Ixabepilone in Metastatic Breast Cancer: Complement or Alternative to Taxanes?
Antoinette R. Tan and Deborah L. Toppmeyer

Targeting the microtubule is a successful strategy in the treatment of solid tumors. There is an ongoing effort to develop newer agents that can stabilize microtubules with improved efficacy and tolerability. Epothilones represent a novel group of microtubule inhibitors that were isolated from the myxobacterium Sorangium cellulosum in the 1990s (1). They are naturally occurring macrolides that are structurally different from the taxanes. Crystallographic studies show that epothilones and taxanes compete for the same binding site on β-tubulin, but the actual binding interaction is different (2). Both taxanes and epothilones promote microtubule assembly; however, epothilones A and B are 2.5-fold more potent than paclitaxel in promoting tubulin polymerization (3). In addition, preclinical studies show that epothilones have low susceptibility to mechanisms of drug resistance. Specifically, epothilones are poor substrates for P-glycoprotein and multi-drug resistance–associated protein 1, and their cytotoxic potential is not affected by mutations in β-tubulin or alterations in tau, a microtubule-associated protein that promotes tubulin stabilization (4, 5).

Ixabepilone (Ixempra, Bristol-Myers Squibb) is the first epothilone to be approved by the Food and Drug Administration (FDA). Ixabepilone is indicated for the treatment of metastatic breast cancer as monotherapy in patients whose tumors are resistant to anthracyclines, taxanes, and capecitabine, and in combination with capecitabine in patients whose disease progresses after an anthracycline and taxane. A semisynthetic second-generation epothilone B analogue, ixabepilone (aza-epothilone B, BMS-247550), is formulated in Cremophor EL. It differs in structure from the natural epothilone in that an oxygen atom is replaced by a nitrogen atom on the macrolide ring, a chemical modification that improves the metabolic stability of the natural product. Preclinical studies show that ixabepilone has significant antitumor activity compared with paclitaxel in paclitaxel-resistant tumor models (3). There are several other epothilones in clinical trials that are not yet FDA approved and are being evaluated for the treatment of breast cancer. These include patupilone (natural epothilone B; EPO906), KOS-1584 (epothilone D analogue), BMS-310705 (water-soluble epothilone B analogue), and sagopilone (ZK-EPO, synthetic third-generation epothilone; refs. 6–12).

Several schedules of ixabepilone have been studied in phase I trials, including daily administration for 3 or 5 days as a 1-h infusion every 3 weeks, as a 3-h infusion every 3 weeks, and weekly dosing (13–16). Neutropenia was dose-limiting on all schedules, and sensory neuropathy less prominent with a daily and weekly schedule. The FDA-approved dose of ixabepilone for metastatic breast cancer is 40 mg/m² as a 3-h i.v. infusion every 3 weeks as monotherapy and in combination with capecitabine.

Several phase II trials of ixabepilone as monotherapy have been conducted in different subsets of patients with advanced breast cancer. Ixabepilone on an every 3-week and daily schedule has shown activity in a population with minimal prior exposure to taxanes. Roché et al. (17) evaluated ixabepilone as first-line therapy in 65 patients with metastatic breast cancer who had received prior adjuvant anthracycline. Ixabepilone was administered at 40 mg/m² as a 3-h infusion every 3 weeks. Only 17% had received a taxane as part of an adjuvant regimen (≥1 year from the last dose). The overall response rate was 41.5% [95% confidence interval (95% CI), 29.4-54.4%]; partial responses occurred in 27 patients. Prominent adverse events included neutropenia (grade 3, 27%; grade 4, 31%) and sensory neuropathy (grade 3, 20%; grade 4, 0%). In a single center phase II study by Denduluri et al. (18), ixabepilone was administered at 6 mg/m² daily for 5 days as a 1-h infusion every 3 weeks to 23 patients with metastatic breast cancer with no prior taxane exposure. The overall response rate was 57% (95% CI, 34.5-76.8%); 13 patients had partial responses and 6 patients had stable disease for at least 6 weeks, which is indicative of ixabepilone antitumor activity in taxane-naïve patients. Major toxicities included grade 4 neutropenia (13%) and grade 3 fatigue (13%). There were no grade 3 or 4 sensory neuropathy events.

Several phase II trials were conducted in metastatic breast cancer patients previously treated with taxanes. In a single institution trial, 37 patients received ixabepilone 6 mg/m² daily for 5 days as a 1-h infusion every 3 weeks (19). All patients had at least one previous treatment with paclitaxel or docetaxel in the neoadjuvant, adjuvant or metastatic setting. The overall response rate was 22% (95% CI, 9.8-38.2%) including one complete response. At this same center, a 3-day schedule of ixabepilone at 8 mg/m² every 3 weeks was investigated in 12 patients with prior taxane exposure (20). No responses were observed, suggesting the inferiority of this alternate schedule. Neutropenia and sensory neuropathy were notable toxicities on both studies. Thomas et al. (21) conducted a study in 49 patients pretreated with taxanes who were given ixabepilone at 40 mg/m² as a 3-h infusion every 3 weeks. This trial initially
treated patients at 50 mg/m² as a 1-h infusion, but the dose was decreased to 40 mg/m² due to neurotoxicity and the duration was increased to 3 hours after increased myelosuppression and mucositis were reported from other studies. The inclusion criteria were strictly defined as progression on docetaxel or paclitaxel as the most recent therapy or within 4 months of the last dose or within 6 months of adjuvant taxanes. The majority of patients (86%) had undergone two or more prior cytotoxic regimens; 98% had received a taxane as the most recent metastatic treatment and 73% had experienced disease progression within 1 month of the last dose of taxane. The response rate was 12% (95% CI, 4.7-26.5%; all partial responses). Prominent adverse events included neutropenia (grade 3, 33%; grade 4, 20%), fatigue (grade 3, 27%), and gastrointestinal disturbances (grade 3, 20%). Grade 3 sensory neuropathy occurred in 12% of patients. Such studies are suggestive of at least partial non–cross-resistance between ixabepilone and other microtubule-targeting agents.

The basis for FDA approval of ixabepilone as a single agent was an international, multicenter phase II trial conducted in 126 metastatic breast cancer patients whose disease was resistant to anthracyclines, taxanes, and capecitabine (22). Resistance to each agent was defined as progressive disease within 8 weeks of last dose of drug in the metastatic setting or recurrence within 6 months of adjuvant or neoadjuvant anthracycline or taxane therapy. Approximately 88% of patients had received two or more prior chemotherapy regimens for metastatic disease. Ixabepilone was administered at 40 mg/m² as a 3-h infusion every 3 weeks. The overall response rate based on independent radiologic review was 11.5% (95% CI, 6.3-18.9%); 13 of 113 patients had a partial response. In addition, 13% experienced stable disease for ≥6 months. Similar to the other trials, neutropenia (grade 3, 31%; grade 4, 23%), sensory neuropathy (grade 3, 13%; grade 4, 1%), and fatigue (grade 3, 13%; grade 4, 1%) were prominent. Based on these results, ixabepilone has efficacy in metastatic breast cancer that is “triple-refractory,” or disease that has progressed after an anthracycline, taxane, and capecitabine.

Anthracyclines and taxanes are the mainstay of adjuvant therapy as well as the cornerstone for treatment of metastatic breast cancer. Capecitabine is the only drug approved as monotherapy for patients whose tumor is resistant to an anthracycline and paclitaxel, or paclitaxel resistant (defined as progressive disease while on treatment with or without an initial response) and whom further anthracycline therapy is contraindicated (23). The rationale for testing the combination of ixabepilone and capecitabine is based on their distinct mechanisms of actions and nonoverlapping toxicities. Phase I/II results revealed that the combination was tolerable and showed antitumor activity (24).

The FDA approval for combination therapy was based on the results of a phase III trial conducted in anthracyline- and taxane-resistant metastatic breast cancer. Seven hundred fifty-two patients were randomized 1:1 to receive either 40 mg/m² of ixabepilone as a 3-h infusion every 3 weeks and 2,000 mg/m²/d of oral capecitabine in divided doses days 1 to 14 every 3 weeks (375 patients) or oral capecitabine alone 2,500 mg/m²/d in divided doses on days 1 to 14 every 3 weeks (377 patients; refs. 25, 26). The primary end point was progression-free survival. There were predefined strict inclusion criteria for chemotherapy resistance. Anthracycline and taxane resistance was defined as tumor progression while on treatment or within 3 months of the last dose in the metastatic setting, or recurrence within 6 months of the last adjuvant or neoadjuvant dose. Patients who were not resistant to anthracyclines but had received a minimum dose of 240 mg/m² doxorubicin or 360 mg/m² epirubicin were eligible. Prior capecitabine was not permitted. After 377 patients were enrolled, the definition of taxane resistance was broadened to progression within 4 months of the last dose in the metastatic setting or within 12 months of the last adjuvant or neoadjuvant dose. Approximately, 40% of patients had received two prior chemotherapy regimens before enrollment on both arms. The combination achieved a higher response rate (35% versus 14%; P < 0.0001) and increased median progression-free survival (5.7 versus 4.1 months; hazard ratio, 0.69; 95% CI, 0.58-0.83; P < 0.0001). Overall survival data were not reported at the time of this publication. Peripheral sensory neuropathy and myelosuppression were more common with the combination. Notably, ixabepilone did not potentiate capecitabine-associated toxicities.

There were 12 treatment-related deaths on the combination arm attributed to neutropenia in patients with abnormal liver function tests (grade ≥2 in five patients and grade 0/1 in seven patients). In patients with hepatic impairment, increases in ixabepilone exposures have been observed (27). According to the FDA, ixabepilone and capecitabine are contraindicated in patients with liver dysfunction defined as aspartate aminotransferase or alanine aminotransferase >2.5 × upper limit of normal or bilirubin >1 × upper limit of normal secondary to increased risk of toxicity and neutropenia-related death. In addition, ixabepilone monotherapy is not recommend in patients with aspartate aminotransferase or alanine aminotransferase >10 × upper limit of normal or bilirubin >3 × upper limit of normal.

Ixabepilone expands the treatment choices for patients with metastatic breast cancer. Results from this phase III study show the activity of epothilones in anthracycline- and taxane-pretreated breast cancer (25). However, the trial does not answer the question of whether combination therapy provides superior activity over sequential treatment, as this was not a crossover design. Other phase III doublet trials combining a microtubule-targeting drug with an antimetabolite have also shown superiority compared with a single agent, including docetaxel/capecitabine versus docetaxel and paclitaxel/gemcitabine versus paclitaxel (28, 29), but prospective, randomized studies with planned crossover therapy have shown that upfront combination versus sequential single-agent treatment does not confer a survival advantage (30, 31).

Compared with both paclitaxel and docetaxel, administration of ixabepilone does not necessitate corticosteroids (unless a hypersensitivity reaction occurs), but premedication with histamine blockers is required. This is a distinct advantage compared with paclitaxel and docetaxel. A major question is whether ixabepilone is superior to either of the solvent-based taxanes or nanoparticle formulation of paclitaxel (i.e., nab-paclitaxel). Head-to-head comparison studies of ixabepilone with taxanes are under way. A randomized phase II trial of two schedules of ixabepilone (weekly × 3 every 4 weeks versus every 3 weeks) plus bevacizumab compared with paclitaxel (weekly × 3 every 4 weeks) plus bevacizumab as first-line therapy for patients with locally recurrent or metastatic breast cancer is completed (NCT00370552). The IXTEND trial is a randomized
phase II study evaluating the combination of ixabepilone and capcitabine compared with docetaxel and capcitabine in patients who have had more than one prior treatment regimen (NCT00546364). There is a planned phase III trial that will evaluate paclitaxel/bevacizumab versus nab-paclitaxel (Abraxane)/bevacizumab versus ixabepilone/bevacizumab as first-line treatment in patients with metastatic breast cancer.

Ixabepilone has also been combined with human epidermal growth factor receptor type 2 (HER2) targeted therapy. The Eastern Cooperative Oncology Group (E2103) evaluated ixabepilone at 15 mg/m² and carboplatin (area under the curve, 2) given weekly on days 1, 8, and 15 of a 28-day cycle with weekly trastuzumab in 59 patients with HER2-positive metastatic breast cancer as first-line therapy (32). The overall response rate was 44% (3 complete responses and 23 partial responses) with a median progression-free survival of 8.0 months. This is comparable to other taxane/trastuzumab combinations (27% versus 9%) and median progression-free survival (4.1 versus 2.1 months) in the cohort of triple-negative patients (33). A randomized phase II trial is being conducted in patients with triple-negative metastatic breast cancer as first-line therapy comparing ixabepilone versus ixabepilone and cetuximab (NCT00633464) with the latter drug chosen to target epidermal growth factor receptor, which is overexpressed in this subtype.

With promising activity in the metastatic setting, ixabepilone as a single agent has been evaluated as neoadjuvant therapy. A total of 161 patients with tumors measuring 3 cm or more were treated with ixabepilone 40 mg/m² as a 3-h infusion every 3 weeks for four cycles (34). The pathologic complete response

### Table 1. Select clinical trials of ixabepilone in metastatic breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Disease characteristics</th>
<th>Prior regimes</th>
<th>No. of pts</th>
<th>Dose and schedule</th>
<th>Clinical outcomes</th>
<th>Peripheral sensory neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roché et al. (17)</td>
<td>II</td>
<td>Prior anthracycline</td>
<td>0</td>
<td>65</td>
<td>Ixabepilone 40mg/m² q3w</td>
<td>ORR, 41.5%; SD, 35%; TTP, 4.8 mo</td>
<td>20 (all grade 3)*</td>
</tr>
<tr>
<td>Low et al. (19)</td>
<td>II</td>
<td>No prior taxane</td>
<td>No limit</td>
<td>23</td>
<td>Ixabepilone 6mg/m² daily for 5 d q3w</td>
<td>ORR, 57%; SD, 26%; TTP, 5.0 mo</td>
<td>13 (grade 2)</td>
</tr>
<tr>
<td>Denduluri et al. (20)</td>
<td>II</td>
<td>Prior taxane (adjuvant, neoadjuvant, or metastatic)</td>
<td>No limit</td>
<td>37</td>
<td>Ixabepilone 6mg/m² daily for 5 d q3w</td>
<td>ORR, 22%; SD, 35%; TTP, 2.6 mo</td>
<td>22 (grade 2)</td>
</tr>
<tr>
<td>Perez et al. (22)</td>
<td>II</td>
<td>Prior taxane in the metastatic setting</td>
<td>Up to 3</td>
<td>49</td>
<td>Ixabepilone 40mg/m² q3w</td>
<td>ORR, 12%; SD, 41%; TTP, 2.2 mo</td>
<td>33 (grade 2)</td>
</tr>
<tr>
<td>Thomas et al. (21)</td>
<td>II</td>
<td>Resistant to anthracycline, taxane, and capcitabine</td>
<td>Up to 3</td>
<td>126</td>
<td>Ixabepilone 40mg/m² q3w</td>
<td>ORR, 11.5%; SD, 13%; PFS, 3.1 mo</td>
<td>30 (grade 2)</td>
</tr>
<tr>
<td>Thomas et al. (25, 26)</td>
<td>III</td>
<td>Prior anthracycline, resistant to anthracycline, and resistant to taxane</td>
<td>Up to 3</td>
<td>752</td>
<td>Ixabepilone 40mg/m² q3w and capcitabine 2,000mg/m²/D1-14 vs capcitabine 2,500mg/m²/D1-14</td>
<td>ORR, 35% vs 14% for capcitabine arm (P &lt; 0.0001) PFS, 5.7 mo vs 4.1 mo for capcitabine arm (P &lt; 0.0001)</td>
<td>27 vs 4 (grade 2)</td>
</tr>
<tr>
<td>Moulder et al. (32)</td>
<td>II</td>
<td>HER2 positive; no prior treatment</td>
<td>0</td>
<td>59</td>
<td>Ixabepilone 15mg/m² and carboplatin (AUC, 2)D1, 8, and 15 q4w, and trastuzumab weekly during CT then q3w for 6 cycles</td>
<td>ORR, 44%; PFS, 8.0 mo</td>
<td>7 (all grade 3)*</td>
</tr>
</tbody>
</table>

Abbreviations: Pts, patients; ORR, overall response rate; SD, stable disease; TTP, time to progression; PFS, progression-free survival; AUC, area under the curve; CT, chemotherapy.

*Grade 2 neuropathy not reported.
rate in the breast was 15%. Previous studies of single agent taxane given in the neoadjuvant setting yield a pathologic complete response rate in the range of 9% to 12.5% (35). Interestingly, in the triple-negative subset the pathologic complete response rate in the breast was 26%. Pretreatment core biopsies were obtained for gene expression profiling, and low expression of estrogen receptor was the most significant predictor for pathologic complete response to ixabepilone (36).

Pharmacogenomic analysis has identified a group of molecular markers that could potentially differentiate sensitivity to paclitaxel versus ixabepilone (37). In this advancing era of personalized cancer therapy, identification of subgroups most likely to benefit from ixabepilone is the ideal strategy. A phase II trial is under way to validate these biomarkers prospectively. In this study, 300 patients with triple-negative breast tumors ≥2 cm will be treated with neoadjuvant doxorubicin and cyclophosphamide for four cycles and then randomized to four cycles of ixabepilone every 3 weeks or weekly paclitaxel for 12 weeks. The primary aim is to identify a gene expression profile that predicts pathologic complete response to paclitaxel compared with ixabepilone (NCT00455533).

Ixabepilone is also undergoing evaluation in the adjuvant setting, but an important consideration is neurotoxicity. Similar to other microtubule agents, neuropathy is the most significant side effect (Table 1). In the phase III trial, grade 2 peripheral sensory neuropathy occurred in 27% of patients on the combination versus 4% with single agent capcitabine. Grade ≥3 neuropathy occurred in ~20% of patients receiving the combination versus 0% with capcitabine alone. This was cumulative, but reversible with a median resolution time to grade 1 in 6 weeks after dose reduction. In the phase II trials, grade 2 neuropathy occurred in 22% to 33% of patients pretreated with taxanes compared with 13% in taxane-naïve patients. In the adjuvant setting, ixabepilone would be given for a finite number of cycles and possibly on a weekly schedule, thereby reducing the occurrence of neuropathy. In addition, a cremophor-free formulation of ixabepilone has undergone phase I testing as a 24-hour infusion every 3 weeks and might be a potential alternative (38). The efficacy and tolerability of ixabepilone as adjuvant treatment will be tested in a large trial, PACS-08, which will randomize 2500 patients with stage II or III triple-negative breast cancer to 5-fluorouracil, epirubicin, and cyclophosphamide (FEC100) for three cycles followed by either docetaxel for three cycles or ixabepilone for three cycles (NCT00630032).

In summary, we have expanded the treatment choices in metastatic breast cancer to include the novel combination of ixabepilone and capcitabine in anthracycline- and taxane-pretreated patients. Furthermore, single agent ixabepilone given as sequential treatment after progression from an anthracycline, taxane, and capcitabine is an alternative therapeutic option for patients with triple-refractory disease. Until comparison trials are completed, ixabepilone complements our current armamentarium of chemotherapy. Future studies will define the optimal position of ixabepilone in the treatment of early and advanced breast cancer.

References

3. Lee FY, Bortzisser R, Fairchild CR, et al. BMS-247550: combination versus 0% with capcitabine alone. This was 2% with single agent capcitabine. Grade 3 neuropathy occurred in 27% of patients on the combination versus 4% with single agent capcitabine. Grade ≥3 neuropathy occurred in ~20% of patients receiving the combination versus 0% with capcitabine alone. This was cumulative, but reversible with a median resolution time to grade 1 in 6 weeks after dose reduction. In the phase II trials, grade 2 neuropathy occurred in 22% to 33% of patients pretreated with taxanes compared with 13% in taxane-naïve patients. In the adjuvant setting, ixabepilone would be given for a finite number of cycles and possibly on a weekly schedule, thereby reducing the occurrence of neuropathy. In addition, a cremophor-free formulation of ixabepilone has undergone phase I testing as a 24-hour infusion every 3 weeks and might be a potential alternative (38). The efficacy and tolerability of ixabepilone as adjuvant treatment will be tested in a large trial, PACS-08, which will randomize 2500 patients with stage II or III triple-negative breast cancer to 5-fluorouracil, epirubicin, and cyclophosphamide (FEC100) for three cycles followed by either docetaxel for three cycles or ixabepilone for three cycles (NCT00630032).

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