

# Management of advanced breast cancer with the epothilone B analog, ixabepilone

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**Abstract:** Despite the activity of standard chemotherapies in advanced breast cancer, disease progression remains inevitable. Most patients exposed to anthracyclines and taxanes develop resistance and a significant subset shows primary resistance. The increasing use of these agents as adjuvant therapy may result in more anthracycline- and taxane-resistant patients in the metastatic setting; few treatment options are available for patients with metastatic breast cancer (MBC) resistant to multiple chemotherapies. The heterogeneity of breast cancer represents another therapeutic challenge. Breast cancers may be classified as luminal, human epidermal growth factor 2 (HER2)-positive, or estrogen receptor-, progesterone receptor-, and human epidermal growth factor 2-negative (ER/PR/HER2-negative, triple negative). HER2-positive and ER/PR/HER2-negative tumors are associated with poor prognosis owing to aggressive disease and poor long-term response to therapy. The epothilone B analog ixabepilone has low susceptibility to multiple mechanisms of resistance and has demonstrated activity in patients with MBC resistant to anthracyclines, taxanes, and/or capecitabine. Ixabepilone is the first epothilone to be approved, as monotherapy or in combination with capecitabine, for treatment of resistant/refractory MBC or locally advanced breast cancer. Treatment with ixabepilone is an option for patients with ER/PR/HER2-negative or HER2-positive disease and/or primary resistance to taxanes.

**Keywords:** breast cancer, drug resistance, epothilone, HER2-positive, ixabepilone, ER/PR/HER2-negative (triple negative)

## Introduction

In the United States, an estimated 184,450 new cases of breast cancer will be diagnosed in 2008. Of these, almost 41,000 patients are expected to die from the disease.<sup>1</sup> Approximately 10% of patients have metastatic disease at the time of diagnosis, and 20% to 85% of patients with early-stage breast cancer will eventually develop metastatic disease.<sup>2,3</sup> Patients with metastatic breast cancer (MBC) treated with anthracycline- and/or taxane-based chemotherapy,<sup>3</sup> have overall response rates (ORR) of 32% to 68%.<sup>4,5</sup> However, the benefits are relatively short-lived; median duration of response (DOR) ranges from 8 to 14 months,<sup>2</sup> median survival is 2 to 3.5 years,<sup>2,3</sup> and the 5-year survival rate is approximately 27%.<sup>6</sup> Progression of MBC remains inevitable, and the majority of patients will eventually die of the disease.<sup>7</sup>

One significant factor that limits the efficacy of standard therapies for MBC is multidrug resistance (MDR), which can be either primary (preceding drug exposure) or acquired resistance (induced by treatment).<sup>4</sup> Drug resistance is considered the cause of treatment failure in more than 90% of all patients with metastatic cancer.<sup>8</sup> Mechanisms

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of MDR include overexpression of  $\beta$ III-tubulin isotypes, and drug efflux transporters such as P-glycoprotein (P-gp) and multidrug resistance protein 1 (MRP1).<sup>9</sup>

Altered expression of  $\beta$ III-tubulin in cancer cells is associated with increased resistance to microtubule inhibitors such as the taxanes.<sup>10</sup> Overexpression of  $\beta$ III-tubulin alters microtubule assembly properties in vitro, resulting in a slower rate of polymerization and decreasing sensitivity to the microtubule-stabilizing taxanes.<sup>11</sup> The decrease in sensitivity to paclitaxel in  $\beta$ III-tubulin overexpressing cells appears associated with reduced binding to  $\beta$ III-tubulin and/or the inability to induce conformational changes that suppress microtubule dynamics.<sup>12</sup> Molecular modeling studies predict that paclitaxel binds to  $\beta$ III-tubulin with reduced affinity versus  $\beta$ I-tubulin.<sup>13</sup>

Increased levels of  $\beta$ III-tubulin have been observed in many tumor types, including breast, lung, ovarian, pancreatic, and prostate cancer cell lines.<sup>10</sup> A univariate analysis in MBC showed a predictive correlation between  $\beta$ III-tubulin expression and clinical response to paclitaxel-based chemotherapy.<sup>14</sup> Patients with lower levels of  $\beta$ III-tubulin had improved tumor control following treatment with paclitaxel than those with high expression of  $\beta$ III-tubulin. Increased  $\beta$ III-tubulin expression has also been associated with poor prognosis as well as shorter progression-free and overall survival in patients with breast, lung, and ovarian cancers.<sup>10,14,15</sup>

Drug efflux transporters reduce intracellular concentrations of hydrophobic drugs such as anthracyclines and taxanes by pumping them out of cells.<sup>9</sup> Strong evidence of the role of these proteins in drug resistance has been obtained using tumor cell lines and animal models.<sup>9</sup> However, evaluation of their role in development of clinical drug resistance has been hampered by differences in methods used to assess their expression and by the heterogeneity of tumor specimens used for analysis.<sup>16</sup> It is important to stress that analysis of a single mechanism does not fully capture the complex interactions between multiple cellular pathways that are necessary to produce the MDR phenotype. Additionally, it is likely that a number of mechanisms with important roles in development of drug resistance remain to be elucidated. Nonetheless, several lines of evidence strongly support an important role for drug efflux transporters in the development of clinical drug resistance. The proteins have been shown to be overexpressed in many human tumor types and their expression is associated with acquisition of drug resistance and with poor response to chemotherapy. Additionally, increased expression levels of P-gp and MRP-1 occur following exposure to chemotherapy in both normal and tumor cells.<sup>17,18</sup>

A meta-analysis of trials in breast cancer demonstrated that over 40% of untreated breast tumors express P-gp (41.2%) and MRP-1 (49%) as assessed by immunohistochemistry (IHC).<sup>19</sup> When assessed using polymerase chain reaction (PCR), expression of P-gp and MRP-1 was detected in 61% and 98% of untreated breast tumors, respectively.<sup>19</sup> Importantly, exposure to chemotherapy increased the expression of both proteins and P-gp expression was linked to a 3-fold increase in the risk of treatment failure.<sup>20,21</sup> The data also indicate a trend toward worse prognosis in breast cancer patients with early expression of MRP1.<sup>19</sup>

Most patients exposed to anthracyclines and taxanes develop resistance<sup>4</sup> precluding long-term use of these agents and further limiting treatment options for this poor prognosis group. Furthermore, up to 55% of patients with MBC have primary taxane-resistance, defined as progressive disease as best response to taxane therapy.<sup>22,23</sup> Treatment options for MBC patients following failure of anthracycline- and taxane-based therapy include agents such as capecitabine, gemcitabine, and vinorelbine. Response rates with gemcitabine and vinorelbine are 16% to 30%, and duration of response ranges from 4 to 7 months.<sup>24</sup> Single-agent capecitabine, which is approved for use in MBC after prior anthracyclines and taxanes, demonstrated ORRs ranging from 9% to 28%, with median duration of response of 5.9 to 7.6 months.<sup>25–27</sup> Efforts have focused on identifying new effective agents or combination regimens that provide benefit to patients with MBC resistant to multiple chemotherapies in terms of improved tumor control and survival.

## Epothilones

Isolated from the myxobacterium *Sorangium cellulosum*, epothilones are a novel class of antineoplastic agents that promote polymerization of microtubules.<sup>28</sup> Epothilones and taxanes occupy overlapping areas in the taxane-binding site on microtubules.<sup>29</sup> However, the unique way in which the epothilones bind leads to differences in their mechanism of action compared with taxanes. Epothilones maintain activity against taxane-sensitive and -resistant cell lines, including those overexpressing  $\beta$ III-tubulin and P-gp. Molecular modeling studies predict distinct  $\beta$ -tubulin binding properties for epothilone A and paclitaxel. A similar binding affinity to  $\beta$ I and  $\beta$ III-tubulin is predicted for epothilone A while paclitaxel is predicted to have higher binding affinity to  $\beta$ I-tubulin.<sup>13</sup> As poor substrates for drug efflux pumps, epothilones are highly active against MDR cell lines, in vitro and in vivo.<sup>28,30</sup> The naturally occurring epothilones patupilone (epothilone B, EPO906), and KOS862 (epothilone D), as well

as the semisynthetic derivatives ixabepilone (BMS-247550, aza-epothilone), KOS-1584 (9,10,-didehydroepothilone), and ZK-epothilone (ZK-EPO, ZK-219477, sagopilone) have shown activity and distinct safety profiles in patients with advanced solid malignancies.<sup>31</sup> Ixabepilone, the first approved drug in this class, is indicated as monotherapy or in combination with capecitabine for the treatment of patients with MBC resistant to anthracyclines, taxanes, and/or capecitabine. The other epothilones mentioned above are in various stages of clinical development, with the exception of KOS862, which has been discontinued in prostate and non-small-cell lung cancer.

## Ixabepilone

Ixabepilone has low susceptibility to common mechanisms of resistance. For example, ixabepilone is active against Pat-21 tumor xenografts.<sup>32</sup> Pat-21 is a tumor model developed from a patient with MBC after failure of paclitaxel plus the MDR reversal drug dexverapamil. The patient had also received doxorubicin, cyclophosphamide, methotrexate, and 5-fluorouracil. Pat-21 cells have high levels of  $\beta$ III-tubulin but do not overexpress P-gp. The overexpression of  $\beta$ III-tubulin in the Pat-21 breast cancer model did not affect sensitivity to ixabepilone, whereas Pat-21 tumor xenografts were resistant to paclitaxel and docetaxel.<sup>32</sup> In addition, ixabepilone is active in taxane-resistant cell lines including the P-gp overexpressing HCT116/VM46 (human colon carcinoma) and A2780Tax (human ovarian carcinoma) with mutated  $\beta$ -tubulin, and maintains activity in taxane-sensitive and -resistant tumor xenografts.<sup>30</sup> In preclinical models, ixabepilone demonstrated synergistic activity when used in combination with capecitabine, cetuximab, trastuzumab, bevacizumab, or ipilimumab.<sup>33–36</sup>

## Efficacy of ixabepilone in metastatic breast cancer

As a single agent or in combination with capecitabine, ixabepilone is efficacious across a range of patients with MBC including taxane-naïve, anthracycline-, taxane-, and/or capecitabine-resistant patients, as well as those with primary resistance to taxanes. Ixabepilone has proven efficacy in different breast cancer subtypes; patients with estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2-negative (ER/PR/HER2-negative, triple negative) or HER2-positive disease have derived clinical benefit from ixabepilone treatment. Ixabepilone has been administered as first-, second or, third line in MBC as well as in the neoadjuvant setting, and has demonstrated efficacy across all lines of therapy evaluated.

## Monotherapy

In a phase II study, Roché and colleagues administered ixabepilone at the recommended dose of 40 mg/m<sup>2</sup> as an intravenous (iv) infusion over 3 hours every 3 weeks as first-line metastatic therapy to 65 MBC patients who had received anthracyclines in the adjuvant setting. Twenty-seven patients had a partial response (ORR 41.5%), median time to progression (TTP) was 4.8 months, and median overall survival (OS) was 22.0 months.<sup>37</sup> The phase II study conducted by Thomas and colleagues reported an ORR of 12% (6 partial responses) in 49 patients with taxane-resistant MBC who received ixabepilone. Median TTP was 2.2 months, with a median OS of 7.9 months.<sup>38</sup> Perez and colleagues conducted a phase II study of ixabepilone in MBC patients with anthracycline-, taxane-, and capecitabine resistance. Of 126 patients treated with ixabepilone, 113 were evaluable for response. The ORR was 11.5%, with 13 partial responses (Table 1). Median progression-free survival (PFS) was 3.1 months, and median OS was 8.6 months.<sup>39</sup>

An alternative dose and schedule of ixabepilone has been evaluated in MBC. Denduluri and colleagues evaluated the activity of ixabepilone 6 mg/m<sup>2</sup>/d iv over 1 hour on days 1 to 5 every 3 weeks in 23 taxane-naïve patients with MBC, 12 of whom (52%) had received prior anthracyclines. The ORR was 57% (13 partial responses), and median TTP was 5.5 months. Seven of 12 (58%) patients who had prior anthracyclines had partial responses.<sup>40</sup> In another phase II study, 37 taxane-refractory MBC patients received ixabepilone 6 mg/m<sup>2</sup>/d iv over 1 hour on days 1 to 5 every 3 weeks. Ixabepilone treatment resulted in an ORR of 22%, with 1 complete response and 7 partial responses (Table 1), and a median TTP of 2.6 months.<sup>41</sup>

## Combination therapy

Based on the single-agent activity and demonstrated synergy in preclinical models<sup>35</sup> an ixabepilone plus capecitabine regimen was evaluated in a phase I/II study with anthracycline- and taxane-resistant MBC patients. The recommended dose for the combination regimen was ixabepilone 40 mg/m<sup>2</sup> iv over 3 h every 3 weeks and oral capecitabine 2000 mg/m<sup>2</sup> administered in 2 divided doses daily on days 1 to 14 every 3 weeks. Of 50 evaluable patients, 1 complete response and 14 partial responses were observed (ORR 30%) and median PFS was 3.8 months.<sup>42</sup> A large randomized phase III study compared the ixabepilone plus capecitabine combination with capecitabine monotherapy in 752 patients with anthracycline- and taxane-resistant MBC.<sup>43</sup> Patients were randomly assigned to receive ixabepilone plus capecitabine (N = 375)

**Table 1** Efficacy of ixabepilone monotherapy in metastatic breast cancer

Investigator	Roché et al <sup>37</sup>	Thomas et al <sup>38</sup>	Perez et al <sup>39</sup>	Low et al <sup>41</sup>	Denduluri et al <sup>40</sup>
Patient population	A-resistant	T-resistant	A-, T-, C-resistant	T-resistant	T-naïve
Patient number	N = 65	N = 49	N = 113	N = 37	N = 23
Dosing schedule	40 mg/m <sup>2</sup> ; 3-hour iv infusion; day 1; Q3W			6 mg/m <sup>2</sup> ; 1-h iv infusion; days 1 to 5 Q3W	
Median ORR (%)	41.5	12.2	11.5	22 [9.8 to 38.2]	57 [34.5 to 76.8]
[95% CI]	[29.4 to 54.4]	[4.7 to 26.5]	[6.3 to 18.9]		
Median PFS (mo)	(TTP) 4.8	(TTP) 2.2	3.1	2.6	(TTP) 5.5
[95% CI]	[4.2 to 7.6]	[1.4 to 3.2]	[2.7 to 4.2]	[NR]	[NR]
Median OS (mo)	22.0	7.9	8.6	[NR]	[NR]
[95% CI]	[15.6 to 27.0]	[6.1 to 14.5]	[6.9 to 11.1]		

**Abbreviations:** A, anthracycline; C, capecitabine; iv, intravenous; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T, taxane; TTP, time to progression.

or capecitabine alone (N = 377) (Table 2). Ixabepilone plus capecitabine treatment led to a 31% decrease in the risk of disease progression (hazard ratio [HR] 0.69; 95% confidence interval [CI], 0.58–0.83;  $p < 0.0001$ ), and a 39% increase in median PFS (5.7 months compared with 4.1 months in the capecitabine monotherapy arm).<sup>44</sup> The combination regimen was superior to capecitabine, with ORRs of 35% vs 14% in the respective treatment arms.<sup>43</sup> The overall survival data are expected in 2009.

## Safety and tolerability of ixabepilone Monotherapy

Ixabepilone has demonstrated a manageable safety profile in chemo-naïve, and in mildly or heavily pretreated patients as a single agent. Neutropenia and peripheral sensory neuropathy

were the most frequently noted grade 3/4 adverse events with the administration of ixabepilone 40 mg/m<sup>2</sup> every 3 weeks; febrile neutropenia was uncommon (Table 3). Grade 3/4 neutropenia reported with ixabepilone 40 mg/m<sup>2</sup> Q3W monotherapy ranged from 53% to 58%, and was generally manageable.<sup>37–39</sup> Febrile neutropenia occurred in  $\leq 6\%$  of patients in these trials (Table 1). At the alternate dosage (6 mg/m<sup>2</sup>/d iv over 1 hour on days 1 to 5 every 3 weeks), grade 3/4 neutropenia occurred in 22% and 35% of patients.<sup>40,41</sup> The incidence of grade 3/4 febrile neutropenia ranged from 0% and 14%.<sup>40,41</sup> Peripheral sensory neuropathy was primarily grade 1/2, even in heavily pretreated patients. Grade 3/4 sensory neuropathy occurring in 12% to 20% of patients was cumulative and mostly reversible, resolving to baseline or grade 1 within a median of 5.4 weeks following dose adjustments or treatment delay.<sup>45</sup> Discontinuation of ixabepilone is

**Table 2** Efficacy of ixabepilone plus capecitabine in metastatic breast cancer

Investigator	Bunnell et al <sup>42</sup>	Thomas et al <sup>43</sup> ; Thomas <sup>44</sup>
Patient Population	A- and T-resistant	A- and T-resistant
Phase	II	III
Patient number	N = 50	N = 375
Dosing schedule	Ixabepilone 40 mg/m <sup>2</sup> ; 3-hour iv infusion; d1 Q3W plus Capecitabine 2000 mg/m <sup>2</sup> , oral, d 1 to 14 Q3W	Ixabepilone 40 mg/m <sup>2</sup> ; 3-hour iv infusion; d1 Q3W plus Capecitabine 2000 mg/m <sup>2</sup> , oral, d 1 to 14 Q3W
Median ORR (%)	30.0	34.7
[95% CI]	[18 to 45%]	[29.9 to 39.7]
Median PFS (mo)	3.8	5.7
[95% CI]	[2.7 to 5.6]	[4.8 to 6.7]
Hazard ratio		0.69
[95% CI]		[0.58 to 0.83]
p-value		$p < 0.0001$

**Abbreviations:** A, anthracycline; iv, intravenous; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T, taxane.

**Table 3** Safety and tolerability of ixabepilone therapy in metastatic breast cancer – selected grade 3/4 adverse events

Investigator	Monotherapy				Combination therapy		
	Roché et al <sup>37</sup>	Thomas et al <sup>38</sup>	Perez et al <sup>39</sup>	Low et al <sup>41</sup>	Denduluri et al <sup>40</sup>	Bunnell et al <sup>42</sup>	Thomas et al <sup>43</sup>
Patient population	A-resistant	T-resistant	A-, T-, C-resistant	T-resistant	T-naïve	A- and T-resistant	A- and T-resistant
Patient number	N = 65	N = 49	N = 126	N = 37	N = 23	I + C N = 62	I + C N = 375 C N = 377
<b>Hematologic</b>							
Neutropenia (%)	58 <sup>a</sup>	53	54	35	22	69 <sup>b</sup>	68
Leukopenia (%)	50	2	49	NR	NR	55 <sup>b</sup>	57
Febrile neutropenia (%)	3	4	3	14	0	2	5
<b>Non-hematologic</b>							
Peripheral sensory neuropathy (%)	20	12	14	3	0	19	21
Peripheral motor neuropathy (%)	5	0	1	NR	4	2	5
Hand-foot syndrome (%)	NA	NA	NA	NA	NA	34	18

<sup>a</sup>n = 64<sup>b</sup>n = 61**Abbreviations:** A, anthracycline; C, capecitabine; I, ixabepilone; NA, not applicable; NR, not reported; T, taxane.

recommended in patients with grade 3 neuropathy  $\geq 7$  days or any grade 4 neuropathy.<sup>46</sup> A 20% dose reduction is recommended in patients with grade 2 neuropathy  $\geq 7$  days or grade 3 neuropathy  $< 7$  days.<sup>46</sup> The trials of the lower ixabepilone dose (6 mg/m<sup>2</sup>/day iv over 1 hour on days 1 to 5 every 3 weeks) reported fewer incidences of grade 3/4 peripheral sensory neuropathy ( $\leq 3\%$ ) (Table 3).<sup>40,41</sup> Grade 3/4 peripheral motor neuropathy was noted in  $\leq 5\%$  of patients at standard ixabepilone dosing.<sup>37–39</sup> Other grade 3/4 adverse events noted with ixabepilone treatment include fatigue (6% to 27%), myalgia/arthritis (3% to 13%), and diarrhea (1% to 11%).<sup>37–41</sup>

## Combination therapy

Adverse events associated with the ixabepilone plus capecitabine combination were consistent with the safety profile of the individual agents (Table 3). Grade 3/4 adverse events reported in patients receiving ixabepilone plus capecitabine included neutropenia (68%), leukopenia (57%), and peripheral sensory neuropathy (21%).<sup>43</sup> There was an increased risk of severe neutropenia, febrile neutropenia, and neutropenia-related toxic death in the ixabepilone plus capecitabine treatment arm versus capecitabine monotherapy. Grade 3/4 febrile neutropenia was 4.8% and 0.5% in the combination and capecitabine monotherapy arms, respectively.<sup>43</sup> Owing to the hepatic metabolism of ixabepilone, investigators noted a higher risk of toxicity in patients receiving Ixabepilone and capecitabine with moderate or severe hepatic impairment at baseline. Neutropenia-related deaths occurred in 7 of 353 patients (1.9%) with moderate (grade 0/1) baseline liver impairment, and in 5 of 16 patients (31%) with severe (grade  $\geq 2$ ) baseline hepatic dysfunction.<sup>43</sup> Dose adjustments have been recommended for patients with moderate or severe liver dysfunction receiving ixabepilone monotherapy.<sup>47</sup> The ixabepilone plus capecitabine combination is contraindicated in patients with AST or ALT  $> 2.5 \times$  upper limit of normal (ULN) or bilirubin  $> 1 \times$  ULN.<sup>46</sup> Conversely, patients with normal or mild hepatic impairment had prolongation of PFS by 2.0 months compared to capecitabine alone (6.2 vs 4.2 months; HR, 0.73).<sup>43</sup> Peripheral sensory neuropathy occurred in 65% of patients in the ixabepilone plus capecitabine arm, and was generally mild to moderate (grade 1/2, 44%; grade 3/4, 21%).<sup>43</sup> Grade 3/4 peripheral sensory neuropathy was manageable with dose adjustments and reversible; 89% of patients had resolution to baseline or grade 1 within a median of 6.0 weeks.<sup>48</sup> Rates of grade 3/4 hand-foot syndrome were nearly equivalent, 18% with ixabepilone plus



capecitabine and 17% with capecitabine monotherapy.<sup>43</sup> In the phase III trial, 11% of patients in the ixabepilone plus capecitabine arm had grade 3/4 myalgia/arthritis versus 0.3% in the capecitabine monotherapy arm.<sup>43</sup> Grade 3/4 fatigue was experienced by 9% versus 3.3% of patients receiving ixabepilone plus capecitabine and capecitabine monotherapy, respectively. Grade 3/4 diarrhea was reported in 6% and 8.5% of patients in the respective arms.<sup>43</sup>

## Efficacy of ixabepilone in specific MBC patient subpopulations

Approximately 10% to 25% of all breast cancer cases are ER/PR/HER2-negative<sup>49–52</sup> and primary taxane resistance has been observed in up to 55% of breast cancer patients.<sup>22,23</sup> Patients who fall into these categories generally have a poorer prognosis and shorter survival compared with their counterparts.<sup>49,51</sup> Effective treatment options are limited for the sizeable portion of breast cancer patients in these subpopulations largely affected by aggressive disease. Ixabepilone has demonstrated efficacy in patients with ER/PR/HER2-negative or HER2-positive disease, as well as those with primary taxane resistance, and represents a novel therapeutic option for these populations (Tables 4 and 5).

Subgroup analyses of ER/PR/HER2-negative patients in 3 phase II trials evaluated the activity of ixabepilone in this poor prognosis population. Eleven of 65 patients in the trial conducted by Roché and colleagues had ER/PR/HER2-negative disease. The response to ixabepilone monotherapy in this subpopulation was 55% with median PFS of 4.6 months.<sup>53</sup> Eighteen of 49 patients in the phase II trial by Thomas and colleagues were ER/PR/HER2-negative; following ixabepilone treatment, the ORR in these patients was 6% and median PFS was 1.6 months.<sup>53</sup> The trial conducted by Perez et al included 42 ER/PR/HER2-negative patients of the 126 enrolled. The ORR was 12%, and median PFS was 2.7 months. In the neoadjuvant setting, the ORR was 64% and the pathologic complete response in breast (pCR<sub>B</sub>) was 26% in patients with ER/PR/HER2-negative disease

receiving up to 4 cycles of ixabepilone 40 mg/m<sup>2</sup> every 3 weeks versus 18% in the overall patient population.<sup>53,54</sup>

Prospective analyses of specific patient subpopulations in the phase III trial of ixabepilone plus capecitabine versus capecitabine alone showed superiority of the combination regimen. In the ixabepilone plus capecitabine arm, 91 patients (24%) were ER/PR/HER2-negative, 164 (44%) were ER-negative, 59 (16%) were HER2-positive, and 150 (40%) had primary taxane resistance. Patients with ER/PR/HER2-negative disease had an ORR of 27% following treatment with the combination versus 9% with the capecitabine monotherapy.<sup>48</sup> The ixabepilone plus capecitabine combination improved median PFS compared with capecitabine alone; 4.1 versus 2.1 months (HR = 0.68).<sup>48</sup> The ER-negative population also had improved median PFS; 4.4 versus 2.8 months (HR = 0.65, *p* < 0.0001). The ORRs were 30% and 10% for ER-negative patients in the combination and capecitabine monotherapy arms, respectively (Table 5)<sup>55</sup> Ixabepilone plus capecitabine improved median PFS in HER2-positive patients; 5.3 versus 4.1 months with capecitabine alone (HR = 0.69, *p* = 0.06). The ORRs were 31% and 8% in the respective arms.<sup>56</sup> Safety and tolerability of ixabepilone in the patient subpopulations were similar to the overall population.<sup>48,53,57</sup>

Subset analyses demonstrated efficacy of ixabepilone mono- or combination therapy in MBC patients with primary taxane resistance, defined as progressive disease as best response to prior taxanes. In the phase III study, patients in the ixabepilone plus capecitabine arm had a median PFS of 5.6 months versus 4.9 months in the capecitabine arm; ORRs were 33% vs 13%, respectively.<sup>57</sup> Similarly, in a phase II trial, ixabepilone was active as monotherapy in MBC patients with primary taxane resistance.<sup>39,57</sup>

## Conclusions

Disease progression in MBC is common. The increasing use of anthracycline- and taxane-based regimens in the adjuvant setting and the development of resistance to these agents

**Table 4** ER/PR/HER2-negative metastatic breast cancer – efficacy of ixabepilone monotherapy

Investigator	Roché et al <sup>37</sup>	Thomas et al <sup>38</sup>	Perez et al <sup>39</sup>
Patient population	A-resistant	T-resistant	A-, T-, C-resistant
Number of ER/PR/HER2-negative patients	N = 11	N = 18	N = 42
Median ORR (%)	55%	6%	12%
Median PFS (months) [95% CI]	4.6 [2.8 to 9.3]	1.6 [1.3 to 2.3]	2.7 [1.5 to 5.9]

**Notes:** Ixabepilone 40 mg/m<sup>2</sup> administered once every 3 weeks.

**Abbreviations:** A, anthracycline; C, capecitabine; ER, estrogen receptor; HER2, human epidermal growth factor 2; NR, not reported; ORR, overall response rate; PR, progesterone receptor; PFS, progression-free survival; T, taxane.

**Table 5** Ixabepilone plus capecitabine in specific MBC subpopulations – efficacy results

Study	Treatment	ER/PR/HER2-negative	ER-negative	HER2-positive	Primary taxane resistance
Phase III N = 375	Ixabepilone 40 mg/m <sup>2</sup> Q3W plus capecitabine 2000 mg/m <sup>2</sup> days 1 to 14 Q3W	(Rugo et al <sup>48</sup> ) n = 91 • ORR: 27% • PFS: 4.1 months (95% CI, 3.4 to 4.4) • HR = 0.68 (95% CI, 0.50 to 0.93)	(Pivot et al <sup>55</sup> ) n = 164 • ORR: 30% • PFS: 4.4 months (95% CI, 4.1 to 5.6) • HR = 0.65 (95% CI, 0.52 to 0.80)	(Lerzo et al <sup>56</sup> ) n = 59 • ORR: 31% • PFS: 5.3 months (95% CI, 3.8 to 7.6) • HR = 0.69 (95% CI, 0.47 to 1.02)	(Yardley et al <sup>57</sup> ) n = 150 • ORR: 33% • PFS: 5.6 months (95% CI, 4.3 to 7.0)
Phase III N = 377	Capecitabine 2500 mg/m <sup>2</sup> days 1 to 14 Q3W	n = 96 • ORR: 9% • PFS: 2.1 months (95% CI, 1.5 to 2.8)	n = 161 • ORR: 10% • PFS: 2.8 months (95% CI, 2.1 to 3.4)	n = 53 • ORR: 8% • PFS: 4.1 months (95% CI, 2.9 to 4.4)	n = 137 • ORR: 13% • PFS: 4.9 months (95% CI, 4.0 to 5.7)

**Abbreviations:** ER, estrogen receptor; HR, hazard ratio; HER2, human epidermal growth factor 2; NR, not reported; ORR, overall response rate; PR, progesterone receptor; PFS, progression-free survival.

limit their efficacy against metastatic disease. Few agents have demonstrated activity after failure of anthracyclines and taxanes and in most cases, with little effect on disease progression.

Higher response rates were observed in taxane naïve and/or anthracycline pretreated patients receiving ixabepilone. Reduced response rates were observed in patients resistant to taxanes or anthracyclines, taxanes and capecitabine (Table 1). These data are consistent with previously observed reduction in therapeutic efficacy in patients who have developed resistance to one or more chemotherapeutic agents and/or with increasing lines of therapy.<sup>58</sup> Nonetheless, consistent with the preclinical data, the results suggest that ixabepilone may overcome and/or circumvent at least some of the cellular mechanisms that block taxane-, anthracycline- and/or capecitabine-induced cytotoxicity.

Overall, the clinical studies have demonstrated that ixabepilone:

- Has low susceptibility to common mechanisms of drug resistance, such as  $\beta$ III tubulin overexpression.
- Is efficacious against anthracycline- and taxane-pretreated MBC.
- Has a manageable safety profile.
- Provides significant clinical benefit to patients with ER/PR/HER2-negative and HER2-positive disease, and/or patients with primary resistance to taxanes.

Based on the data from the phase II and III trials in MBC, ixabepilone received approval from the United States Food and Drug Administration (FDA) for use in combination with capecitabine for the treatment of patients with MBC resistant to anthracyclines and taxanes, and as monotherapy for MBC patients resistant or refractory to anthracyclines, taxanes, and capecitabine. However, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) did not approve marketing authorization for ixabepilone citing concerns over treatment-related neuropathy.

A recently completed analysis of survival data from the 2 large phase III ixabepilone trials in MBC demonstrated a trend towards increased OS that did not reach statistical significance.<sup>59</sup> However, an OS benefit was reported in patients treated with ixabepilone following a pre-defined Cox Regression analysis with data adjusted according to prognostic factors.<sup>60</sup>

A number of ongoing trials are evaluating ixabepilone in combination with other chemotherapeutic and biologic agents for treatment of a variety of tumor types. A preliminary report indicates that ixabepilone in combination with epirubicin is active in patients with MBC.<sup>61</sup> Additionally, an overall

response rate of 53.8% was reported for ixabepilone in combination with trastuzumab in patients with HER2-positive metastatic breast cancer.<sup>62</sup> The results of additional trials examining ixabepilone combination therapy in patients with MBC are anticipated in 2009.

## Disclosures

The author has no conflicts of interest to disclose.

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