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# Metastatic Breast Cancer: Advances in Treatment and Management

## TARGET AUDIENCE

This activity was developed for oncology nurses and pharmacists who wish to enhance their competence concerning the treatment of patients with metastatic breast cancer.

## LEARNING OBJECTIVES

After completing this activity, the reader should be able to:

- Discuss the impact of metastatic breast cancer and key parameters for disease stratification
- Describe the role of prognostic/genetic markers and tumor histology in classifying breast cancer subtypes and predicting treatment response
- Review advances in the treatment of metastatic breast cancer, including the role of endocrine therapy, chemotherapy, targeted therapy, and bisphosphonates, with emphasis on targeted therapies
- Examine effective patient-tailored treatment approaches, based on recent data and clinical practice guidelines

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- Joanna Schwartz, PharmD, BCOP, has nothing to disclose.

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## COMMERCIAL SUPPORT

### ACKNOWLEDGMENT

This activity is supported by an educational grant from Eisai, Inc.

Although an estimated 207,090 cases of breast cancer will be diagnosed in the United States in 2010,<sup>1</sup> mortality rates from the disease have been on the decline since 1990, especially in women younger than 50 years of age.<sup>2</sup> This decrease is likely attributable to early detection through screening, increased general awareness, and improved therapies.<sup>2</sup> Nevertheless, breast cancer remains the second leading cause of cancer-related death in women, and is responsible for more than 40,000 deaths a year in the United States alone.<sup>1,2</sup> The majority of breast cancer-related deaths are a result of complications from recurrent or metastatic disease.

Metastatic breast cancer (MBC) is uncommon at initial presentation, occurring in only about 6% of newly diagnosed cases.<sup>2,3</sup> However, approximately 30% of women initially diagnosed with earlier stages of breast cancer eventually develop recurrent advanced or metastatic disease.<sup>3,4</sup> The 5-year relative survival rate for patients with MBC is only 23%.<sup>1</sup> Given this poor prognosis, researchers continue to focus their efforts on the development of more effective and tolerable treatments that may provide prolonged survival and improved quality of life. Investigators are also striving to more clearly identify biomarkers in breast cancer that can be used to assess prognosis and guide the selection of therapies, in the hopes of offering more indi-

vidualized treatment. As integral members of the oncology team, it is essential that nurses and pharmacists are aware of the latest advances in the treatment and management of MBC, including safety and efficacy data from clinical trials evaluating novel biologic and cytotoxic agents, as well as administration guidelines and side-effect management strategies pertaining to these therapies.

## Breast Cancer Disease Stratification: Predictive and Prognostic Markers

Advances have recently been made in the area of molecular profiling, which may help clinicians more accurately classify subtypes of breast cancer, as well as predict risk of recurrence and response to therapy.<sup>5</sup> A number of genes have been identified as important predictive markers of chemotherapeutic and targeted therapy efficacy, and may be used to guide more patient-specific treatment. The technology of DNA microarray gene expression profiling has led to a system of classifying breast cancer into the following major subtypes: estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative (luminal A and B subtypes); ER-negative/HER2-negative (basal subtype); HER2-positive; and tumors that are similar to normal breast tissue (normal breast-like).<sup>6</sup> Retrospective analyses have shown that characteristic relapse-free survival and overall survival (OS) are associated with

these gene expression subtypes.<sup>6</sup> Key tumor markers and their role in the management of breast cancer are shown in **Table 1**.<sup>7</sup>

Additional gene-based approaches have been developed for prognostic and predictive purposes. *OncotypeDX* is a 21-gene assay used to estimate the risk of recurrence in patients with early-stage, ER-positive, node-negative breast cancer, and to identify patients who may be successfully treated with tamoxifen alone (without chemotherapy).<sup>6,7</sup> This test uses reverse transcription polymerase chain reaction on RNA isolated from paraffin-embedded breast cancer tissue. MammaPrint is an assay that uses microarray technology to analyze a 70-gene expression profile from frozen breast tumor tissue of patients with early-stage, node-negative disease to determine their risk of developing distant metastases.<sup>6,8</sup> Both of these multi-gene expression tests are commercially available and have been incorporated into several diagnostic protocols. It is important to note, however, that results from prospective trials evaluating the clinical value of these assays have yet to be reported, although 2 such trials (TAILORx and MINDACT) are currently under way.

## Current Management Strategies for Patients With MBC

Although survival rates for MBC have improved over the past 20 years, the primary goal of treatment is still palliation.

The decision-making process regarding the choice of agents and the sequencing and duration of therapy for metastatic disease is complex, and requires consideration of numerous key factors, including the pathology, histology, and clinical characteristics of the tumor(s), axillary node status, hormone receptor (HR) and HER2 status, and patient-related factors (eg, age, menopausal status, and comorbid conditions).<sup>6</sup>

## HR-Positive MBC

The goals of systemic therapy for recurrent or metastatic disease are prolonging survival and improving quality of life. Therefore, treatments with minimal toxicity are usually preferred and often include endocrine therapies (as opposed to cytotoxic therapies). Patients with HR-positive MBC (ie, those with tumors that are ER- and/or progesterone receptor [PR]-positive) may benefit from initial endocrine therapy. Recent data support treatment with a selective aromatase inhibitor (AI) for postmenopausal women with previous antiestrogen therapy who are within 1 year of antiestrogen exposure.<sup>6</sup> For postmenopausal women who are antiestrogen naïve or more than 1 year from previous treatment with an antiestrogen, tamoxifen or an AI is an appropriate therapeutic option.<sup>6</sup> In this setting, AIs have shown a modestly superior outcome compared with tamoxifen.<sup>6</sup>

Sequential treatment with endocrine therapy may be beneficial at the time of

disease progression.<sup>6</sup> Subsequent endocrine therapy may include nonsteroidal AIs (anastrozole or letrozole); a steroidal AI (exemestane); fulvestrant; tamoxifen or toremifene; megestrol acetate; fluoxymesterone; or ethinyl estradiol.<sup>6</sup> For women with HR-positive metastatic disease who have been previously treated with an AI or antiestrogen, fulvestrant is an option that appears to be well tolerated as a monthly injection, with an efficacy profile similar to anastrozole and a longer duration of response.<sup>6</sup>

### ER-Negative MBC

Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines indicate an absence of benefit with endocrine therapy in women with ER-negative, invasive breast cancer, based on large, randomized, clinical trials.<sup>6,9</sup> Chemotherapy has been shown to be more effective in the treatment of patients with this type of breast cancer (compared with adjuvant endocrine therapy),<sup>6,10</sup> with a dose-dense regimen of doxorubicin, cyclophosphamide, and paclitaxel showing the greatest benefit in terms of reducing the risk for recurrence and death.<sup>11</sup>

### HER2-Positive MBC

HER2 protein overexpression occurs in 20% to 25% of breast tumors, often leading to aggressive disease and poor outcomes.<sup>12</sup> Consequently, successful targeting of HER2-positive tumors is an important therapeutic goal. Patients with this type of MBC may benefit from treatment with trastuzumab as monotherapy or in combination with select chemotherapy agents; or with a combination of capecitabine plus lapatinib for patients who are refractory to treatment with an anthracycline, a taxane, and trastuzumab. The preferred first-line agents for treating HER2-positive disease are listed in Table 2.<sup>6</sup>

Trastuzumab, a recombinant human anti-HER2 monoclonal antibody, specifically targets signaling mechanisms of HER2, which inhibits the growth of tumor cells that overexpress the receptor. The addition of trastuzumab to anthracycline or taxane chemotherapy in patients with HER2-positive breast cancer has been shown to significantly improve time to progression, rate of objective response, and median survival.<sup>13</sup> Trastuzumab combined with other chemotherapeutic agents is also a viable option, and a number of combinations are available.<sup>6</sup> Clinical trials evaluating trastuzumab combined with other targeted agents, including pertuzumab and lapatinib, are currently under way.<sup>12</sup>

Cardiac toxicity is a concern with trastuzumab treatment, particularly when this agent is combined with an anthracycline.<sup>6,14</sup> According to NCCN

**Table 1** Key Tumor Markers in Breast Cancer<sup>7</sup>

Tumor Marker	Role
Estrogen receptor (ER) Progesterone receptor (PR)	Determine whether the cancer is likely to be successfully treated with hormone therapy, such as tamoxifen.
Human epidermal growth factor receptor 2 (HER2)	Determines whether the cancer can be treated with an anti-HER2 treatment, such as trastuzumab; in some cases, may indicate whether additional treatment with chemotherapy may be beneficial.
Cancer antigen 15-3 (CA 15-3) Cancer antigen 27.29 (CA 27.29) Carcinoembryonic antigen (CEA)	Found in 50% to 90% of patients with metastatic disease, these tumor markers may point to early recurrence or indicate whether the cancer is responding to treatment.
Urokinase plasminogen activator (uPA) Plasminogen activator inhibitor (PAI-1)	High levels of these markers may indicate that the cancer is aggressive; these markers may guide the use of chemotherapy after surgery for patients with node-negative disease.

guidelines, trastuzumab should not be administered concurrently with an anthracycline because of the risk of cardiac toxicity, except as part of the neoadjuvant regimen of trastuzumab plus paclitaxel followed by cyclophosphamide/epirubicin/fluorouracil.<sup>6</sup> Close monitoring of cardiac function is advised for patients receiving trastuzumab therapy.<sup>6</sup> Less serious side effects associated with this agent include nausea, vomiting, hot flashes, and joint pain.<sup>14,15</sup>

**The goals of systemic therapy for recurrent or metastatic disease are prolonging survival and improving quality of life.**

Resistance to trastuzumab often develops over time.<sup>16</sup> One strategy for overcoming this resistance involves switching patients to lapatinib, a dual tyrosine kinase inhibitor that blocks HER2 signaling through an alternative mechanism.<sup>16</sup> Lapatinib was approved by the US Food and Drug Administration (FDA) in 2007 for use in combination with capecitabine for the treatment of patients with advanced or metastatic disease whose tumors overexpress HER2 and who have received prior therapy, including an anthracycline, a taxane, and trastuzumab.<sup>17,18</sup> In February 2010, lapatinib received approval for an expanded indication in combination with letrozole for the treatment of postmenopausal women with HR-positive/HER2-positive MBC for whom hormonal therapy is indicat-

ed.<sup>17,18</sup> The approved labeling includes a caution stating that hepatotoxicity is a potentially serious adverse effect associated with lapatinib.<sup>18</sup>

### HR-Negative MBC and HR-Positive, Endocrine-Refractory MBC

Cytotoxic chemotherapy is recommended for patients with HR-negative MBC as well as HR-positive disease refractory to endocrine treatment. The NCCN guidelines recommend first-line single-agent chemotherapy until progression of disease.<sup>6</sup> However, the adverse events associated with this therapy may necessitate dose reductions or treatment cessation.<sup>6</sup> Preferred single-agent and combination chemotherapy regimens for HR-negative and HR-positive, endocrine-refractory breast cancer, as outlined in these guidelines, are shown in Table 3.<sup>6</sup>

### Recent Advances in the Treatment of MBC

Treatment options for patients with MBC continue to expand as investigators learn more about the biology of the disease and the process of metastasis. Recent advances in treatment include the development of novel targeted agents, new formulations of existing drugs, and more effective combination regimens.

### Microtubule-Targeting Agents

#### Eribulin Mesylate

Eribulin mesylate, a nontaxane microtubulin, was highlighted as a "notable advance" in the treatment of breast cancer in ASCO's annual report titled *Clinical Cancer Advances 2010*.<sup>19</sup> Representing a new class of agents, eribulin is an analog of a chemical derived from a marine sponge. This drug was approved by the FDA in November 2010 for the treatment of patients with MBC who previously received at least 2

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chemotherapy regimens. This decision was based on preliminary results of the pivotal phase 3 EMBRACE trial (N = 762), in which a significant improvement in OS (median of 2.47 months) was seen with eribulin compared with treatment of physician's choice (TPC).<sup>20</sup> Results from an updated analysis of this trial, presented at the 2010 San Antonio Breast Cancer Symposium, were consistent with these earlier findings, with a median OS of 13.2 months for eribulin versus 10.5 months for TPC.<sup>21</sup> The most recently updated NCCN practice guidelines list eribulin as a preferred single agent for recurrent or metastatic disease.<sup>6</sup>

The most common adverse events (incidence  $\geq 25\%$ ) associated with this agent include neutropenia, asthenia/fatigue, anemia, peripheral neuropathy, nausea, and constipation.<sup>22</sup>

### Ixabepilone

Ixabepilone, a semisynthetic analog of epothilone B, received FDA approval in 2007 as both a single agent and in combination with capecitabine for the treatment of locally advanced and metastatic disease.<sup>6</sup> Phase 2 clinical trials evaluating ixabepilone monotherapy in the first-line setting have reported significant activity in patients who have received prior therapy with anthracyclines and taxanes.<sup>23</sup>

In a pivotal phase 3 trial comparing ixabepilone plus capecitabine versus

**Table 2** NCCN Guidelines: Preferred First-Line Therapies for HER2-Positive Breast Cancer<sup>6</sup>

Preferred First-Line Agents
Trastuzumab with: <ul style="list-style-type: none"> <li>• Paclitaxel + carboplatin</li> <li>• Docetaxel</li> <li>• Vinorelbine</li> <li>• Capecitabine</li> </ul>
Preferred Chemotherapy Agents for Trastuzumab-Exposed HER2-Positive Breast Cancer
Lapatinib plus capecitabine <ul style="list-style-type: none"> <li>• Trastuzumab plus other first-line agents</li> <li>• Trastuzumab plus capecitabine</li> <li>• Trastuzumab plus lapatinib (without cytotoxic therapy)</li> </ul>
<small>HER2 indicates human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network.</small>

capecitabine alone in patients with resistance to previous anthracycline and taxane therapy, a significant improvement in progression-free survival (PFS) was seen with the combination regimen (6.2 months vs 4.4 months, respectively;  $P = .0005$ ).<sup>24</sup>

The most common adverse events ( $\geq 20\%$  incidence) associated with ixabepilone include peripheral neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain.<sup>24</sup>

### Nab-paclitaxel

Nanoparticle albumin-bound (*nab*)-paclitaxel is a solvent-free, albumin-bound 130-nm particle form of paclitaxel that was developed to avoid toxicities associated with the cremophor vehicle used in solvent-based paclitaxel. This agent was approved by the FDA in January 2005 for the treatment of breast cancer after failure of combination therapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.<sup>25</sup> A phase 3 trial ( $N = 454$ ) compared *nab*-paclitaxel with a conventional formulation of the drug in MBC, showing a higher target-lesion response and objective response rates with *nab*-paclitaxel.<sup>25</sup> In a separate phase 2 trial ( $N = 302$ ) in previously untreated MBC, *nab*-paclitaxel demonstrated significantly longer PFS than docetaxel by both independent radiologist assessment (12.9 vs 7.5 months, respectively;  $P = .0065$ ) and investigator assessment (14.6 vs 7.8 months, respectively;  $P = .012$ ).<sup>26</sup>

### Novel Combinations for HER2-Positive MBC

In a recent phase 3 trial, dual HER2-targeted therapy with lapatinib and trastuzumab showed an increase in PFS compared with lapatinib alone (12 weeks vs 8.1 weeks;  $P = .008$ ) in

**Table 3** NCCN Guidelines: Preferred First-Line Chemotherapies for Patients With HR-Negative or HR-Positive, Endocrine-Refractory Breast Cancer<sup>6</sup>

Single Agents
Anthracyclines <ul style="list-style-type: none"> <li>• Doxorubicin</li> <li>• Epirubicin</li> <li>• Pegylated liposomal doxorubicin</li> </ul>
Taxanes <ul style="list-style-type: none"> <li>• Paclitaxel</li> <li>• Docetaxel</li> <li>• Albumin-bound paclitaxel</li> </ul>
Antimetabolites <ul style="list-style-type: none"> <li>• Capecitabine</li> <li>• Gemcitabine</li> </ul>
Nontaxane Microtubule Inhibitors <ul style="list-style-type: none"> <li>• Eribulin</li> <li>• Vinorelbine</li> </ul>
Combination Regimens
Cyclophosphamide, doxorubicin, and fluorouracil (FAC/CAF)
Fluorouracil, epirubicin, cyclophosphamide (FEC)
Doxorubicin, cyclophosphamide (AC)
Epirubicin, cyclophosphamide (EC)
Doxorubicin in combination with either docetaxel or paclitaxel (AT)
Cyclophosphamide, methotrexate, fluorouracil (CMF)
Docetaxel, capecitabine
Gemcitabine, paclitaxel
<small>HR indicates hormone receptor; NCCN, National Comprehensive Cancer Network.</small>

patients with heavily pretreated MBC and disease progression on trastuzumab therapy.<sup>27</sup> In addition, according to recent data, the combination of lapatinib, trastuzumab, and paclitaxel was associated with a significant improve-

ment in tumor response rate compared with individual agents in patients with HER2-positive disease.<sup>28</sup>

According to preliminary findings from a phase 1b/2 trial, trastuzumab-DM1 (T-DM1) plus pertuzumab demonstrated encouraging safety and efficacy in women with HER2-positive, locally advanced or metastatic disease who were previously treated with trastuzumab.<sup>29</sup> T-DM1, an HER2-targeted antibody-drug conjugate, is composed of the cytotoxic agent DM1, an antimicrotubule agent, conjugated to the monoclonal antibody trastuzumab.<sup>29,30</sup> Pertuzumab, a humanized monoclonal antibody, is the first HER2-directed dimerization inhibitor for the treatment of HER2-positive breast cancer. T-DM1 and pertuzumab bind to different HER2 receptors; combining these agents has shown synergistic antitumor activity in HER2-positive xenograft models.<sup>29,30</sup>

### Emerging Therapies for Triple-Negative Disease

Triple-negative breast cancer (TNBC) is a term used to describe tumors that lack expression of ER, PR, and HER2. This type of breast cancer is associated with rapid disease progression and poor prognosis. Therefore, advances in treatment for this subtype of disease are particularly noteworthy. A recent study found that TNBC patients with *BRCA1/BRCA2* mutations appear to have better survival than patients without these mutations.<sup>31</sup>

### PARP Inhibitors

Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors appear to have clinical activity in *BRCA1/BRCA2*-associated cancer. Results from a phase 2 study ( $N = 123$ ) showed that the PARP inhibitor, iniparib, plus chemotherapy was associated with significantly prolonged OS in TNBC, compared with chemotherapy alone

(12.3 months vs 7.7 months, respectively; hazard ratio for death, 0.57;  $P = .01$ ).<sup>32</sup> In addition, another PARP inhibitor, olaparib, is being investigated for its potential activity when combined with paclitaxel.<sup>33</sup> In a small study ( $N = 10$ ), 4 patients achieved a partial response with this combination; however, acceptable dose intensity was delayed or not achieved because neutropenia was reported in a number of patients.<sup>34</sup> In another small study ( $N = 24$ ), no responses were observed in patients with TNBC treated with olaparib plus paclitaxel.<sup>33</sup>

### Cetuximab

Cetuximab, an antibody that targets epithelial growth factor receptor, is being studied for its potential role in treating TNBC. Based on results of a recent phase 2 trial ( $N = 173$ ), adding cetuximab to cisplatin chemotherapy in heavily pretreated patients with TNBC resulted in twice the response rate and twice the time to progression compared with patients who received cisplatin alone.<sup>35</sup>

### Bone Disease in Patients With MBC

Bone metastasis, which occurs in approximately 70% of patients with advanced breast cancer,<sup>36</sup> can lead to significant skeletal morbidity, including bone pain, pathologic fracture, hypercalcemia of malignancy, and spinal cord compression.<sup>36</sup> Patients with breast cancer who are treated with AIs (eg, anastrozole, letrozole, exemestane) are at increased risk for bone loss and fractures.<sup>37</sup> Bisphosphonates have demonstrated efficacy in delaying the onset and reducing the incidence of skeletal-related events (SREs) associated with bone metastasis.<sup>38</sup> The recently approved agent, denosumab, has also been shown to be effective in preventing these events in patients with bone metastases from solid tumors.<sup>39</sup>

## Update on Bevacizumab Use in Breast Cancer

In February 2008, the FDA granted accelerated approval of bevacizumab in combination with paclitaxel for the first-line treatment of HER2-negative MBC. This approval was based on results of E2100, a phase 3 trial in which initial treatment with this combination almost doubled PFS compared with paclitaxel alone in women with recurrent or metastatic disease (11.8 months vs 5.9 months, respectively;  $P < .001$ ).<sup>1</sup> Subsequent phase 3 trials also demonstrated longer PFS when bevacizumab was added to various first-line chemotherapeutic regimens for MBC, but these gains were not as clinically significant as those seen in the E2100 trial.<sup>2,3</sup> A recent meta-analysis of these trials failed to show an improvement in OS with the addition of bevacizumab.<sup>4</sup>

Given the fact that bevacizumab use has been associated with serious adverse events, including

hypertension, bleeding, and febrile neutropenia,<sup>2,3,5</sup> the FDA is now questioning whether the benefits of this drug outweigh the risks for women with MBC.<sup>6</sup> After consideration of the data, the agency's review panel announced that it was revoking this indication.<sup>6</sup> The manufacturer of bevacizumab has requested a hearing to maintain their drug as a treatment option for HER2-negative MBC.<sup>7</sup> It should be noted, however, that the European Medicines Agency and the National Comprehensive Cancer Network have both indicated that bevacizumab plus paclitaxel should remain a therapeutic option for women with this type of breast cancer.<sup>8</sup>

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## Bisphosphonate Therapy

The use of bisphosphonates is considered a palliative care measure in patients with MBC; these agents may also play a role in preventing skeletal complications associated with bone loss.<sup>6</sup> The 2 intravenous (IV) bisphosphonates approved by the FDA for the treatment of bone metastases are zoledronic acid and pamidronate. Both of these agents have been studied in numerous clinical trials, and zoledronic acid appears to be superior to pamidronate in patients with lytic breast metastasis.<sup>6</sup> Recent data also suggest that zoledronic acid may have antitumor properties.<sup>40</sup> Zoledronic acid and pamidronate may help to decrease the pain related to bone metastasis, thereby reducing the need for supplemental analgesics in some patients.<sup>41</sup>

Generally, IV bisphosphonates are well tolerated. However, osteonecrosis of the jaw (ONJ), a rare but serious complication, may occur.<sup>6</sup> Most reported cases of ONJ during bisphosphonate therapy have been associated with dental procedures such as tooth extractions. A dental examination is recommended prior to treatment, and invasive procedures during therapy should be avoided whenever possible.<sup>6</sup>

In addition, serum creatinine should be monitored prior to each dose of zoledronic acid or pamidronate. According to recent data, short-term use ( $\leq 12$  months) of these agents is associated with a low risk of renal dysfunction.<sup>41</sup> However, the effects of extended therapy have not been studied extensively.<sup>41</sup>

## Denosumab

Denosumab, a fully human monoclonal antibody, was approved by the FDA in November 2010 for the prevention of SREs in patients with bone metastases from solid tumors.<sup>39</sup> This novel agent inhibits bone resorption by specifically targeting the receptor activator of nuclear-factor kappa beta ligand (RANKL) and its receptor, RANK, key mediators of osteoclast formation and function.<sup>42</sup>

Phase 3 data presented at the 2010 San Antonio Breast Cancer Symposium showed that denosumab was superior to zoledronic acid in delaying the time to first on-study SREs by 18%, and denosumab delayed the time to first-and-subsequent on-study event by 22%.<sup>43</sup> Moreover, in patients with advanced breast cancer and bone metastases who were at risk, the median time to first on-study SRE was 5 months longer in the denosumab group compared with the zoledronic acid group. Denosumab was also associated with less pain, less interference with daily functioning, and improved health-related quality of life, based on other data presented at this meeting.<sup>43</sup>

In general, the rate of adverse events

associated with denosumab was similar to the rate observed with zoledronic acid; cases of ONJ were rare, and hypocalcemia was more frequent in the denosumab arm.<sup>39</sup> Calcium levels must be monitored in patients receiving denosumab, and administration of calcium, magnesium, and vitamin D may be required.<sup>39</sup> The most common adverse events associated with denosumab were fatigue/asthenia, hypophosphatemia, and nausea; dyspnea was the most common serious adverse event.<sup>39</sup>

## HER2 protein over-expression occurs in 20% to 25% of breast tumors, often leading to aggressive disease and poor outcomes.

### Conclusion

Extended survival and improved quality of life are of paramount importance in patients with MBC. Advances in systemic, hormonal, and targeted therapies are yielding novel approaches and protocols that hold promise for improving clinical outcomes. Addressing pain and other disease-related comorbidities and preventing SREs are also key aspects of managing patients with MBC. The approach to treatment continues along the path of personalized care plans that are based on tumor/disease profile, patient-specific factors, and patient and physician preferences. Increasing attention is being directed toward the use of genetic markers and other tools that help clinicians stratify patients who will receive maximal benefit from a specific therapy while sparing those patients who may not benefit from such regimens. Research continues to focus on the development of novel therapies that increase response and survival time for patients with MBC, while minimizing toxicity and other adverse events. ●

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# Novel Targeted Agents for the Treatment of Metastatic Breast Cancer

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**B**reast cancer is the most common female malignancy worldwide, with an annual global incidence of over 1 million and a resulting 450,000 deaths.<sup>1</sup> Although the diagnosis of localized breast cancer is more common since the advent of screening mammogram guidelines, the number of women diagnosed with metastatic disease is still significant.<sup>2</sup> The prognosis for advanced metastatic breast cancer (MBC) is very poor, with only 1 in 5 women surviving for 5 years.<sup>2</sup>

Anthracyclines and taxanes are among the most active drugs used to treat breast cancer; however, a significant number of patients become resistant to these therapies over time, resulting in low response rates.<sup>3,4</sup> In some cases, resistance is due to the expression of multidrug-resistant (MDR) protein products of the MDR gene, such as P-glycoprotein. This results in the production of drug efflux pumps, which actively transport many chemotherapy agents, such as taxanes, out of cancer cells.<sup>5</sup>

Drug resistance is especially problematic for patients with triple-negative breast cancer (TNBC) and/or breast cancer with the *BRCA* mutation (deficiency), as these types of malignancies are inherently resistant to most cytotoxic therapies.<sup>6</sup> In the case of TNBC, patients who develop resistance are left with very limited treatment options, as they are not candidates for hormonal or targeted agents, due to a lack of tumor receptors. Furthermore, TNBC is the most aggressive type of breast cancer and is associated with the poorest prognosis.<sup>7</sup>

There is an important need for novel agents to address these challenges in the treatment of breast cancer. Two new cytotoxic drug classes, epothilones and halichondrins, and 1 new targeted drug class, poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, have been developed to meet this need.

## Novel Microtubule-Targeting Agents

### *Ixabepilone*

*Ixabepilone* was the first agent from the epothilone class to be approved by the US Food and Drug Administration (FDA) for the treatment of metastatic or locally advanced breast cancer. Epothilones are naturally occurring macrolide antibiotics, produced by the myxobacterium *Sorangium cellulosum*, and are nontaxane microtubule inhibitors. The taxanes exert their cytotoxic

**Table** Phase 3 Trial of Ixabepilone Plus Capecitabine Versus Capecitabine Alone in MBC Resistant to Anthracyclines and Taxanes<sup>9</sup>

	Ixabepilone + Capecitabine	Capecitabine	P Value
Median PFS, months	6.2	4.2	.0005
ORR, %	43	29	.0001
Best response, N (%)			
CR	16 (3)	11 (2)	
PR	184 (40)	122 (26)	
SD	170 (37)	182 (39)	
PD	57 (12)	111 (24)	

CR indicates complete response; MBC, metastatic breast cancer; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

effect by binding tubulin, and stabilizing the microtubule and inhibiting its disassembly, ultimately leading to cell death by apoptosis. Although epothilones have a similar mechanism of action, these novel agents bind to tubulin at a different site. Importantly, epothilones appear to retain activity in cell lines expressing the P-glycoprotein pump, which, as mentioned earlier, is a known cause of resistance to agents such as taxanes.<sup>8</sup>

### In the case of TNBC, patients who develop resistance are left with very limited treatment options.

The combination of *ixabepilone* plus *capecitabine* was evaluated in a phase 3 randomized double-blind clinical trial of patients with MBC resistant to treatment with anthracyclines and taxanes. As shown in the **Table**, this combination was associated with significantly longer median progression-free survival (PFS) than *capecitabine* alone (6.2 vs 4.2 months;  $P = .0005$ ), as well as a higher response rate (43% vs 29%;  $P < .0001$ ).<sup>9</sup> *Ixabepilone* monotherapy has also demonstrated clinical activity in patients with MBC after failure of *capecitabine* in several phase 2 trials, with objective response rates ranging from 12% to 18%.<sup>10-12</sup>

The main toxicities observed in clin-

ical trials of *ixabepilone* have included peripheral neuropathy, fatigue, myalgia/arthralgia, diarrhea, neutropenia, and less commonly, hypersensitivity infusion reactions. *Ixabepilone* is reconstituted with a supplied diluent containing polyethoxylated castor oil, which is a known cause of reactions with other agents, such as *paclitaxel*.<sup>13</sup>

Based on data from the above-mentioned trials, *ixabepilone* was approved by the FDA in 2007 for the following indications: (1) in combination with *capecitabine* for treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated, and (2) as single-agent therapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and *capecitabine*.<sup>14</sup>

According to the approved package labeling, *ixabepilone* should be administered intravenously (IV) over 3 hours at a dose of 40 mg/m<sup>2</sup> (to a maximum of 88 mg for patients with a body surface area >2.2 m<sup>2</sup>) every 3 weeks. Patients should be premedicated with a histamine-1 antagonist such as *diphenhydramine* and a histamine-2 antagonist such as *ranitidine* 1 hour before *ixabepilone* and should be closely monitored for hypersensitivity reactions prior to the first 2 infusions. *Ixabepilone* is extensively metabolized by the liver, and the package labeling contains specific dosing recommendations for patients with hepatic impairment.<sup>14</sup> In fact, the combination of *ixabepilone* and *capecitabine* is contraindicated

when the total bilirubin rises over the upper limit of normal. This prescribing information should be consulted for specific dose adjustments for patients with elevated liver function tests or significant toxicities, such as neutropenia or neuropathy. Complete blood counts, examination for neurologic symptoms, and liver function tests should be performed prior to every dose, and the use of strong cytochrome P-450 3A4 inhibitors (including grapefruit juice) should be avoided.<sup>14</sup>

### *Eribulin Mesylate*

*Eribulin mesylate* is a novel microtubule inhibitor with a distinct mechanism of action. Other microtubule inhibitors, such as taxanes, vinca alkaloids, and epothilones, inhibit both growth and shortening of microtubules. In contrast, *eribulin* suppresses microtubule growth with no effect on microtubule shortening, and also sequesters tubulin into nonfunctional aggregates. It is a synthetic analog of the marine natural macrolide *halichondrin B*, which was first isolated from the Japanese sponge *Halichondria okadai*, and is the first in class of the *halichondrins*.<sup>15</sup>

*Eribulin* was FDA approved in November 2010 for the treatment of patients with MBC who have previously received anthracyclines and taxanes, based on the results of the pivotal phase 3 EMBRACE trial. This study was designed to represent common practice situations in that the 762 enrolled patients with metastatic or locally recurrent breast cancer had been heavily pretreated with 2 to 5 previous chemotherapy regimens that included an anthracycline and a taxane.<sup>16</sup> Furthermore, patients were randomized to *eribulin* or a treatment of physician's choice (TPC), which could be any monotherapy (cytotoxic, hormonal, biologic) or supportive care only. This choice was considered representative of actual practice scenarios, since there is no current standard of care for breast cancer patients after failure of anthracyclines and taxanes. The primary end point of this trial was overall survival (OS); secondary end points were objective response rate, PFS, and duration of response. Median OS was significantly prolonged with *eribulin* compared with TPC (13.12 vs 10.65 months, a difference of 2.47 months;  $P = .041$ ). The 1-year survival was 53.9% with *eribulin* and 43.7% with TPC (**Figure 1**).<sup>16</sup> Although the trial did not show a statis-

tically significant improvement in PFS (albeit a strong trend in favor of eribulin), the results are still significant in that eribulin is the first agent to demonstrate an OS advantage for MBC since docetaxel was approved more than 10 years ago.

The main toxicities observed in the eribulin arm of the trial were neutropenia, anemia, peripheral neuropathy, alopecia, nausea (mostly mild), myalgia/arthralgia, fatigue, constipation, and QT prolongation (rare).<sup>16</sup> According to the package labeling, eribulin should be avoided in those with congenital long QT syndrome, and electrolytes should be corrected prior to initiating therapy, and monitored periodically during treatment.<sup>17</sup>

Eribulin should be administered IV over 2 to 5 minutes at a dose of 1.4 mg/m<sup>2</sup> on days 1 and 8 of a 21-day cycle. Because eribulin is extensively hepatically cleared with some metabolites being renally cleared, the package labeling should be consulted for suggested dosing modifications for mild-to-moderate hepatic impairment and/or a creatinine clearance <50 mL/min. There is no safety data or dosing recommendations for those with a creatinine clearance <30 mL/min. Patients should be assessed for peripheral neuropathy and with complete blood counts prior to each dose, and therapy should be delayed for significant neuropathy or an absolute neutrophil count <1000/mm<sup>3</sup> and/or platelets <75,000/mm<sup>3</sup>. The package labeling should also be consulted for suggested dosage reductions in the event of very low blood counts, febrile neutropenia, or toxicities that do not resolve within 7 days.<sup>17</sup>

#### PARP Inhibitors for MBC

PARP inhibitors appear to be among the most promising agents being studied for the treatment of BRCA-mutated breast cancer and TNBC. Both BRCA1 and BRCA2 are involved in the repair of DNA damage (in particular, double-strand DNA breaks), which arises from exposure to chemotherapy. This process is known as homologous recombination. DNA damage is essential in the treatment of cancer, as it triggers cell cycle arrest and cell death.<sup>18</sup> In women with BRCA-mutated breast cancer, the tumor loses the wild-type allele of BRCA1 or 2 and is left with a nonfunctioning BRCA1 or 2 protein.<sup>19-21</sup> When this occurs, another pathway of DNA repair, known as base excision repair, allows the cancer cell to recover from DNA damage. This pathway is dependent on the function of enzymes called PARPs, which repair single-strand DNA breaks. Investigators have hypothesized that PARP inhibition, in conjunction with the loss of DNA repair via BRCA-dependent mecha-

Two new agents, ixabepilone and eribulin, are novel microtubule agents that have been FDA approved and provide options for patients who are resistant or intolerant to other therapies.

nisms, may result in synergistic tumor cell death (Figure 2).<sup>22</sup> Triple-negative tumors, while not all stemming from BRCA mutation, share characteristics with BRCA1-associated breast tumors and may harbor other genetic lesions that impair double-strand repair.<sup>21</sup>

Currently, there are 8 PARP inhibitors in clinical trial development worldwide, but only 3 agents are being evaluated in late-stage clinical trials: olaparib, veliparib, and iniparib. To date, the largest and most promising trials of PARP inhibitors in breast cancer include a phase 2 multicenter, single-arm trial of olaparib in patients with refractory, advanced BRCA-mutated breast cancer,<sup>23</sup> and a randomized, phase

2 trial investigating iniparib in combination with gemcitabine and carboplatin in patients with TNBC.<sup>24</sup> Additionally, results of a small phase 2 trial of veliparib in combination with temozolomide in patients with advanced refractory breast cancer (not restricted to BRCA or triple-negative status) were recently presented at the 2010 American Society of Clinical Oncology annual meeting. Although these were only preliminary findings, several excellent clinical responses were reported, including 1 complete response and 2 partial responses in 24 evaluable patients.<sup>25</sup>

In the phase 2 single-agent study,<sup>23</sup> 54 women with recurrent MBC and con-

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firmed BRCA mutations were administered olaparib 100 or 400 mg orally twice daily. The overall response rate was 22% in the 100-mg group and 41% in the 400-mg group. In the phase 2 combination study,<sup>24</sup> 123 women with metastatic TNBC were randomized to either gemcitabine and carboplatin alone, or the same agents in combination with IV iniparib on days 1, 4, 8, and 11 of a 21-day cycle. Updated results of this trial showed that the combination with iniparib extended OS by approximately 4 months compared with gemcitabine/carboplatin alone (12.3 vs 7.7 months,  $P = .01$ ).

Results of these studies indicate the potential of PARP inhibition as a tumor-specific target in specific patient populations, considering most of the participants had been refractory to several prior therapies. As a class, the PARP inhibitors are well tolerated, and the most common toxicities seen in clinical trials have included low-grade fatigue and nausea.<sup>23-25</sup> Before PARP inhibitors can be considered for possible wider use outside of clinical trials, it will be necessary to identify the best candidates for this therapy and to determine which agents will be most effective when used in combination with specific PARP inhibitors. In addition, the clinical activity of these agents needs to be assessed in ongoing randomized, comparative, phase 3 trials.

#### Conclusions

Limited options make the successful treatment of MBC difficult. Current treatment options include anthracyclines, taxanes, and capecitabine. Resistance to these classes of drugs is often acquired, thus highlighting the need for newer agents capable of managing treatment-resistant disease. Two new agents, ixabepilone and eribulin, are novel microtubule agents that have been FDA approved and provide options for patients who are resistant or intolerant to other therapies. The addition of these therapies into the breast cancer armamentarium has expanded treatment options for patients with MBC. Several PARP inhibitors are in late-phase development and in the future may provide promising treatment options to specific patients, especially women with BRCA mutations or TNBC. Continued research into these agents will be necessary to further

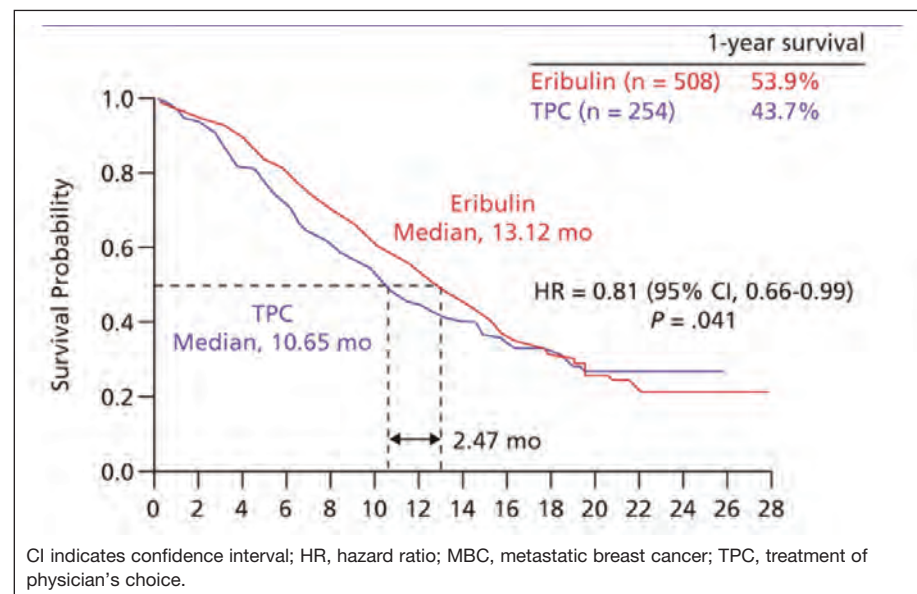


Figure 1. Survival data from a phase 3 trial of eribulin versus treatment of physician's choice in previously treated patients with MBC.<sup>16</sup>

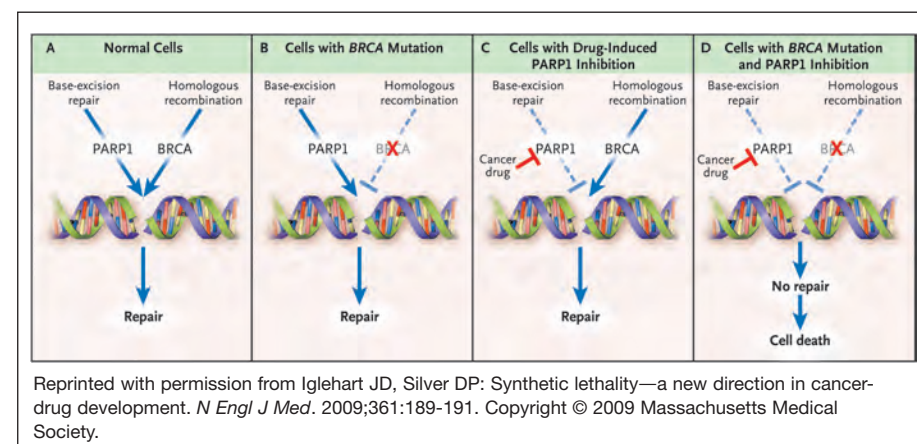


Figure 2. Mechanism of cell death from synthetic lethality, as induced by inhibition of poly(adenosine diphosphate-ribose) polymerase 1 (PARP1).<sup>22</sup>

define their place in therapy. Further results of ongoing studies with all of these agents are keenly awaited. ●

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