

# Ixabepilone in metastatic breast cancer

*First-in-class antineoplastic agent offers a new chemotherapy option where other drugs have failed*

## What's new, what's important

Ixabepilone (Ixempra) belongs to a novel class of drugs, epothilones. Epothilones are non-taxane microtubule-stabilizing agents. The tubulin polymerizing activity of ixabepilone is stronger than that of paclitaxel. It has proven efficacy in taxane-resistant settings. Ixabepilone has a low susceptibility to tumor-resistance mechanisms, including efflux transporters such as P-glycoprotein (P-gp) and multidrug-resistance protein-1 (MRP1). The US Food and Drug Administration approved the use of ixabepilone in combination with capecitabine (Xeloda) in patients with metastatic or locally advanced breast cancer who are resistant or refractory to taxane and anthracycline therapy. Ixabepilone is also approved as a monotherapy in patients who are resistant or refractory to taxanes, anthracyclines, and capecitabine.

The recommended dose is 40 mg/m<sup>2</sup> administered IV over 3 hours every 3 weeks. Patients should be premedicated with diphenhydramine and cimetidine or ranitidine an hour prior to infusion with ixabepilone. Steroid premedication is not routinely recommended. Ixabepilone in combination with capecitabine is contraindicated in patients with AST (aspartate aminotransferase) and ALT (alanine transaminase) levels more than 2.5 times normal limits or a bilirubin level greater than the upper normal limit.

Ixabepilone is being tested in combination with a number of biologicals and cytotoxic agents. The availability of this new drug is an exciting development for patients with metastatic breast cancer.

— Jame Abraham, MD  
Section Editor

**I**xabepilone (Ixempra) is the first semisynthetic epothilone B analog. Epothilones are naturally occurring substances that promote cell death by stabilizing cell microtubules and inducing apoptosis. Epothilone B analogs are simi-

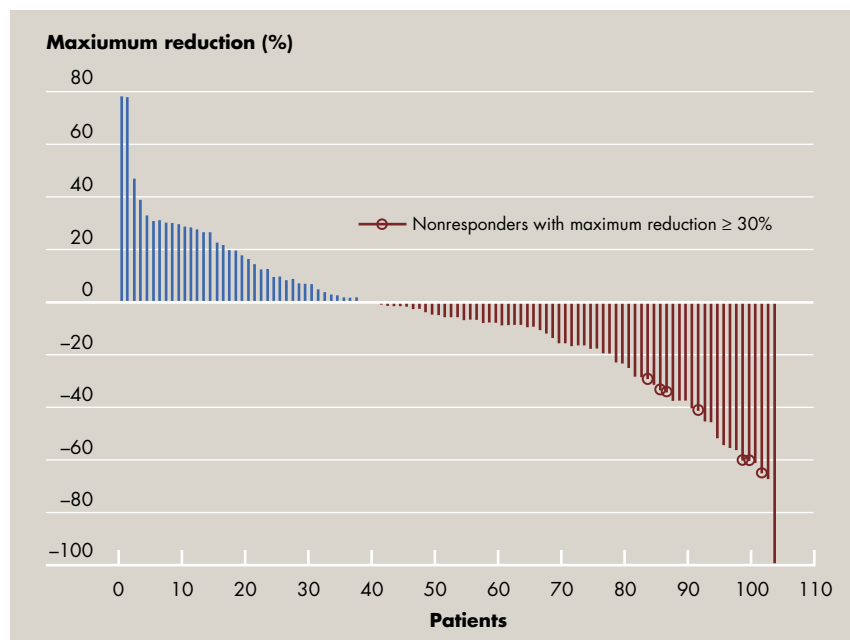
lar to taxanes in their ability to target and stabilize microtubules but are less susceptible to multiple mechanisms of drug resistance. In preclinical evaluations, ixabepilone exhibited activity over a variety of tumors and in drug-resistant cell lines and xenograft

models. It was recently examined in two phase II studies in patients with metastatic breast cancer (MBC).<sup>1,2</sup> The results of one of these trials<sup>2</sup> and a phase III study of ixabepilone in combination with capecitabine (Xeloda)<sup>3</sup> led to the recent regulatory approval of the drug for use in MBC resistant to other chemotherapies.

## Ixabepilone alone as first-line therapy

In one of two phase II trials reported in the *Journal of Clinical Oncology*,<sup>1</sup> 65 women who received prior anthracycline adjuvant therapy were given ixabepilone, 40 mg/m<sup>2</sup>, by 3-hour IV infusion every 3 weeks as first-line treatment for MBC. The median patient age was 52 years. The majority of patients had two or more involved sites (77%) or visceral metastases (85%). In all, 98% of the women had undergone surgery, 89% had received radiation therapy, and 71% had been given hormonal therapy. Patients received a median of 6 treatment cycles

Summary by Matt Stenger, MS; reviewed by Linda D. Bosserman, MD, Wilshire Oncology Medical Group, Inc., La Verne, CA.



**FIGURE 1** Maximum percentage change by target lesion per patient. Adapted, with permission, from Perez et al.<sup>2</sup>

(range, 1–14).

The objective response rate to ixabepilone in this study was 41.5% (partial response in 27 patients); stable disease occurred in 23 patients (35.4%). The median time to tumor response was 6 weeks (range, 5–17 weeks), median time to disease progression was 4.8 months, median duration of response was 8.2 months, and median survival was 22.0 months. Treatment-related adverse events (Table 1) were manageable. Grade 1/2 alopecia occurred in most patients. Mild to moderate, primarily sensory, neuropathy was common and mostly reversible. Grade 3/4 neutropenia occurred in more than half of the patients. Other grade 3/4 nonhematologic toxicities were infrequent.

### Ixabepilone monotherapy for drug-resistant tumors

In the second phase II study,<sup>2</sup> 126 heavily pretreated patients with MBC resistant to anthracyclines (doxorubicin or epirubicin), taxanes (paclitaxel or docetaxel [Taxotere]), and capecitabine (Xeloda) were treated with the same ixabepilone regimen. The median patient age was 51 years. The Karnofsky performance score was 80–90 in 70% of the patients and 100 in 26%. Visceral disease was present in the liver and/or lungs in 86% of the women tested.<sup>4</sup> Prior adjuvant/neoadjuvant therapy had been given to 75% of the women, and 88% had received two or more prior lines of treatment for metastatic disease.

Patients received a median of 4 treatment cycles (range, 1–16). The objective response rate, as assessed by an independent radiology facility (IRF) in 113 evaluable patients, was 12.4% (partial response in 14 patients), with 57 patients (50.4%) having stable disease. According to investigator assessment of the 126 patients receiving treatment, the objective tumor response rate, based on RECIST (Response Evaluation Criteria in Solid Tumors) criteria, was 18.3% (partial response in 23 pa-

tients), with 55 patients (43.7%) having stable disease. Among evaluable patients, 13.3% had stable disease for more than 6 months, median time to response was 6.1 weeks (range, 5–19 weeks), median duration of response was 5.7 months, median progression-free survival was 3.1 months, and median overall survival was 8.6 months.

Figure 1 shows the degree of tumor change in individual patients, indicating marked tumor regression in some of the responders. Tumor response to ixabepilone monotherapy was observed across subgroups prospectively defined for age, hormone receptor status, and presence or absence of liver metastases. Tumors in nine responders had not responded to multiple lines of treatment for metastatic disease. Response occurred in 5 of 42 IRF-assessed patients with tumors that were triply negative for estrogen, progesterone, and HER2 (human epidermal growth factor receptor 2) receptors.

Ixabepilone treatment was well tolerated in this group of patients. Treatment-related adverse events were manageable and mostly low grade (Table 2). Peripheral neuropathy was the most common nonhematologic adverse event. Resolution of grade 3/4 peripheral neuropathy occurred after a median of 5 weeks. Grades 3 and 4 neutropenia occurred in 31% and 23% of patients, respectively.<sup>4</sup>

### Ixabepilone combined with capecitabine

In an open-label phase III study reported at the 2007 Annual Meeting of the American Society of Clinical Oncology,<sup>3</sup> a total of 752 breast cancer patients with metastatic or locally advanced disease resistant to anthracycline and taxane therapy were randomized to receive treatment with ixabepilone (40 mg/m<sup>2</sup> IV over 3 hours every 3 weeks) plus capecitabine (1,000 mg/m<sup>2</sup> twice daily for 14/21 days) or capecitabine (1,250 mg/m<sup>2</sup> twice daily for 14/21 days) alone. The median age was 53 years; 84% of the patients had

**TABLE 1**

Treatment-related adverse events (frequency ≥ 5%) in 65 anthracycline-experienced MBC patients receiving ixabepilone (40 mg/m<sup>2</sup> every 3 weeks)

Adverse event	Percentage of patients with adverse event	
	Any grade	Grade 3/grade 4
<b>Dermatologic/skin</b>		
Alopecia	92	0/0
Rash/desquamation	22	0/0
Nail changes	17	0/0
Other	6	0/0
<b>Pain</b>		
Myalgia	65	8/0
Arthralgia	32	5/0
Headache	14	0/0
Other pain	14	2/0
Neuropathic pain	12	5/0
Abdominal pain/cramping	8	0/0
<b>Gastrointestinal</b>		
Nausea	54	2/0
Stomatitis/pharyngitis	32	5/0
Diarrhea	29	3/0
Vomiting	26	5/2
Constipation	20	0/0
Anorexia	18	0/0
Taste disturbance	11	0/0
<b>Constitutional</b>		
Fatigue	68	6/0
Fever	14	0/0
<b>Neurologic</b>		
Sensory neuropathy	71	20/0
Motor neuropathy	6	5/0
<b>Infection/febrile neutropenia</b>		
Infection without neutropenia	14	2/0
Infection with grade 3/4 neutropenia	6	6/0
<b>Hematologic (worst grade)</b>		
Leukopenia	92	42/8
Anemia	92	3/0
Neutropenia	89	27/31
Thrombocytopenia	40	0/0

MBC = metastatic breast cancer

Adapted from Roché et al<sup>1</sup>

visceral disease, 48% had received one prior treatment, and 43% had received two or more prior lines of therapy for metastatic disease. Patients in the combination arm received a median of 5 cycles of treatment, whereas those in

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*From the Community Oncologist's Perspective*

## Ixabepilone: another first down on the way to the goal line in breast cancer therapy

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**W**ith the US Food and Drug Administration's October approval of ixabepilone (Ixempra) as a treatment option for metastatic breast cancer (MBC), the question for oncologists becomes how and when to best use this promising, first-in-class, semisynthetic epothilone B analog. In a disease blessed with many potentially effective agents, we now have to determine where this new agent can be used to accomplish our main goal—defining a treatment plan that meaningfully and tolerably prolongs disease control and survival until we find a cure.

No other agent to date has been shown to produce a significant response in MBC patients whose disease has progressed on an anthracycline, a taxane, and capecitabine (Xeloda). The 12%–18% response rate associated with ixabepilone, which seems to occur in the first 2–4 treatment cycles, and the nearly 9-month median survival afforded by the drug make it the best option for this group of patients. For patients with a good performance status whose disease has progressed after treatment with the standard therapies, ixabepilone offers the best proven alternative to prolong their lives. Having an agent that offers a 62% chance of response or stable disease (whether judged by the treating physician or an independent, blinded reviewer) after documented progression on the three other agents gives us another reason to offer further lines of therapy to heavily pretreated patients. The fact that nine responders to ixabepilone had not previously responded to our three most-powerful

agents against breast cancer is particularly notable, as is the observation that some triple-negative tumors—tumors that were estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) negative—responded. These findings can't help but encourage us to pursue more trials of earlier therapeutic uses of ixabepilone with the hope that its new and unique mechanism of action can improve outcomes in less heavily pretreated patients.

In the phase II study reported by Roché et al, who tested ixabepilone as first-line therapy of MBC in patients who had received adjuvant anthracycline therapy, the overall response rate (partial responses plus stable disease) was 77%. Although this rate is nice, it doesn't seem that overwhelming when you note that median survival was only 22 months, the same as we have come to expect for first-line therapies of MBC. In fact, noting that 71% of the patients in the study had received hormone therapy earlier, based, hopefully, on confirmed ER or PR positivity, would have led to an expectation of at least 2-year survival in that subgroup.

Further information from this study is necessary. Were the patients offered further hormone therapy or further chemotherapy, and could that explain the lack of longer survival? Or, did the ER-, PR-, and ER-/PR-/HER2- patients not respond, leading to an overall lower survival rate? Are there some subgroups of patients who do significantly better with ixabepilone and others who respond but not as well?

As a community oncologist, my

take is that ixabepilone is a particularly promising new drug with tolerable and manageable toxicities that can, for some patients, add a significant benefit. As we read more and more about molecular profiling, these studies should encourage us to push strongly for research into predictive models for the growing armamentarium of drugs that are effective in breast cancer. We all know that some of our patients can go 10 years or more with sequential therapies that are each able to shrink or control their disease for some meaningful period. When this time runs out and we should stop is a moving target, as we've all seen heavily pretreated patients respond once again and gain another 6–9 months of life. It becomes more and more difficult for us to unequivocally say, "There is no further therapy likely to prolong your life. We must move on to supportive care only." In fact, my long-lived patients with metastatic disease are the ones who say that they've known they are terminal since they were first diagnosed, but their willingness to keep trying new therapies has kept them alive. So why not try the next agent available, even if it has less than a 10% chance of providing benefit that outweighs its toxicity?

Development of effective molecular models is clearly on our therapeutic horizon. They can't be developed fast enough so that payers, doctors, and patients can have realistic expectations about which patients with which tumor types may benefit while sparing toxicities for those who will not benefit. I know first hand from the nine patients I had in Dr. Perez's study of heavily pretreated patients

whether they responded or not or suffered more neurosensory pain or low blood counts. Every patient and her family remained grateful for the opportunity to participate in this clinical trial and would enter another, if available, in the hope of delaying death. We should welcome ixabepilone into our assortment of treatment options

for MBC while encouraging research into its molecular biology to guide us better to the most effective use and sequencing of our growing therapeutic armamentarium, not only in breast cancer but other tumors as well. Ixabepilone is clearly another first down toward our goal of curing MBC.

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## Ixabepilone in MBC

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the capecitabine-monotherapy arm received 4 cycles.

Progression-free survival (defined as time to radiologic progression, clinical progression of measurable skin lesions, or death from any cause) was superior in the group receiving capecitabine with ixabepilone compared with the group receiving capecitabine alone (5.7 months vs 4.1 months; hazard ratio, 0.69;  $P < 0.0001$ ). The objective tumor response rate, as determined by RECIST criteria, was also superior in the combination-treatment arm (34.7% vs 14.3% for capecitabine monotherapy), as was the median duration of response (6.4 months vs 5.6 months, respectively). Overall survival data are not yet available from this trial.

Peripheral neuropathy was common in the group treated with both drugs. In all, 65% of patients receiving ixabepilone in addition to capecitabine experienced sensory neuropathies and 16% reported motor neuropathies, compared with 16% and < 1% of those who had been given capecitabine alone. Other adverse reactions that were seen more frequently in the combination-therapy arm than in the monotherapy arm included fatigue/asthenia (60% vs 29%), nausea (53% vs 40%), diarrhea (44% vs 39%), leukopenia (41% vs 5%), vomiting (39% vs 24%), myalgia/arthralgia (39% vs 5%), neutropenia (32% vs 9%), alopecia (31% vs 3%), stomatitis/mucositis (31% vs 20%), and musculoskeletal pain (23% vs 5%).

Subgroup analyses of poor-prog-

nosis patients with HER2+ tumors, revealed at the 2007 Breast Cancer Symposium in September, substantiated the superiority of ixabepilone/capecitabine combination therapy over capecitabine alone in HER2+ breast cancer patients whose disease has progressed after prior anthracycline/taxane treatment.<sup>5</sup> Further, the improvement in progression-free survival and overall response rates seen in the entire study population was independent of estrogen-receptor status.<sup>6</sup>

### References

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6. Pivot XB, Lee RK, Thomas ES, et al. Phase III study of ixabepilone plus capecitabine in patients with metastatic breast cancer (MBC) resistant to anthracyclines/taxanes: subgroup analysis by estrogen receptor (ER) status. Presented at the 2007 Breast Cancer Symposium; September 7-8, 2007; San Francisco, Calif. Abstract 221.

**TABLE 2**

Treatment-related adverse events (frequency  $\geq 5\%$ ) in 126 MBC patients with anthracycline-, taxane-, and capecitabine-resistant disease receiving ixabepilone (40 mg/m<sup>2</sup> every 3 weeks)

Adverse event	Percentage of patients with adverse event	
	Any grade	Grade 3/grade 4
<b>Nonhematologic</b>		
Peripheral sensory neuropathy	60	13/1
Fatigue/asthenia	50	13/1
Myalgia/arthralgia	49	8/0
Alopecia	48	0/0
Nausea	42	2/0
Stomatitis/mucositis	29	6/1
Vomiting	29	1/0
Diarrhea	22	1/0
Musculoskeletal pain	20	3/0
Anorexia	19	2/0
Constipation	16	2/0
Abdominal pain	13	2/0
Headache	11	0/0
Peripheral motor neuropathy	10	1/0
Dyspnea	9	1/0
Nail disorder	9	0/0
Pain	8	3/0
Palmar-plantar erythrodysesthesia syndrome	8	2/0
Pyrexia	8	1/0
Dizziness	7	0/0
Dysgeusia	6	0/0
Gastroesophageal reflux	6	0/0
Hot flush	6	0/0
Hypersensitivity	5	1/0
<b>Hematologic*</b>		
Leukopenia	90	36/13
Anemia	84	6/2
Neutropenia	79	31/23
Thrombocytopenia	44	6/2

\* Worst on-study grade by National Cancer Institute Common Toxicity Criteria

MBC = metastatic breast cancer

Adapted from Perez et al<sup>2</sup>

From the Administrator's Desk

## Preparing your practice to use a new cancer therapy

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**I**n today's payment environment, the US Food and Drug Administration's (FDA) approval of a new cancer therapy sets off a definable series of steps for the practice administrator to properly prepare your organization for treating patients. With the wonderful new drug pipeline we have experienced these past 10 years, it became prudent to develop a standardized list of the information needed to accomplish this. The summary downloadable from *Community Oncology's* Web site ([www.communityoncology.net/journal/0411.html](http://www.communityoncology.net/journal/0411.html)) was filled out for ixabepilone (Ixempra) 2 days after the FDA approved it on October 26. When new drugs become available, information about them needs to be disseminated to every level of the practice, not just the patient.

**Doctors** need to know the FDA indications to ensure that the proper patients are offered the new therapy. They need a list of the most common side effects and any unusual ones, as well as any dosing modifications to adjust for laboratory abnormalities, concomitant medications, or concurrent illnesses. Increasingly, doctors also need information on the cost of new therapies and how that might impact patients when they evaluate one regimen against another. In the case of ixabepilone, with its unique efficacy when standard breast cancer drugs have failed, no doubt many patients will be eager to have access to this promising therapy.

**Nurses/pharmacists** need to know the type and level of expected side effects to prepare and monitor their patients. They also need a sense of the requirements for nausea control (Hes-

keth level), as well as other common side effects. And, they need administration instructions, dosing ranges, and any special administration requirements (handling instructions, infusion time, special tubing or bags, etc).

**Patients** need to know the dosing schedule and potential side effects, what to watch for, and what to do if common symptoms occur. They also need to know about the cost of the medication and coverage benefits of their health plan to prepare for co-pays and other costs. Many patients also need information about options for co-pay assistance or free-care coverage. They want to have written material about the drug, which may be only the package insert when a drug first becomes available. Important information can be highlighted by the nurse or practitioner during the teaching visit.

**Billing/collection staff** need to know the dosing units, associated supplies, and common administration codes associated with delivery of the drug.

**Authorization staff** need to know the FDA indications for the drug so that they can ensure the patient meets the criteria for coverage; the codes for the diseases associated with the use(s) of the drug; the common indications for the drug either alone or in combination with other drugs; the common dose ranges or common range of vials used; and the common support medications needed to control nausea, anemia, neutropenia, hypersensitivity, or other adverse reactions that have to be pre-authorized with the regimen.

**Administrators** have to know that a new therapy is available and what it

will be used for to get a sense of how common the drug will be used in their practice, in order to program drug-ordering systems. Administrators need contact information for drug and support information, free-care programs, drug-replacement program requirements, co-pay assistance plans, and other therapeutic indications that might be covered under a drug-replacement plan *if* an accepted, but not yet FDA approved, use is given but payment is denied by the insurer. Price is also key for anticipating the impact of increased drug inventory costs on the practice.

Administrators ensure that nursing in-service training is scheduled and that nurses get the support they need to be comfortable administering a new drug that might have unique or novel toxicities. It is great when the drug has been given as part of a clinical trial, as ixabepilone was in our practice, so that a few nurses on staff will have had hands-on experience that they can share with other nurses. As helpful as this is, however, we had ixabepilone in the FDA approval trial back in mid- to late-2004. Now, 3 years later, many of the daily details of that experience need refreshing.

When doctors hear hoof beats, it is often those of patients wanting access to the latest new "zebra" drug with the hope of a better outcome. When administrators hear hoof beats about a new drug, however, we know the stampede of our care teams is about to trample us with calls unless we prepare ahead in a comprehensive way. I hope sharing our approach can help you keep everyone contented and out to pasture!

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