable disease), the primary study endpoint, compared with patients who did not also receive iniparib (56% vs 34%; P=.01). The objective response rate was also higher in this group (52% vs 32%; P=.02). Likewise, median PFS was prolonged (5.9 vs 3.6 months, HR, 0.59; P=.01), as was median OS (12.3 vs 7.7 months, HR, 0.57; P=.01) with the addition of iniparib. Surprisingly, given the additional toxicity seen when combining other PARP inhibitors with chemotherapy, no significant difference in the frequency of adverse events was observed between the 2 treatment groups.

Based on these highly promising data, a multicenter, open-label, randomized phase III clinical trial of iniparib was completed, again in women with triple-negative metastatic breast cancer.[14] This study, with a planned enrollment of 420 patients, has the same 2 treatment arms: gemcitabine plus carboplatin alone or in combination with iniparib. Unfortunately, in a recent press release, the drug's manufacturers stated that the study failed to meet the pre-specified criteria for significance in the primary endpoints of PFS and OS.[15] However, to date, specific data have not been presented, so it is not yet possible to scrutinize the results. The company did report that in a pre-specified analysis, significant improvements in OS and PFS were noted among patients treated in the second- and third-line setting. This suggests iniparib may still have potential in patients with triple-negative breast cancer.

TDM-1

One of the most significant drugs introduced for metastatic breast cancer during the 1990s was the targeted biologic agent trastuzumab, a monoclonal antibody directed against the HER2/neu receptor. A member of a family of growth factor receptors, HER2 is over-expressed in up

to one-quarter of breast cancers and is associated with a more aggressive phenotype.[16-18] In patients with metastatic breast cancer that over-expresses HER2, trastuzumab is widely used in combination chemotherapy as first-line treatment and in subsequent lines of therapy; less often, trastuzumab is used as a single agent. Since the introduction of trastuzumab, patients with HER2-positive metastatic breast cancer may now enjoy a better prognosis than some of those with HER2-negative disease, despite its more aggressive natural history.

The novel antibody-drug conjugate trastuzumab-DM1 (T-DM1) was developed to exploit the clinical efficacy of trastuzumab and also to utilize its targeting specificity. T-DM1 comprises trastuzumab (T) conjugated by a non-reducible thioether bond to a derivative of maytansine (DM1), a highly active but otherwise toxic microtubule binding cytotoxic.[19] In preclinical studies, T-DM1 had significant activity in both trastuzumab- and lapatinib (another HER2-targeted agent)-resistant cells.[20] The antitumor activity of T-DM1 may be attributed to both the antibody-dependent cellular cytotoxicity (ADCC) and signaling inhibiting properties of trastuzumab and the mitotic catastrophe and subsequent apoptosis secondary to DM1.[21]

In a phase I study of T-DM1, 24 patients with HER2-positive metastatic breast cancer who had progressed on trastuzumab-based therapy (median 4 prior therapies for metastatic disease) were treated with escalating doses of T-DM1.[22] This study defined a maximum tolerated dose of T-DM1 (3.6 mg/kg), with transient thrombocytopenia dose-limiting at 4.8 mg/kg. The pharmacokinetic parameters of T-DM1 were also established, including a half-life of 3.5 days, which appears substantially shorter than that of conventional trastuzumab. Most adverse events were grade 1-2 and reversible; they included thrombocytopenia (54.2%), elevated transaminases (41.7%), fatigue (37.5%), anemia (29.2%), and nausea (25.0). There were no reports of nausea, vomiting, alopecia, or neuropathy higher than grade 1. Of note, there were no cardiac effects requiring dose modification. Among 15 patients who received T-DM1 at the maximum tolerated dose, 5 had objective responses and a further 6 had stable disease.

A single-arm phase II clinical trial (TDM4258g) was subsequently conducted, which evaluated T-DM1 in 112 patients with HER2-positive metastatic breast cancer with disease progression after receiving HER2-directed treatment and who had received prior chemotherapy.[23] After a follow-up of 1 year or more, a 25.9% (95% CI, 18.4–34.4) objective response rate was reported by independent assessment, and the median PFS was 4.6 months (95% CI, 3.9–8.6). Interestingly, patients with higher (at or exceeding the median by quantitative reverse transcriptase polymerase chain reaction) HER2 expression levels achieved higher response rates than those who had lower levels of HER2 expression. The most frequent grade 3/4 adverse events included hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). There were no grade 3 or greater falls in LVEF, although 2 patients had a decline in LVEF to below 45%.

A second similar sized single-arm phase II trial (TDM4374g) in patients who had received prior trastuzumab, lapatinib, an anthracycline, taxane, and capecitabine reported as an abstract showed similar results.[24]

These encouraging data led to a multicenter, open-label, randomized, phase II clinical trial that evaluated T-DM1 as a first-line therapy in 137 patients with HER2-positive metastatic breast cancer, preliminary results of which were recently reported.[25] Patients received either T-DM1 or standard treatment with trastuzumab plus docetaxel; those in the control were allowed to cross over to T-DM1 upon disease progression. After a median follow-up of 6 months, similar rates of objective response were achieved in the T-DM1 and trastuzumab/plus docetaxel (47.8% vs 41.4%) arms; OS data were not available at the time of this presentation. Notably, however, only half as many patients treated with T-DM1 compared with trastuzumab plus docetaxel experienced a grade 3/4 adverse event (37.3% vs 75.0%). Although trastuzumab plus docetaxel was associated with significant grade 3 or 4 neutropenia (52.9%), leucopenia (25.0%), and febrile neutropenia (10.3%), no such toxicities were reported in the T-DM1 arm. All grades of alopecia were much less common with T-DM1 than trastuzumab plus docetaxel (1.5% vs 66.2%, respectively); this was also true for all grades of diarrhoea (10.4% vs 45.6%). By contrast, fatigue of any grade was seen with nearly equal frequency in both treatment arms (46.3% vs 46.2%). Again, there was no unexpected cardiac toxicity.

Other Emerging Agents

Everolimus is a small molecule that inhibits the mammalian target of rapamycin (mTOR), an intracellular regulator of both angiogenic and proliferative tumor progression pathways. mTOR lies in the PI3K/Akt pathway, the activation of which is suspected to contribute to resistance to endocrine therapies. Thus, a randomized phase II trial was conducted to evaluate the efficacy of adding everolimus to tamoxifen in postmenopausal patients with metastatic breast cancer who had progressed while on an aromatase inhibitor.[26] Indeed, patients who received the combination of everolimus plus tamoxifen achieved a significantly superior rate of clinical benefit compared with tamoxifen alone (61.1% vs 42.1%). Furthermore, the time to progression (TTP) was nearly twice as long in the combination arm (8.5 vs 4.5 months). A phase III trial is ongoing, comparing the efficacy and safety of exemestane plus everolimus with exemestane

plus placebo in postmenopausal women with estrogen receptor–positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole.[27]

AMG 479 is a fully human monoclonal antibody that inhibits binding of both insulin-like growth factor (IGF)-1 and -2 to the IGF-1 receptor (IGF1R). In a randomized, phase II trial of postmenopausal advanced breast cancer patients who had progressed after endocrine therapy, further endocrine therapy (either exemestane or fulvestrant) was administered with either AMG 479 or placebo.[28] The median PFS was statistically equivalent between the AMG 479 and placebo arms (3.9 vs 5.7 months, respectively; HR, 1.17; 95% CI, 0.91–1.50; *P*=.435), suggesting no clinical benefit conferred by this new agent.

Finally, recent decisions from the FDA regarding the approval of bevacizumab in metastatic breast cancer have raised questions about the use of anti-angiogenic therapy in this setting. Likewise, initially promising data with sunitinib, a small molecule inhibitor of several tyrosine kinases (TKIs), including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), were not confirmed when the agent was administered in combination with chemotherapy. In randomized phase II studies, either docetaxel[29] or capecitabine[30] were given with or without sunitinib to women with metastatic breast cancer. In both studies, no improvement in efficacy (PFS, response rate, or OS) was apparent, but there were more grade 3 and 4 adverse events in the combination arms. Data with sorafenib, which has activity against VEGF and PDGF but also against other TKIs, are more encouraging. Similar, randomized phase II studies administering capecitabine[31] or paclitaxel[32] either alone or in combination with sorafenib showed improvements in overall response rates, PFS, and TTP.

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Non-Taxane Microtubule Inhibitors in Metastatic Breast Cancer

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Limitations of Conventional Taxanes

The approval of the taxanes paclitaxel and docetaxel during the 1990s for the treatment of metastatic breast cancer made a significant impact on patient outcomes, leading to the consideration of both of these agents as a standard of care.[1] However, despite their demonstrated high rates of initial efficacy, patients treated with either taxane often suffer from disease progression relatively quickly, experience significant toxicity, and achieve a median OS of less than 2 years.

For example, in the Eastern Cooperative Oncology Group (ECOG) 1193 phase III study, first-line treatment of metastatic breast cancer patients with paclitaxel resulted in an overall response rate of 34%, a median time to treatment failure of 6.0 months, and a median OS of 22.2 months.[2] Likewise, in the Cancer and Leukemia Group B (CALGB) 9840 phase III trial, first- or second-line weekly paclitaxel was associated with an overall response rate of 42% but a median TTP and median OS of only 9 months and 24 months, respectively.[3] In both studies, patients treated with paclitaxel frequently experienced grade 3/4 neurotoxicity (ie, peripheral neuropathy) and hematologic toxicity (including neutropenia).

Similar results have also been observed in clinical studies of docetaxel. Second-line treatment of metastatic breast cancer with docetaxel resulted in overall response rates of 19.9–29.8%, depending on dose, but a median TTP of 12.7–16.6 weeks and a median OS of 10.3–12.3 months.[4] The majority of patients treated with docetaxel in this study experienced grade 3/4 neutropenia (76.4–93.4%).

The phase III TAX 311 study compared docetaxel with paclitaxel in the treatment of progressive metastatic breast cancer.[5] Docetaxel was demonstrated to be superior to paclitaxel in terms of median OS (15.4 vs 12.7 months, HR, 1.41; 95% CI, 1.15–1.73; P=.03), median TTP (5.7 vs 3.6 months, HR, 1.64; 95% CI, 1.33–2.02; P<.0001), and overall response (32% vs 25%; P=.10); however, these outcomes still leave room for great improvement.

Subsequently, the nanoparticle albumin-bound (nab) version of paclitaxel was introduced in 2005. This formulation was developed to avoid many of the toxicities normally associated with the cremophor solvent, and was also found to consistently demonstrate superior efficacy compared with standard paclitaxel. This greater efficacy is largely attributed to the ability to administer higher taxane doses coupled with the improved drug bioavailability of nab-paclitaxel.[6] In a phase III study that directly compared nab-paclitaxel with standard paclitaxel in patients with metastatic breast cancer, the new formulation achieved significantly higher rates of overall response, both in the entire patient population (33% vs 19%; P=.001) as well as among patients receiving first-line therapy (42% vs 27%; P=.029).[7] Importantly, despite a 49% higher dose of standard paclitaxel compared with nab-paclitaxel, the incidence of grade 4 neutropenia was significantly lower among patients who received nab-paclitaxel compared with standard paclitaxel (9% vs 22%; P<.001).

Rationale for the Development of Nontaxane Inhibitors of Microtubule Dynamics

These studies demonstrate that despite the significant initial efficacy observed with both standard taxanes as well as nab-paclitaxel, metastatic breast cancer patients quickly experience disease progression (often within 1 year), often suffer significant hematologic and nonhematologic toxicities, and have a poor prognosis (median OS of approximately 2 years or less). Additionally, taxane resistance (either intrinsic or acquired) is a widespread issue, manifested by the P-glycoprotein drug efflux pump, alterations in taxane-binding sites within the tubulin protein, and changes in microtubule assembly properties.[8] However, microtubules remain an attractive target for the development of anticancer

agents due to their key role in mitosis, importance in cell cycle progression, and the resulting cellular apoptosis that ensues when microtubules are inhibited. Thus, much effort has focused on the clinical development of nontaxane inhibitors of microtubule dynamics.

Another promising agent is ispinesib, an inhibitor of kinesin spindle protein.[9] In a phase II trial in women with locally advanced or metastatic breast cancer, ispinesib produced several partial responses.[10]

Epothilones

The epothilones are microtubule-stabilizing agents that, like taxanes, induce mitotic arrest and cellular apoptosis by suppressing microtubule dynamics and promote tubulin stabilization.[11,12] Although evidence suggests that epothilones interact with the β-subunit of tubulin and occupy the same site as taxanes, they utilize independent molecular interactions that allow them to overcome most microtubule mutation-dependent taxane resistance.[8,13-15] Most preclinical studies of epothilones involve those originally isolated from the myxobacterium *Sorangium cellulosum* (epothilone A and epothilone B), but their high potency and their ability to overcome taxane resistance has led to the development of several epothilone analogs. The most clinically advanced of these is the epothilone B analog ixabepilone, which is the first US Food and Drug Administration (FDA)-approved epothilone, indicated for the treatment of metastatic breast cancer (either in combination with capecitabine in patients after failure of an anthracycline and a taxane, or as monotherapy in patients after failure of an anthracycline, a taxane, and capecitabine).

In a multicenter, single-arm, phase II trial, single-agent ixabepilone was administered to metastatic breast cancer patients (N=126) who were heavily pretreated (88% had ≥2 prior lines of chemotherapy in the metastatic setting) and had disease progression after treatment with an anthracycline, taxane, and capecitabine.[16] The overall response was 11.5% (95% CI, 6.3–18.9%) when assessed by an independent radiology facility and 18.3% (95% CI, 11.9–26.1%) when assessed by the investigator. However, 50% of patients achieved stable disease; of these, 14.3% had stable disease of a duration of at least 6 months. The median PFS and median OS were 3.1 months and 8.6 months, respectively. Grade 3/4 peripheral neuropathy was experienced by 14% of patients.

Two phase III clinical trials have also evaluated ixabepilone in metastatic breast cancer. In the pivotal international CA163-046 study, metastatic breast cancer patients (N=752) with anthracycline-pretreated/resistant and taxane-resistant disease were randomized to receive either ixabepilone plus capecitabine or capecitabine alone.[17] Compared with single-agent capecitabine, patients treated with the combination of ixabepilone plus capecitabine experienced significantly prolonged median PFS (4.2 vs 5.8 months), and a 25% reduction in the estimated risk of disease progression (HR, 0.75; 95% CI, 0.64–0.88; *P*=.0003). Twice as many patients in the combination arm also achieved an objective response (14% vs 35%; *P*<.0001). A secondary endpoint in this trial, OS, was also analyzed.[18] Although a trend towards improved median OS was observed in the combination arm compared with single-agent capecitabine, this difference was not significant (12.9 vs 11.1 months; HR, 0.9; 95% CI, 0.77–1.05; *P*=.19).

In a similarly designed confirmatory phase III study, metastatic breast cancer patients (N=1,221) previously treated with an anthracycline and a taxane were randomized to treatment with either ixabepilone plus capecitabine or single-agent capecitabine.[19] Although the primary endpoint of the previous phase III trial was PFS, the primary endpoint of this study was OS. Like the CA163-046 study, no significant difference in median OS was demonstrated between the 2 treatment groups (16.4 vs 15.6 months, HR, 0.9; 95% CI, 0.78–1.03; *P*=.1162) within the overall population. However, when the analysis was adjusted for performance status and other prognostic factors, patients treated with the combination achieved a significantly superior OS compared to patients treated with single-agent capecitabine (HR, 0.85; 95% CI, 0.75–0.98; *P*=.0231). This trial also confirmed results seen in the pivotal phase III trial, demonstrating that patients treated with ixabepilone plus capecitabine achieved significantly prolonged median PFS (6.2 vs 4.2 months, HR, 0.79; *P*=.0005) and a significantly higher rate of objective response (43% vs 29%; *P*<.0001).

Importantly, a pooled analysis that focused on patients with reduced performance status from these 2 phase III trials was recently published.[20] This analysis found that those patients with a reduced performance status (Karnofsky performance status 70–80) who were treated with the ixabepilone plus capecitabine combination achieved significant improvements in median OS compared with those who were treated with single-agent capecitabine (12.3 vs 9.5 months; HR, 0.75; *P*=.0015). Conversely, there was no significant difference in median OS between the 2 treatment groups among patients with a high (90–100) Karnofsky performance status (16.7 vs 16.2 months; HR, 0.98; *P*=.8111). However, significant improvements in both median PFS and objective response rates were achieved regardless of performance status. For combination-treated versus single-agent–treated patients, the median PFS was 4.6 versus 3.1 months (HR, 0.76; *P*=.0021), and 6.0 versus 4.4 months (HR, 0.58; *P*=.0009) for low and high performance status patients, respectively. The objective response rates were 35% versus 19%, and 45% versus 28% for low and high performance status patients, respectively.

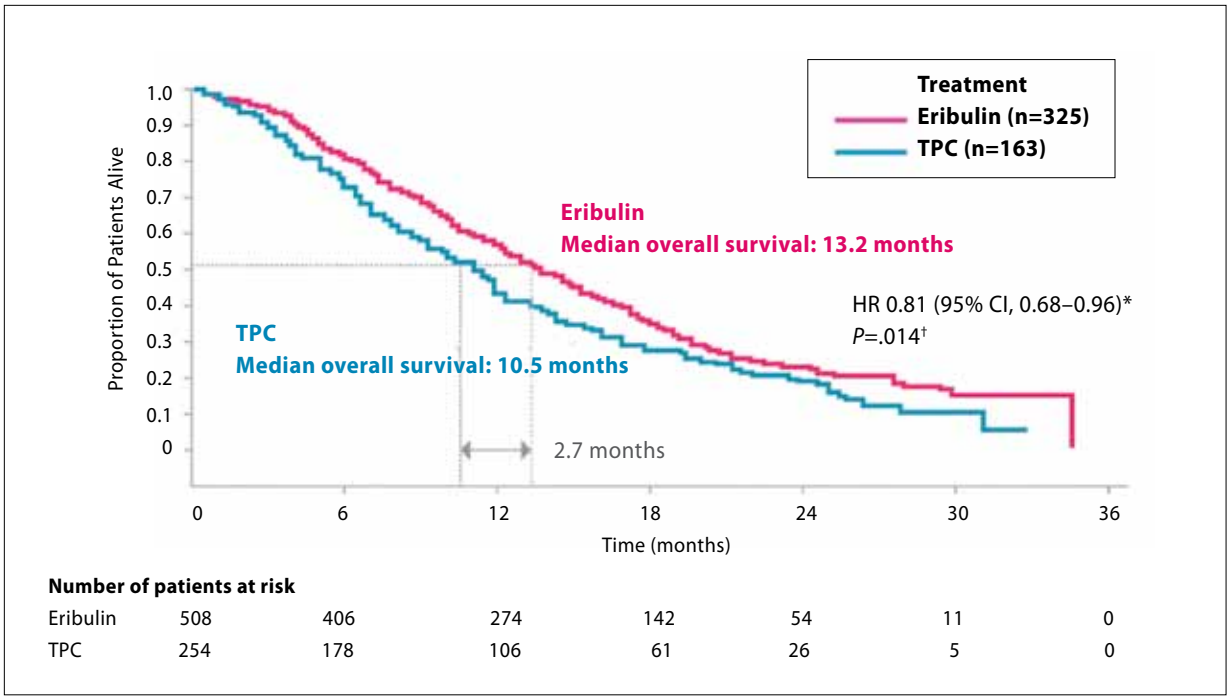

Figure 1. Overall survival in the EMBRACE trial based on an updated survival analysis.

CI=confidence interval; EMBRACE=Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin; HER2=human epidermal growth factor receptor type 2; HR=hazard ratio; TPC=treatment of physician's choice.

*HR Cox model including geographic region, HER2/neu status, and prior capecitabine therapy as strata. †Nominal *P* value from stratified log-rank test.

Several other epothilones are currently at various phases in clinical development for metastatic breast cancer. These include epothilone D (KOS-862) and its analog KOS-1584, patupilone (epothilone B), ZK-EPO, and BMS-310705. Each of these agents has shown promising activity in pretreated or resistant disease.[14]

Eribulin

Another major nontaxane inhibitor of microtubule dynamics that has recently gained approval from the FDA and the European Medicines Agency is the structurally modified halichondrin B synthetic analog eribulin mesylate. Eribulin has a unique mechanism of action, in that it acts to inhibit the microtubule growth phase but does not affect the microtubule shortening phase.[21-25] This results in sequestration of the tubulin monomers into nonproductive aggregates and leads to cellular apoptosis. Eribulin is currently indicated for the treatment of metastatic breast cancer patients who have received 2 or more prior chemotherapy regimens for late-stage disease.

Two open-label, single-arm, phase II clinical trials demonstrated the efficacy and safety profile of eribulin in patients with extensively pretreated disease. In the first of these trials, study 201, metastatic breast cancer patients (N=103) previously treated with an anthracycline and a taxane were treated with single-agent eribulin.[26] Patients were heavily pretreated (median of 4 prior chemotherapy regimens). An independently-reviewed objective response rate of 11.5% (95% CI, 5.7–20.1%) was achieved; all of these were partial responses, and the median duration of response was 5.6 months. The median PFS and median OS were 2.6 months and 9.0 months, respectively. In the second phase II trial, study 211, patients (N=299) with either locally advanced or metastatic breast cancer who had received prior treatment with an anthracycline, a taxane, and capecitabine, were also treated with single-agent eribulin.[27] Patients had heavily pretreated disease, with a median of 4 prior chemotherapy regimens. The independently-reviewed objective response rate in this cohort was 9.3% (95% CI, 6.1–13.4%); again, all were partial responses, and the median duration of response was 4.1 months. Very similar rates of median PFS and median OS were observed in this study (2.6 months and 10.4 months, respectively).

Based on these positive results, eribulin was investigated in the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin) study, an international, multicenter, open-label, randomized, phase III clinical trial.[28] In this study, patients (N=762) with locally recurrent or metastatic breast cancer were randomized (2:1) to receive treatment with either single-agent eribulin or with another treatment of their physician's choice. The treatment of physician's choice was restricted to any single-agent chemotherapy (96%; most commonly vinorelbine, gemcitabine, or capecitabine), hormonal therapy (4%), or biologic agent (0%) approved for the treatment of cancer; radiotherapy (0%); or symptomatic treatment alone (0%). All patients had received between 2–5 prior chemotherapy regimens (median 4 prior chemotherapy regimens) that included an anthracycline and a taxane (unless contraindicated). Upon randomization, patients were stratified according to geographic location, prior capecitabine exposure, and HER2 status. Unlike the previous phase II trials in which the primary endpoint was objective response, the primary endpoint of the EMBRACE study was OS.

Significantly, patients who received eribulin achieved improved median OS compared with patients who received a treatment of physician's choice (13.2 vs 10.5 months; HR, 0.81; 95% CI, 0.68–0.96; *P*=.014); this outcome represents a clinically meaningful increase of 23% for eribulin-treated patients (Figure 1). In an exploratory subset analysis, OS was higher among eribulin-treated patients across all stratification factors, with the exception of patients from the geographic region including Eastern Europe, Russia, and Turkey. In the independent review, no significant difference was achieved in median PFS between the eribulin and treatment of physician's choice arms (3.7 vs 2.2 months, HR, 0.87; 95% CI, 0.71–1.05, *P*=.137). However, this difference became significant by investigator assessment (HR, 0.76; 95% CI, 0.64–0.90; *P*=.002), likely due to fewer patients being censored. An objective response was reported in more patients in the eribulin arm compared with the control arm (12% vs 5%; *P*=.002); interestingly, 3 of the responses in the eribulin arm were complete responses.

A subgroup analysis of the EMBRACE study was also recently reported, demonstrating the benefit of eribulin across patient subgroups.[29] However, while in each of the subgroups eribulin was numerically favored compared with treatment of physician's choice, few achieved statistical significance. Among hormone receptor–positive patients, eribulin conferred a 17% decreased risk of death (HR, 0.83; 95% CI, 0.64–1.06); in hormone receptor–negative patients, eribulin-treated patients had a 34% decreased risk of death (HR, 0.66; 95% CI, 0.45–0.99). Among HER2-positive and HER2-negative patients, the decrease in risk of death associated with eribulin treatment was 24% (HR, 0.76; 95% CI, 0.47–1.24%) and 19% (HR, 0.81; 95% CI, 0.64–1.02%), respectively.

Investigation of the potential for eribulin in metastatic breast cancer continues, and 1 other open-label, randomized, controlled, parallel-group phase III clinical trial has been completed in patients with locally advanced/recurrent or metastatic disease.[30] In study 301 (N=1,102), the efficacy of eribulin specifically as a second-line therapy compared with capecitabine is under investigation, with OS and PFS as primary endpoints. The results of each of these studies are eagerly awaited. Further, single-agent eribulin will be assessed as a first-line therapy for patients with locally recurrent or metastatic breast cancer in 2 phase II trials (recruiting either HER2-negative or HER2-positive patients).[31,32]

Toxicities Associated With Ixabepilone and Eribulin

Ixabepilone treatment is associated with causing new or worsened peripheral neuropathy in a majority (65%) of patients.[33] Specifically, when ixabepilone was administered in the phase II trial, 14% of patients experienced grade 3/4 peripheral neuropathy, which typically resolved after a median of 5.4 weeks.[16] When given in combination with capecitabine, rates of grade 3/4 peripheral neuropathy ranged from 21–24%, and occurred more frequently than in patients treated with capecitabine alone.[17,19]

Neutropenia is the more significant toxicity associated with eribulin. As demonstrated in the EMBRACE study, eribulin-treated patients frequently experienced grade 3/4 neutropenia (45%), grade 3/4 leukopenia (14%), and grade 3/4 peripheral neuropathy (9%).[29] Although neutropenia was the most commonly reported grade 3/4 adverse event in patients treated with eribulin, it was effectively managed with dose delays, dose reductions, and granulocyte colony-stimulating factor. A closer analysis of the rates of grade 3/4 neutropenia according to treatment choice (vinorelbine: 40%; taxanes: 29%; and gemcitabine: 27%) showed that eribulin was associated with a similar rate of neutropenia as vinorelbine, which is also known to cause this toxicity. The incidence of peripheral neuropathy was relatively similar between eribulin-treated and taxane-treated patients, and it was the most common adverse event leading to treatment discontinuation in eribulin-treated patients (5%). Among patients who experienced grade 3/4 peripheral neuropathy with eribulin treatment and chose to continue therapy, symptoms improved to grade 2 or less following dose delays or dose reductions. Alopecia (all grades) was also reported in the eribulin arm (45%)

Because of the significant peripheral neuropathy associated with both ixabepilone and eribulin, a phase II randomized trial has been initiated to compare the

incidence and severity of neuropathy-associated toxicities among patients with advanced breast cancer treated with either single-agent eribulin or single-agent ixabepilone.[34] Recruitment for this trial has been completed, and the study is ongoing.

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Discussion

Linda T. Vahdat, MD There is an ever-increasing number of clinical trials of emerging agents in the setting of metastatic breast cancer. Their results are published in peer-reviewed journals, presented at international meetings, and even picked up by the press. In this environment of information overload, it can sometimes be difficult to sort through and dissect the results. However, the importance of carefully considering these results in the context of how to best integrate them into clinical practice has never been more important.

For the typical metastatic breast cancer patient, most physicians are faced with the challenge of shrinking the disease to allow the patient to become asymptomatic. Because the patient will never be cured of her cancer, maintaining and even improving quality of life is of utmost need. Thus, balancing the efficacy of the anticancer therapy with its associated toxicity is critical, so as not to expose the patient to the harmful effects of a drug that will have little to no improved effect on her survival compared with less aggressive therapies. It is in these cases where the newly emerging targeted agents may make the most impact, as they are often associated with a more manageable toxicity profile compared with the traditional agents.

Christopher Twelves, MD When I approach novel clinical trial data, I consider 2 main points. First, I assess if the data are presented clearly and represent a clinically meaningful impact to the patient. Second, I examine the trial population and relate it to the types of patients I typically encounter in the clinic. Very often, the trial populations are somewhat younger and have a somewhat better performance status. Therefore, if the toxicity profile appears to be marginally tolerated in the trial population, we must extrapolate these findings to our generally poorer performance status patients with care.

Javier Cortés, MD, PhD I think that while in general this may be true, the patients in the EMBRACE study could be reasonably well extracted to the population of metastatic breast cancer patients seen in clinical practice. Because of the success and clinical activity eribulin demonstrated in the late-line setting, combined with its favorable toxicity profile, we are eager to assess this agent in the first-line, second-line, and adjuvant settings.

Christopher Twelves, MD Also when evaluating clinical trial results, it is reassuring when the data are found to be statistically robust and largely recapitulate what was observed in the previous phase II studies. This also allows for the larger consideration of all the treated population together, through each of the phase II and III trials. For the EMBRACE studies in particular, this means that approximately 850 patients have been administered eribulin, demonstrating consistent patterns in terms of levels of both activity and toxicity.

Linda T. Vahdat, MD Yes, I do not think I have ever seen a series of trials in which the efficacy and toxicity of the data were so similar across the span of 3 phase II/III trials.

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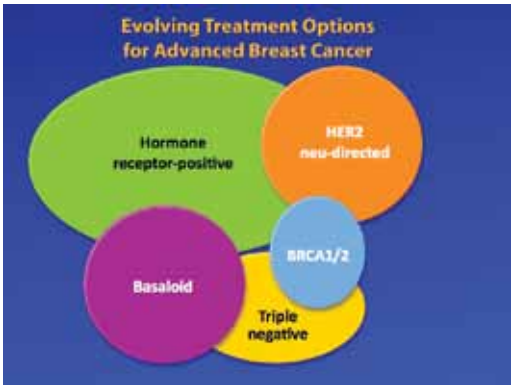

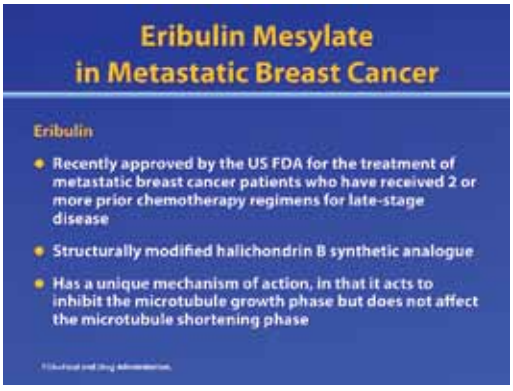

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