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# Treatment beyond taxanes, emerging new cytotoxic agents

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ABSTRACT

Until recently, taxanes were considered the first choice of therapy for patients with metastatic breast cancer (MBC). However, the clinical utility of the taxanes is limited in some patients by the emergence of drug resistance. Moreover, these agents are increasingly used as adjuvant therapy, increasing the population of patients with prior exposure once the disease has metastasised. Current approved treatment options after prior taxane therapy include capecitabine, liposomal doxorubicin and *nab*-paclitaxel – as single agents and/or in combination. Vinorelbine and gemcitabine may also be used. Most recently, the epothilones, a novel group of microtubule-stabilising agents, have shown promising activity in patients with MBC, including those resistant to taxanes and other cytotoxic drugs. Currently, three epothilone B synthetic derivatives, ixabepilone (BMS-247550), patupilone (EPO906), and sagopilone (ZK-EPO) are in development. This article will examine the latest data for these next-generation cytotoxics in the treatment of MBC.



## 1. Introduction

Chemotherapy has been the mainstay of care for metastatic breast cancer (MBC) for the last four decades. The 1960s saw the emergence of alkylating agents and antimetabolites, followed shortly thereafter by doxorubicin and other anthracyclines like epirubicin and subsequently by vinorelbine in the mid-1980s. The taxanes paclitaxel and docetaxel were introduced in the early 1990s and, with their ability to extend progression-free survival (PFS), they, along with the anthracyclines, have formed the mainstay of breast cancer chemotherapy since.

A recent meta-analysis confirmed taxane therapy with or without an anthracycline as the current standard for the first-line therapy of MBC.[1] However, taxanes are increasingly being used as adjuvant therapy earlier in the disease course, increasing the population of patients with prior exposure to these drugs once the disease has metastasised. Future efficacy may be reduced by the development of drug resistance once patients have been pre-treated with these agents; in the case of anthracyclines it is also limited by reaching maximum cumulative doses. The possible benefits of rechallenge with anthracyclines and taxanes are poorly defined. Rechallenge may be possible in patients exposed to low cumulative doses and with a relapse-free survival after adjuvant chemotherapy of more than 12 months. However, few data are available to support this approach and the value of rechallenge may be further limited if there is an underlying molecular mechanism conferring drug resistance.

This paper explores current data to support the use of alternative chemotherapeutics for patients with taxane pre-treated MBC focusing on the role of the novel microtubule-stabilising agents, the epothilones.

## 2. Where next when taxanes and anthracyclines fail?

An array of alternative chemotherapy agents have demonstrated activity in patients with taxane pre-treated

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**Table 1 – Developmental chemotherapeutics for metastatic breast cancer**

| Agent | Derivation | Clinical data/status | Source |
|---|---|---|---|
| **Novel taxanes** | | | |
| Ortataxel | 14-β-hydroxy-10-deacetylbaccatin III derivative (related to docetaxel) | Phase II in MBC ($N = 76$ evaluable):<br>• Disease control rate: 45%<br>• Partial response rate: 7% | Beer et al. (2008) [7] |
| Larotaxel | 14-β-hydroxy-10-deacetylbaccatin III derivative (related to docetaxel) | Phase II study in combination with trastuzumab in HER2+ MBC ongoing ($N = 26$ evaluable):<br>• Partial response rate: 42.3%<br>Phase II in MBC as third line<br>• 43% of patients had stable disease<br>• Median duration of response was 13.1 weeks<br>• Median PFS was 13 weeks, median OS was 43.3 weeks | Dieras et al. (2008) [8]<br>Ozguroglu et al. (2008) [9] |
| **Epothilones** | | | |
| Ixabepilone | Semi-synthetic epothilone B derivative | Phase III study in combination with capecitabine in MBC ($N = 752$).<br>• Response rates:<br>Ixabepilone + capecitabine: 42.1%<br>Capecitabine alone: 22.5% ($P = 0.0001$)<br>• Median PFS:<br>Ixabepilone + capecitabine: 5.3 months<br>Capecitabine alone: 3.8 months ($P = 0.0011$) | Thomas et al. (2007) [10] |
| Patupilone (EPO-906) | Epothilone B natural product | Phase II in patients with CNS metastases from breast cancer (ongoing)<br>Phase III ovarian cancer/solid tumours (ongoing) | Study code: NCT00450866<br>Study code: NCT00262990 |
| Sagopilone (ZK-EPO) | Synthetic epothilone D derivative | Phase II breast cancer currently recruiting | Study code: NCT00313248 |
| **Other novel agents** | | | |
| Vinflunine | Vinca alkaloid derivative | Phase II monotherapy study yielded a partial response rates of 30% in pre-treated MBC<br>Phase III study in combination with capecitabine and gemcitabine ongoing | Campone et al. (2006) [11] |
| Eribulin | Synthetic analogue of halichondrin B | Phase II study in patients with LABC or MBC previously treated with anthracycline, taxane and capecitabine therapy ($N = 269$):<br>• Overall response rate: 9.3%<br>• Median duration of response: 4.1 months<br>• Median overall survival: 10.4 months | Vahdat et al. (2008) [12] |

CNS: central nervous system; HER2: human epidermal growth factor receptor 2; LABC: locally advanced breast cancer; MBC: metastatic breast cancer; PFS: progression-free survival.

or taxane-resistant metastatic breast cancer, including capecitabine, vinorelbine, gemcitabine and liposomal doxorubicin. [2–6]

A number of agents of different classes are currently in development with the hope of overcoming the challenge of taxane- and/or anthracycline-resistance in breast cancer patients with advanced disease. These include novel taxanes and new taxane formulations (e.g. *nab*-paclitaxel), the epothilones, vinflunine, eribulin (Table 1) and novel combinations of existing agents such as irinotecan + capecitabine and 5,10-methylene-tetrahydrofolic acid + fluorouracil. An emerging group of drugs with promising activity in patients with MBC, including those resistant to taxanes and other cytotoxic drugs, are the epothilones. [10,13–15]

## 3. Novel taxanes

One approach to overcoming the issue of intrinsic or acquired resistance to the taxanes has been to identify novel taxane moieties less susceptible to resistance mechanisms (Table 1). Ortataxel is one such novel taxane that is not a substrate for the ATP binding cassette (ABC) transporter, P-glycoprotein (P-gp), that is responsible for taxane resistance via increased drug efflux. [16] Data from a recent phase II single-arm study in patients with taxane-resistant breast cancer are encouraging, with a partial response rate of 7% and a stable disease rate of 38% among 85 patients with advanced or metastatic, taxane-resistant breast cancer. [7] Two deaths due to liver failure were recorded and were judged to be drug related.

Other significant adverse events included neutropenia (57% grade 3/4), fatigue and malaise.

Larotaxel, a semisynthetic taxane moiety, is also under evaluation for patients with MBC, and the results of a recent open-label phase II trial are indicative of good activity in combination with the human epidermal growth factor receptor 2 (HER2)-targeted antibody trastuzumab.[8] Among 26 patients with HER2 positive MBC, 11 (42.3%) achieved a partial response. The combined tolerability of these two agents was manageable, with the most common grade 3/4 adverse events being febrile neutropenia/neutropenic infection, diarrhoea and asthenia.

## 4. Epothilones – a novel class of agents

The epothilones are a novel group of microtubule-stabilising agents. Currently, three epothilone B synthetic derivatives, ixabepilone (BMS-247550), patupilone (EPO906), and sagopilone (ZK-EPO) are in development (Table 1). Ixabepilone is the epothilone analogue currently most advanced in clinical development. While not yet approved for use in Europe, ixabepilone was recently approved by the US Food and Drug Administration for the treatment of metastatic or locally advanced breast cancer in combination with capecitabine after failure of an anthracycline and a taxane or as a monotherapy after failure of an anthracycline, a taxane and capecitabine.[17]

The epothilones are structurally different from the taxanes although their mode of action appears to be similar as the epothilones promote tumour cell death by arresting cell cycle progression at the G2/M phase by interfering with tubulin polymerisation.[18,19] These agents also differ in the way in which they bind to tubulin, which may have implications for their activity. The preclinical activity of these two groups of agents differ, particularly with respect to epothilone activity against taxane-resistant human cancer cell lines. Specifically there is evidence for greater potency and significant activity of the epothilones in taxane-resistant tumours.[20–22]

As discussed by Coley in this supplement,[16] the epothilones have low susceptibility to some of the common types of drug resistance, particularly those affecting taxane-resistance of relevance in the management of MBC.[23,24] Indeed, preclinical studies have demonstrated an apparent lack of cross-resistance between epothilones and taxanes, making sequential therapy a rational approach.

## 5. Ixabepilone in the treatment of advanced breast cancer

### 5.1. *Phase II studies*

The phase II study programme for ixabepilone in MBC consisted of five clinical studies that included both taxane-naive and pre-treated patients, and those with multi-resistant advanced breast cancer.[10,13–15,25,26] One further study evaluated the efficacy of ixabepilone in the neoadjuvant breast cancer setting.[27]

Among patients not previously treated with a taxane, the response rate to ixabepilone ranged from 42% to 57%, with a further 26% to 35% of patients achieving stable disease (disease control rates of 83% and 77%).[14,25] As might be expected, the response rate was somewhat lower (22%) among patients who had previously been treated with a taxane, with a further 35% of patients achieving stable disease to yield a disease control rate of 57%.[26] For patients with taxane-resistant and taxane-refractory disease (as defined by strict criteria) the response rate was 12% with a stable disease rate of 41% to give a disease control rate of 53%.[15] Median time to progression was 2.2 months and median survival was 7.9 months.[15] In the study reported by Perez and coworkers,[13] eligible patients were those whose disease was resistant to multiple chemotherapy agents including taxanes, anthracyclines and capecitabine. Among these difficult-to-treat patients the response rate to ixabepilone was 18%, with an additional 15% of patients achieving stable disease (disease control rate 33%). The median progression-free survival was 3.1 months.[13]

Overall in these phase II trials ixabepilone demonstrated encouraging efficacy in MBC, even in heavily pre-treated patients and those with multi-drug-resistant disease.

### 5.2. *Phase III programme*

The phase III programme for ixabepilone focused on the efficacy of this agent in combination with capecitabine and consisted of two international, randomised, open-label trials including CA163-046, a pivotal study in patients with anthracycline- and taxane-resistant MBC,[10] and CA163-048, a confirmatory trial in patients pre-treated with or resistant to anthracyclines and taxanes. These two studies recruited >1900 patients with metastatic or locally advanced breast cancer who had previously been treated with or were resistant to taxanes and anthracyclines, and Hortobagyi et al. have reported a comparative analysis of these two studies.[28] Patients were randomised to receive either ixabepilone (40 mg/m$^2$ over 3 hours on day 1 of a 3-week cycle) plus capecitabine (2000 mg/m$^2$/day on days 1 to 14 of a 3-week cycle) or capecitabine alone (2500 mg/m$^2$/day on days 1 to 14 of a 3-week cycle).

*Ixabepilone plus capecitabine for treatment-resistant disease*

Strict entry criteria to define treatment resistance were applied in study 046 such that only patients with disease recurrence within 12 months of prior adjuvant taxane therapy or 6 months of prior adjuvant anthracycline therapy were eligible for the study. For patients with prior therapy for metastatic disease,

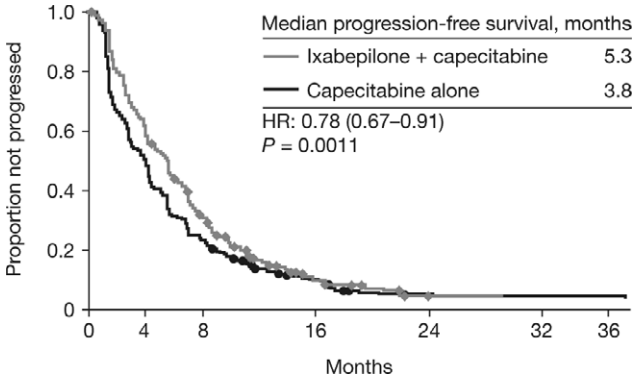


**Fig. 1 – Investigator-assessed progression-free survival during ixabepilone plus capecitabine vs capecitabine alone among patients with advanced breast cancer resistant to taxanes and anthracyclines.** [10]

resistance criteria were disease progression on treatment or within 4 months of taxane therapy or 3 months after anthracycline therapy. In study 046, patients not resistant to anthracyclines were also eligible if they received a minimum cumulative anthracycline dose of doxorubicin 240 mg/m$^2$ or epirubicin 360 mg/m$^2$. Study 046 was the first such study to apply very strict definitions of treatment resistance. For the 046 and 048 trials the primary endpoints were progression-free survival (PFS) and overall survival (OS), respectively.

The study populations were well balanced between the treatment arms in both studies with respect to demographic and clinical characteristics, with two-thirds of patients having a good performance status (Karnofsky Index 90–100) and 20–25% having triple-negative disease at study commencement.

In the pivotal 046 trial (n = 752), ixabepilone plus capecitabine was superior to capecitabine alone for the primary endpoint of PFS (5.3 vs 3.8 months, hazard ratio [HR] 0.78; 95% confidence interval [CI]: 0.67–0.91; $P = 0.0011$; investigator assessed PFS) (Fig. 1). [28] Ixabepilone plus capecitabine was also superior in terms of the overall response rate (35% vs 14%; odds ratio 3.2; $P = 0.0001$). [10] Investigator-assessed response rates were consistent (ixabepilone plus capecitabine = 42% vs capecitabine = 23%). [28] For OS in this study, there was a trend in favour of ixabepilone plus capecitabine although the difference did not reach statistical significance. Median OS was 12.9 months in the ixabepilone combination arm and 11.1 months in the capecitabine alone arm (HR 0.90; 95% CI: 0.77–1.05; $P = 0.1936$) [28] (Fig. 2).

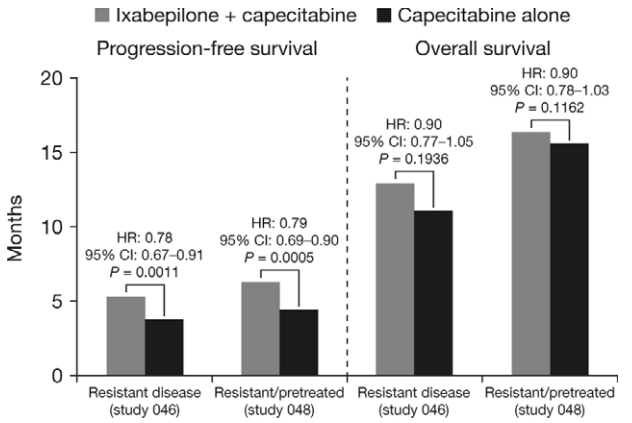


**Fig. 2 – Progression-free and overall survival during ixabepilone plus capecitabine vs capecitabine alone among patients with advanced breast cancer resistant to or pre-treated with taxanes and anthracyclines.** [28]

*Ixabepilone plus capecitabine in pre-treated and resistant disease*

In the confirmatory trial (study 048; n = 1221), a mixture of patients with treatment resistance and pre-treatment with taxanes were recruited. [28]

Although PFS was a secondary endpoint, data were comparable with that observed in study 046, with a median investigator-assessed PFS of 6.2 months for ixabepilone combination therapy and of 4.4 months for capecitabine alone (HR 0.79; 95% CI: 0.69–0.90; $P = 0.0005$) (Fig. 2). The investigator-assessed response rates were consistent with those observed in study 046, with an overall response rate in study 048 of 43% in the ixabepilone combination therapy arm and 29% for capecitabine alone. [28]

Median OS, the primary endpoint in this study, again favoured ixabepilone combination therapy although statistical significance was not reached. In this case the median OS was 16.4 months for ixabepilone plus capecitabine and 15.6 months for capecitabine alone (HR 0.90; 95% CI: 0.78–1.03; $P = 0.1162$) (Fig. 2).

*Tolerability of ixabepilone plus capecitabine*

In the phase III trials comparing ixabepilone +/– capecitabine, capecitabine-related toxicities were similar for both treatment groups. [10,28] Overall, treatment-related adverse events were mostly grade 1/2 and generally reversible. Peripheral neuropathy was common (typically sensory) grade 1 or 2, cumulative, and generally reversible. Peripheral sensory neuropathy occurred in ~65% of patients receiving ixabepilone plus capecitabine (grade 2, 27% of patients; grade 3, 22% of patients; grade 4, 1% of patients). [10] Peripheral neuropathy was the single most commonly encountered grade 3/4 non-haematological adverse event when ixabepilone was added to capecitabine. In the pivotal 046 study, this toxicity affected 23% of patients in the ixabepilone combination arm compared with no cases in the capecitabine arm. [10] and 24% of patients compared with 1% of patients, respectively, in the confirmatory 048 study. [28]

In both studies the median time to resolution of neuropathy (time from onset or worst grade to

baseline or grade 1) was 6 weeks and 6.2 weeks, respectively. Hand–foot syndrome was the next most commonly encountered non-haematological adverse event and occurred with comparable frequency between the combination and monotherapy arms in both studies (18% and 17%, respectively, in study 046 and 21% and 20%, respectively, in study 048).[10,28] Ixabepilone was not associated with central neurotoxicity.

The most commonly encountered haematological adverse event was neutropenia and this was higher in treatment arms containing ixabepilone in both phase III studies. In the pivotal study, 68% of patients experienced grade 3/4 neutropenia in the combination arm compared with 11% in the capecitabine monotherapy arm.[10] Consistent with this, 73% of patients who received combination therapy in the confirmatory study experienced neutropenia compared with 8% of patients in the capecitabine only arm.[28] However, the incidence of grade 3/4 febrile neutropenia was low throughout both trials (ixabepilone plus capecitabine vs capecitabine: 046, 4% vs 1%; 048, 4% vs 2%).[10,28] In both trials the proportion of patients who received growth factors (for prophylactic or any other reasons) was approximately 20%.

## 6. Other novel agents in development

Several additional chemotherapeutic agents are in clinical development; key agents are summarised in Table 1. The novel vinca alkaloid-based microtubule inhibitor, vinflunine, has also been evaluated in the treatment of MBC. A phase II study in patients with MBC who had received prior treatment with an anthracycline and/or a taxane revealed a partial response rate of 30%, a median PFS of 3.7 months and a median OS of 14.3 months.[11] A further phase II study of vinflunine in combination with trastuzumab as first-line therapy in patients with HER2-positive MBC has also yielded encouraging results, with 92% of the 13 patients evaluable at the time of reporting remaining progression free 6 months after starting treatment.[29] Vinflunine is currently in phase III development in combination with capecitabine and gemcitabine.

Eribulin, a synthetic analogue of halichondrin B, has also been evaluated for the treatment of locally advanced or metastatic breast cancer among patients previously treated with an anthracycline, a taxane and capecitabine.[12] Patients who had progressed during or within 6 months of their last chemotherapy regimen were eligible for inclusion in the single-arm phase II study. The response rate was 9.3% with a median duration of response of 4.1 months and a median OS of 10.4 months. Thus eribulin was active in this heavily pre-treated population.

## 7. Conclusions

Treatment selection for patients with MBC is complicated by a limited complement of agents approved for use in this setting, the accumulation of resistance to the most effective agents (taxanes and anthracyclines) as a consequence of prior exposure, or the attainment of maximal cumulative doses (anthracyclines). However, a number of novel agents are in development and meaningful disease control can be achieved in breast cancer patients with advanced disease. These include novel taxane-based moieties such as ortataxel and larotaxel, which it is hoped will be less susceptible to cellular mechanisms of taxane resistance. Promising data are also emerging for other novel derivatives of established agents, including the vinca alkaloid-based vinflunine and the synthetic analogue of halichondrin B, eribulin.

The epothilones are a novel class of agents that are less susceptible to the drug resistance mechanisms that limit the utility of the taxanes in resistant and pre-treated MBC patients. Of these, ixabepilone is the most developmentally advanced, with phase III data from two studies in patients with pre-treated and resistant locally advanced and metastatic breast cancer now available. Across both phase III studies, the increase in median PFS duration was approximately 40% when ixabepilone combined with capecitabine was compared with capecitabine alone. The corresponding decrease in the risk for progression was approximately 20%. Thus ixabepilone represents a rational alternative for patients who have previously been treated with an anthracycline or a taxane or for whom drug resistance has been confirmed following recurrence or treatment failure.

The life expectancy for patients with MBC is significantly curtailed and treatment choices are few. New derivatives of existing chemotherapeutic agents and the emergence of the epothilones, a novel class of chemotherapeutics less susceptible to cellular mechanisms of drug resistance, offer hope for this difficult-to-treat group of patients.

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## References

1. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol* 2008;**26**:1980–6.

2. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pre-treated metastatic breast cancer. *Eur J Cancer* 2004;**40**:536–42.
3. Ibrahim NK, Samuels B, Page R, et al. Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. *J Clin Oncol* 2005;**23**:6019–26.
4. Keller AM, Mennel RG, Georgoulias VA, et al. Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. *J Clin Oncol* 2004;**22**:3893–901.
5. Livingston RB, Ellis GK, Gralow JR, et al. Dose-intensive vinorelbine with concurrent granulocyte colony-stimulating factor support in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1997;**15**:1395–400.
6. Modi S, Currie VE, Seidman AD, et al. A phase II trial of gemcitabine in patients with metastatic breast cancer previously treated with an anthracycline and taxane. *Clin Breast Cancer* 2005;**6**:55–60.
7. Beer M, Lenaz L, Amadori D; Ortataxel Study Group. Phase II study of ortataxel in taxane-resistant breast cancer. *J Clin Oncol* 2008;**26**(15S): abstract 1066.
8. Dieras V, Viens P, Vayret C, et al. Larotaxel (L) in combination with trastuzumab in patients with HER2+ metastatic breast cancer (MBC): interim analysis of an open phase II label study. *J Clin Oncol* 2008;**26**(15S): abstract 1070.
9. Ozguroglu M, Mansutti M, Kerr R, et al. Multicenter, phase II study of larotaxel in patients (pts) with metastatic breast cancer (MBC) progressing after anthracyclines, taxanes and capecitabine. *Ann Oncol* 2008;**19**(Suppl 8):154P.
10. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2007;**25**:5210–17.
11. Campone M, Cortes-Funes H, Vorobiof D, et al. Vinflunine: a new active drug for second-line treatment of advanced breast cancer: results of a phase II and pharmacokinetic study in patients progressing after first-line anthracycline/taxane-based chemotherapy. *Br J Cancer* 2006;**95**:1161–6.
12. Vahdat LT, Twelves C, Allison MK, et al. Phase II study of eribulin mesylate (E7389) in patients (pts) with locally advanced or metastatic breast cancer (MBC) previously treated with anthracycline, taxane, and capecitabine therapy. *J Clin Oncol* 2008;**26**(15S): abstract 1084.
13. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2007;**25**:3407–14.
14. Roché H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. *J Clin Oncol* 2007;**25**:3415–20.
15. Thomas E, Tabernero J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. *J Clin Oncol* 2007;**25**:3399–406.
16. Coley H. Mechanisms and consequences of chemotherapy resistance in breast cancer. *EJC Suppl* 2009;**7**(1):3–7.
17. *IXEMPRA™ Kit (Ixabepilone) for injection* [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2007.
18. Bollag DM, McQueney PA, Zhu J, et al. Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action. *Cancer Res* 1995;**55**:2325–33.
19. Lee FY, Borzilleri R, Fairchild CR, et al. BMS-247550: a novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. *Clin Cancer Res* 2001;**7**:1429–37.
20. Fumoleau P, Coudert B, Isambert N, Ferrant E. Novel tubulin-targeting agents: anticancer activity and pharmacologic profile of epothilones and related analogues. *Ann Oncol* 2007;**18**(Suppl 5):v9–15.
21. Harrison M, Swanton C. Epothilones and new analogues of the microtubule modulators in taxane-resistant disease. *Expert Opin Invest Drugs* 2008;**17**:523–46.
22. Lee FY, Smykla R, Johnston K, et al. Preclinical efficacy spectrum and pharmacokinetics of ixabepilone. *Cancer Chemother Pharmacol* 2009;**63**:201–12.
23. Lee JJ, Swain SM. Development of novel chemotherapeutic agents to evade the mechanisms of multidrug resistance (MDR). *Semin Oncol* 2005;**32**:S22–6.
24. Pivot X, Dufresne A, Villanueva C. Efficacy and safety of ixabepilone, a novel epothilone analogue. *Clin Breast Cancer* 2007;**7**:543–9.
25. Denduluri N, Low JA, Lee JJ, et al. Phase II trial of ixabepilone, an epothilone B analogue, in patients with metastatic breast cancer previously untreated with taxanes. *J Clin Oncol* 2007;**25**:3421–7.
26. Low JA, Wedman SB, Lee JJ, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer. *J Clin Oncol* 2005;**23**:2726–34.
27. Baselga J, Gianni L, Llombart A, Manikhas G, Kubista E, Steger G. Predicting response to ixabepilone: genomic study in patients receiving single agent ixabepilone as neoadjuvant treatment for breast cancer. *Breast Cancer Res Treat* 2005;**94**(S31): abstract 305.
28. Hortobagyi GN, Perez E, Vrdoljak E, et al. Analysis of overall survival (OS) among patients (pts) with metastatic breast cancer (MBC) receiving either ixabepilone (I) plus capecitabine (C) or C alone: results from two randomized phase III trials. *ASCO Breast Cancer Symposium* 2008: abstract 186.
29. Peacock NW, Spigel DR, Mainwaring MG, et al. Preliminary results of a multicenter phase II trial of vinflunine (with trastuzumab in HER2+ pts) as first-line in metastatic breast cancer. *J Clin Oncol* 2007;**25**(18S): abstract 1043.