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Ixabepilone

In Locally Advanced or Metastatic Breast Cancer

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Contents

Abstract

▲ Ixabepilone, an analogue of the natural product epothilone B, stabilizes microtubules resulting in cell cycle arrest and apoptosis. It is indicated for the treatment of locally advanced or metastatic breast cancer in the US.

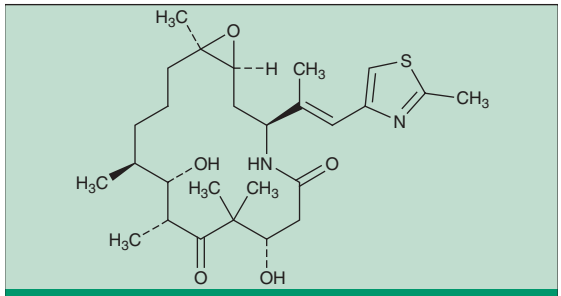
▲ Ixabepilone has shown antitumour activity in tumour cell lines *in vitro* and in several animal tumour models, including those that display key mechanisms of resistance to other anticancer agents.

▲ In a randomized, nonblind, multicentre, phase III trial in women with locally advanced or metastatic breast cancer that was pretreated with, or resistant to, anthracyclines and resistant to taxanes, progression-free survival was significantly longer in ixabepilone plus capecitabine recipients compared with recipients of capecitabine monotherapy (median 5.8 vs 4.2 months).

▲ The response rate to ixabepilone monotherapy was 11.5% in a noncomparative, multicentre, phase II trial in women with locally advanced or metastatic breast cancer resistant to anthracyclines, taxanes and capecitabine.

▲ The most common grade 3 or 4 treatment-related adverse events in both trials were myelosuppression and peripheral sensory neuropathy.

Features and properties of ixabepilone (BMS-247550; Ixempra®)	
Approved indication in the US	
Metastatic or locally advanced breast cancer in combination with capecitabine after failure of an anthracycline and a taxane, or as monotherapy after failure of an anthracycline, a taxane and capecitabine	
Mechanism of action	
Induces microtubule polymerization and stabilization by binding to β-tubulin subunits resulting in cell cycle arrest and apoptosis	
Dosage and administration	
Dosage	40 mg/m^2 over 3 h
Route of administration	Intravenous infusion
Frequency of administration	Every 3 wk
Pharmacokinetic profile (after a 3-h infusion of ixabepilone 40 mg/m^2 in patients with advanced solid tumours and lymphomas)	
Mean peak plasma concentration	247 ng/mL
Mean area under the plasma concentration-time curve	2406 ng • h/mL
Mean elimination half-life	35 h
Treatment-related adverse events	
Most common grade 3 or 4 events	Neutropenia, leukopenia, peripheral sensory neuropathy, fatigue/asthenia



Ixabepilone

The goals of treatment for metastatic breast cancer are maximizing the health-related quality of life, palliating symptoms and prolonging survival.[1] For patients with hormone-sensitive metastatic breast cancer, endocrine therapy is recommended as the first treatment option.[1,2] When cytotoxic chemotherapy is required, anthracyclines and taxanes are recommended and are widely used.[1] However, resistance to these agents can develop or be inherent and, with their increased use in the adjuvant or neoadjuvant setting, they may no longer be an option if the cancer progresses. Furthermore, cumulative anthracycline use is restricted due to an increased risk of cardiotoxicity.[1] There are limited options for treatment of advanced breast cancer after failure of, or resistance to, anthracyclines or taxanes.[1,3]

A number of different mechanisms of resistance to anticancer drugs have been identified.[4-7] One of the key mechanisms of resistance to anthracyclines and taxanes is overexpression of efflux pump proteins, such as P-glycoprotein (P-gp) and multidrug resistance-associated protein-1.[5-7] These proteins pump the anticancer drugs out of the target tumour cells, resulting in subtherapeutic intracellular concentrations.[7] Other mechanisms of resistance, such as β-tubulin mutations or overexpression of the βIII-tubulin isoform, affect the efficacy of taxanes, because taxanes stabilize microtubules by acting on the βII-tubulin isoform.[5,7]

Ixabepilone (Ixempra®) is a semi-synthetic lactam analogue of the natural product epothilone B, which, like the taxanes, stabilizes microtubules resulting in cell cycle arrest and cell death.[8] However, unlike some other agents, ixabepilone can overcome several key mechanisms of resistance, providing a treatment option for tumours that are resistant to other anticancer drugs.[5]

The focus of this review is the use of ixabepilone as monotherapy in patients with locally advanced or metastatic breast cancer that is resistant or refractory to anthracyclines, taxanes and capecitabine, or in combination with capecitabine in patients with locally advanced or metastatic breast cancer that is resistant to treatment with a taxane and an anthracycline, or in patients whose cancer is taxane-resistant and for whom further therapy with anthracyclines is contraindicated. Although ixabepilone is also been investigated for the treatment of other types of cancer, and in combination with other chemotherapy agents (reviewed by Denduluri and Swain[9] and Pivot et al.[10]), these potential uses are beyond the scope of this review.

Medical literature on the use of ixabepilone in locally advanced or metastatic breast cancer was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference list of published articles.

1. Pharmacodynamic Profile

The pharmacodynamic properties of ixabepilone have been reviewed in detail elsewhere;[6,7] this section provides an overview of the pharmacodynamics of the drug.

- Like other epothilones, ixabepilone induces microtubule polymerization and stabilization by binding to β-tubulin subunits.[11] This causes cell cycle arrest at the G2-M transition and induces apoptosis. The taxanes have a similar mechanism of action, and it is thought that taxanes and epothilones share common pharmacophores and bind to the same or an overlapping site on β-tubulin subunits.[12,13] However, in an assay of tubulin polymerization, ixabepilone was ≈2.5-fold more potent than the taxane paclitaxel.[13]
- Microtubule bundle formation in peripheral blood mononuclear cells (used as a marker of drug

binding) was dose dependent and peaked at the end of a 1-hour infusion of ixabepilone 14.8–59.2 mg/m^2 in patients in a phase I study (n = 17).[14] At the end of a 1-hour infusion of ixabepilone 40 mg/m^2, 63% of peripheral blood mononuclear cells exhibited microtubule bundle formation; 24 hours after the infusion, this value was 16–23%.[14]

- Ixabepilone has been associated with increases in the levels of markers of microtubule stabilization.[15] Detyrosinated α-tubulin and acetylated α-tubulin levels increased in *in vitro* cultured cell lines exposed to ixabepilone. Moreover, in tumour cells isolated from patients with metastatic renal cell cancer receiving ixabepilone 6 mg/m^2/day for 5 days, the increase from baseline was 2- to 25-fold for detyrosinated α-tubulin (for 11 of 13 serial biopsies) and 2- to 100-fold for acetylated α-tubulin (for 11 of 12 serial biopsies).[15]
- The cytotoxic activity of ixabepilone was demonstrated *in vitro* in a variety of tumour cell lines (including breast, ovarian, colon, prostate, lung and squamous cell carcinoma lines), including several cell lines that were resistant to paclitaxel.[6,13] The 50% inhibitory concentrations (IC_{50}) in 21 tumour cell lines ranged from 1.4 to 34.5 nmol/L,[13] and in another study, IC_{50} values ranged from 1.4 to 45.7 nmol/L in 31 of 35 human breast cancer cell lines.[6]
- *In vivo*, ixabepilone was active against a variety of human tumour xenografts in mice,[6,13] including several paclitaxel-insensitive or -resistant models.[13] Log cell kill ranges were 1.0 to >5 for ixabepilone and 0.3–2.2 for paclitaxel in seven paclitaxel-resistant tumours in one study; in the paclitaxel-sensitive tumour models in the same study, ixabepilone antitumour activity was comparable to that of paclitaxel.[13]
- Ixabepilone is able to overcome several key mechanisms of resistance to other chemotherapy agents, including the overexpression of P-gp or βIII-tubulin, and β-tubulin mutations.[6,13]
- Ixabepilone was significantly more effective than paclitaxel in terms of log cell kill in two P-gp-positive multidrug-resistant breast cancer models in mice, 16C/ADR (3.5 vs 1.4; p = 0.0048) and MCF7/ADR (0.5 vs 0; p = 0.04).[6] Furthermore, ixabepilone was significantly more effective than docetaxel in a βIII-tubulin-overexpressing paclitaxel-resistant breast cancer model (Pat-21) in terms of log cell kill (1.6 vs 0; p = 0.003).[6]
- In a murine model of A2780Tax ovarian carcinoma, paclitaxel resistance is attributed to a β-tubulin gene mutation; log cell kill values using this model were 2.5 for ixabepilone and 0.8 for paclitaxel (statistical analysis not reported).[13]
- Ixabepilone displayed synergistic antitumour activity when used in combination with capecitabine (study available as an abstract).[16] In a human colon tumour xenograft,[16] the antitumour efficacy of combination therapy was significantly ($p \leq 0.035$) greater than monotherapy with ixabepilone or capecitabine at the maximum tolerated dose (1.9 vs 0.8 and 0.4 log cell kill).
- Sensitivity to ixabepilone may be predicted by preclinical markers, including estrogen receptor (ER) and microtubule-associated protein *tau* gene expression.[17] In a study of neoadjuvant treatment with ixabepilone in women with invasive breast cancer (n = 134),[17] ER and *tau* gene expression were inversely related to a pathological complete response in the breast, with positive predictive values of 37% and 29%, and negative predictive values of 92% and 89%. A 10-gene penalized logistic regression model, which included ER and *tau*, had positive and negative predictive values of 45% and 89%.[17]

2. Pharmacokinetic Profile

This section focuses on the pharmacokinetic values in 14 patients who received the recommended dosage of ixabepilone (40 mg/m^2) administered via a 3-hour infusion in a study in 61 patients with cancer (advanced solid tumours and lymphomas).[18] Additional pharmacokinetic data have been obtained from the US manufacturer's prescribing information.[8]

Several fully published studies have investigated the pharmacokinetics of ixabepilone using other than the recommended administration schedule, such as a 1-hour infusion every 3 weeks[19,20] or

daily administration of a lower dose of ixabepilone.[21] These studies determined the maximum tolerated dose and dose-limiting toxicities for ixabepilone, but are not discussed in detail here as the recommended infusion time was subsequently changed to 3 hours to minimize the incidence of neurotoxicity.[18] Pharmacokinetic data from a study of ixabepilone administered as a 3-hour infusion to Japanese patients were consistent with those of non-Japanese patients.[22] There are no published studies investigating the pharmacokinetics of ixabepilone administered in combination with capecitabine.

- A geometric mean peak ixabepilone plasma concentration (C_{max}) of 247 ng/mL was reached during a 3-hour infusion of ixabepilone 40 mg/m^2 in patients with cancer.[18] C_{max} typically occurred at the end of the infusion (median time to C_{max} was 2.97 hours).
- The geometric mean area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC_∞) for ixabepilone 40 mg/m^2 infused over 3 hours was 2406 ng • h/mL.[18]
- Ixabepilone has a large volume of distribution; the mean volume of distribution at steady state was 1476 L following a 3-hour infusion of ixabepilone 40 mg/m^2, reflecting extensive tissue binding.[18] The range of binding to human serum proteins was 67–77% *in vitro*.[8]
- Metabolism of ixabepilone is extensive and occurs in the liver, mainly via cytochrome P450 (CYP) 3A4 isoenzymes; ixabepilone is metabolized to over 30 inactive metabolites.[8]
- The mean plasma elimination half-life following a 3-hour infusion of ixabepilone 40 mg/m^2 was 35 hours and the mean total body clearance was 35.3 L/h.[18]
- Due to extensive metabolism, only low amounts of unchanged ixabepilone were eliminated in the urine (5.6% of the dose) and faeces (1.6%) after an intravenous dose of ^{14}[C]-ixabepilone.[8] Approximately 86% of the dose was recovered as metabolized drug in faeces (65%) and urine (21%) within 7 days.[8]
- The pharmacokinetics of ixabepilone are affected by hepatic impairment.[8,23] Patients with mild (bilirubin >1–1.5 × upper limit of normal [ULN], or AST >1 × ULN and bilirubin <1.5 × ULN) to severe (bilirubin >3 × ULN and any AST level) hepatic impairment (n = 56), experienced increases in AUC_∞ of 22–81% relative to AUC_∞ values for patients with normal hepatic function (n = 17).[8] Ixabepilone is contraindicated, or dosage reductions are recommended, for patients with hepatic impairment depending on the degree of impairment (see section 5 for details).
- As ixabepilone is extensively metabolized by CYP3A4, coadminstration of CYP3A4 inhibitors or inducers may affect exposure to ixabepilone.[8]
- Concomitant use of ixabepilone and potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, telithromycin, voriconazole and grapefruit juice) should be avoided if possible, or the ixabepilone dosage reduced (see section 5).[8] Coadministration with ketaconazole increased exposure to ixabepilone (measured by AUC_∞) by a mean of 79%.[24]
- Concomitant use of strong CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, rifabutin and phenobarbital) may decrease ixabepilone plasma concentrations to subtherapeutic levels.[8]
- Although coadministration of ixabepilone and capecitabine affects exposure to the individual drugs, this interaction is not considered to be clinically significant.[8] Relative to ixabepilone and capecitabine monotherapy, combination therapy decreased C_{max} values for ixabepilone and capecitabine by 19% and 27%, respectively, and increased the AUC value for 5-fluorouracil (the active metabolite of capecitabine) by 14%.[8]

3. Therapeutic Efficacy

The efficacy of ixabepilone in combination with capecitabine in the treatment of advanced breast cancer has been compared with that of capecitabine monotherapy in a randomized, nonblind, multicentre, multinational, phase III clinical trial in 752 women with locally advanced or metastatic breast cancer that was pretreated with or resistant to anthracyclines and resistant to taxanes.[25] In addition,

a noncomparative, multicentre, multinational, phase II trial has investigated the use of ixabepilone as monotherapy in 126 women with locally advanced or metastatic breast cancer resistant to anthracyclines, taxanes and capecitabine.[26]

Data from subgroup analyses of the phase III trial are also discussed (available only as abstracts).[27,28]

The efficacy of ixabepilone has also been investigated in a second large (n = 1221), randomized, phase III trial (preliminary data available as an abstract[29]) and in a number of smaller (n < 100), fully-published, phase II trials in patients with locally advanced or metastatic breast cancer;[30-34] however, as patient populations in these trials did not meet US-approved labelling restrictions based on prior taxane or anthracycline use (e.g. pretreated with taxanes, but prior anthracycline use not specified), data from these trials are not discussed here.

In the key studies, the definitions of resistance were disease progression while receiving treatment, or within 2[26] or 3[25] months of last treatment, for metastatic breast cancer, or recurrence within 6 months of adjuvant or neoadjuvant treatment with anthracyclines or taxanes.[25,26] In the phase III study,[25] the definition of taxane resistance was changed during the study to include recurrence within 4 months of the last dose of treatment for metastatic breast cancer or with 12 months of receiving adjuvant treatment. Patients not resistant to anthracyclines could be included if they had received minimum cumulative anthracycline doses of doxorubicin 240 mg/m^2 or epirubicin 360 mg/m^2.[25,26]

Other eligibility criteria in the phase III trial[25] included a maximum of three prior chemotherapy regimens (sequential neoadjuvant/adjuvant treatment counted as one regimen) in any setting, and for the phase II trial,[26] a maximum of five prior chemotherapy regimens (including not more than three for metastatic breast cancer). Patients were required to have a Karnofsky performance score ≥70.[25,26]

Exclusion criteria in both trials included brain metastases or grade ≥2 neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events version 3 [CTCAE]).[25,26] The phase III study also excluded patients with liver dysfunction; this was originally defined as grade ≥2 liver function tests measured by ALT ≥2.5 × ULN or bilirubin ≥1.5 × ULN, except for patients with liver metastases, but was changed during the study to exclude patients with grade ≥2 liver function tests for ALT, AST or bilirubin irrespective of liver metastases.[25]

Ixabepilone 40 mg/m^2 was administered as a 3-hour intravenous infusion on day 1 of a 3-week cycle in both studies.[25,26] In the phase III comparative study, patients in the ixabepilone plus capecitabine group also received oral capecitabine 2000 mg/m^2 in two divided doses on days 1–14 of a 3-week cycle.[25] In the comparator group, patients received oral capecitabine 2500 mg/m^2 in two divided doses on days 1–14 of a 3-week cycle.[25]

Histamine H_1 and H_2 receptor antagonists were administered prior to ixabepilone in the phase III study to prevent hypersensitivity reactions.[25] Doses of ixabepilone or capecitabine could be reduced, delayed or discontinued based on tolerability; treatment was continued until disease progression or unacceptable toxicity (up to a maximum of 18 cycles in the phase II study).[25,26]

In Combination with Capecitabine

The primary efficacy endpoint for the phase III study was progression-free survival (time from randomization to disease progression or death) in the intent-to-treat (ITT) population.[25] Tumour progression was assessed by independent radiology review. Secondary efficacy endpoints included tumour response rate, time to response, duration of overall response and overall survival.

Patients were aged 25–79 years (median 52 and 53 years in the combination group and capecitabine groups, respectively) and most (89% and 90%) had two or more disease sites.[25] In both treatment groups, 92% of patients had received prior chemotherapy in the metastatic setting, and 44% had anthracycline resistance. Resistance to taxanes had been experienced by 11% of patients in the ixabepilone plus capecitabine group and 12% of patients in the capecitabine group in the neoadjuvant/adjuvant setting, and 87% and 85% of patients, respectively, in the metastatic setting.[25]

For patients in the combination treatment group, the median number of treatment cycles was five (range 1–37) compared with four (range 1–33) in the capecitabine group.[25] Dosage reductions of ixabepilone or capecitabine were required by 51% and 45% of patients in the combination group, and in 37% of patients receiving capecitabine monotherapy. Most patients received ≥70% of their planned dose intensity; 88% and 62% in the combination group received the planned ixabepilone or capecitabine dosage, as did 82% in the capecitabine monotherapy group.[25]

- Ixabepilone plus capecitabine increased progression-free survival by 40% relative to capecitabine monotherapy in women with locally advanced or metastatic breast cancer that was pretreated with or resistant to anthracyclines and resistant to taxanes, when assessed by independent radiology review and the investigators (5.8 vs 4.2 and 5.3 vs 3.8 months) [figure 1].[25]
- Based on Kaplan-Meier curves, the estimated risk of disease progression was reduced by 25% (hazard ratio [HR] 0.75; 95% CI 0.64, 0.88; stratified log-rank p = 0.0003) with ixabepilone plus capecitabine combination therapy relative to capecitabine monotherapy.[25]
- The improvement in progression-free survival was also seen across a range of prospectively defined patient subgroups including patients with higher Karnofsky performance scores (>90), those with more than two disease sites, and those with visceral metastases.[25]
- Ixabepilone plus capecitabine also showed beneficial effects in patients who were hormone receptor-negative.[27,28] In 401 patients with ER-negative or receptor status unknown tumours, the HR for progression-free survival in ixabepilone plus capecitabine versus capecitabine monotherapy recipients was 0.65 (95% CI 0.52, 0.80).[27] In the subgroup of 187 patients with triple-negative (i.e. ER/progesterone receptor/human epidermal growth factor receptor 2-negative) disease, progression-free survival was 4.1 months in ixabepilone plus capecitabine recipients versus 2.1 months in capecitabine monotherapy recipients (HR 0.68; 95% CI 0.50, 0.93).[28]
- The objective response rate was significantly higher in the ixabepilone plus capecitabine group than in the capecitabine group (34.7% vs 14.3%; p < 0.0001) [figure 2].[25] Most of these responses were partial responses; one patient in the ixabepilone plus capecitabine group and no patients in the capecitabine group experienced a complete response to treatment. The percentage of patients who experienced a complete or partial response or stable disease for at least 6 months was 51% and 30% in the ixabepilone plus capecitabine and capecitabine monotherapy groups, respectively.[25]
- The median response duration for ixabepilone plus capecitabine recipients was 6.4 months (95% CI 5.6, 7.1) versus 5.6 months (95% CI 4.2, 7.5) for capecitabine recipients, and the time to response was 11.7 weeks for ixabepilone plus capecitabine recipients and 12.0 weeks for capecitabine monotherapy recipients. Overall survival data are not yet available.[25]
- In a cost-utility study based on data from the phase III trial and conducted from a US healthcare

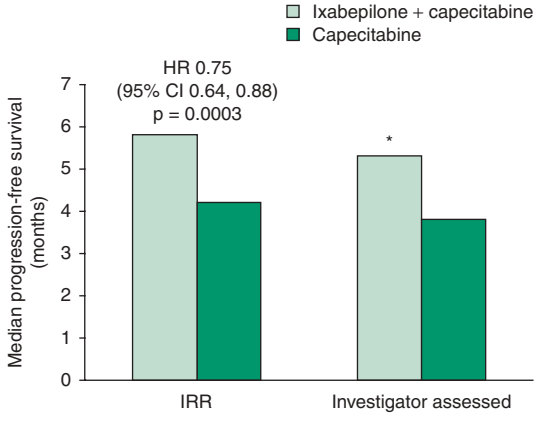


Fig. 1. Efficacy of ixabepilone plus capecitabine vs capecitabine monotherapy in prolonging progression-free survival in women with locally advanced or metastatic breast cancer.[25] In a nonblind, multicentre, phase III trial, patients were randomized to receive ixabepilone 40 mg/m^2 administered as a 3-h intravenous infusion on d 1 of a 3-wk cycle plus oral capecitabine 2000 mg/m^2 on d 1–14 of a 3-wk cycle (n = 375), or oral capecitabine 2500 mg/m^2 on d 1–14 of a 3-wk cycle (n = 377). The respective median number of treatment cycles was five and four. Progression was assessed by independent radiology review (IRR; primary endpoint) or the investigators. **HR** = hazard ratio; * p = 0.0011 vs capecitabine.

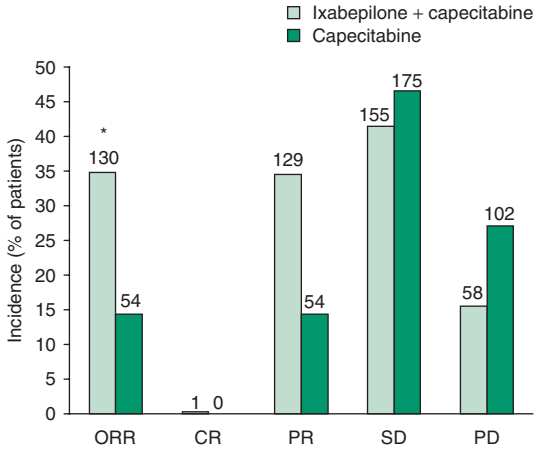


Fig. 2. Efficacy of ixabepilone plus capecitabine vs capecitabine monotherapy assessed by objective tumour response rates in women with locally advanced or metastatic breast cancer.[25] In a nonblind, multicentre, phase III trial, patients were randomized to receive ixabepilone 40 mg/m^2 administered as a 3-h intravenous infusion on d 1 of a 3-wk cycle plus oral capecitabine 2000 mg/m^2 on d 1–14 of a 3-wk cycle (n = 375), or oral capecitabine 2500 mg/m^2 on d 1–14 of a 3-wk cycle (n = 377). The respective median number of treatment cycles was five and four. Tumour response was assessed by independent radiology review. Objective response rate (ORR; secondary endpoint) included complete responses (CR) and partial responses (PR). Other outcomes were stable disease (SD) or progressive disease (PD). Tumour responses were not determined for 32 and 46 ixabepilone plus capecitabine or capecitabine monotherapy recipients, respectively. Numbers above the bars are the numbers of patients. * $p < 0.0001$ vs capecitabine (p-value only reported for ORR).

system perspective, ixabepilone plus capecitabine combination therapy was associated with an estimated additional overall medical cost of $US 31 000 (2008 values) per 1-month gain in quality-adjusted survival relative to capecitabine monotherapy.[35]

Monotherapy

The primary endpoint in the phase II study was objective response rate assessed by an independent radiology facility (measured in all treated patients [n = 126] and in response-assessable patients [those with measurable disease that met the resistance criteria; n = 113]).[26] Secondary endpoints were duration of response, time to response, progression-free survival (all assessed by an independent radiology facility) and overall survival.[26]

The median age of patients was 51 years (range 30–78 years).[26] Sixty-four percent of patients had three or more disease sites and 77% of patients had visceral disease of the liver and/or lung. Most patients (88%) had received two or three prior chemotherapy regimens in the metastatic setting. The median number of cycles of ixabepilone treatment was four (range 1–16) and the median dose intensity was 12.8 mg/m^2/week (range 0.2–14.2 mg/m^2/week). The planned dose of ixabepilone 40 mg/m^2 was administered in 80% of cycles.[26] The number of patients assessable for response was 113.[26]

- Antitumour activity was observed in women with locally advanced or metastatic breast cancer resistant to anthracyclines, taxanes and capecitabine following treatment with ixabepilone.[26] A total of 25% of patients achieved either a partial response (13 patients) or experienced stable disease for at least 6 months (15 patients).[26]
- The objective response rate in the response-assessable population was 11.5% (95% CI 6.3, 18.9); it was 11.1% in the ITT population (95% CI 6.2, 17.9).[26] All responses were partial.
- Stable disease was the best response achieved for 50% of patients, and 13.3% (95% CI 7.6, 20.9) of patients experienced stable disease for at least 6 months (response-assessable population).[26]
- The median duration of response was 5.7 months (95% CI 4.4, 7.3) and the median time to response was 6.1 weeks (range 5–19 weeks).[26] Progression-free survival lasted a median of 3.1 months (95% CI 2.7, 4.2) and median overall survival was 8.6 months (95% CI 6.9, 11.1).[26]

4. Tolerability

This section focuses on descriptive adverse event data from the trials discussed in section 3.[25,26] Treatment-related adverse events were graded based on CTCAE criteria.[25,26]

In Combination with Capecitabine

- Treatment-related adverse events in patients who received ixabepilone plus capecitabine in the phase III clinical trial were mostly mild to moderate (grade

1 or 2) in severity; treatment was discontinued due to adverse events in 18% of patients in the ixabepilone plus capecitabine group and in 7% of patients in the capecitabine group.[25]

- The rate of death within 30 days of the last dose of treatment (all causes) was 9% in the ixabepilone plus capecitabine group and 11% in the capecitabine group.
- The haematological events leukopenia (90% vs 54%; combination group vs capecitabine), anaemia (90% vs 70%) and neutropenia (89% vs 43%) were the most common adverse events (all grades of severity) overall in ixabepilone plus capecitabine recipients.[25]
- Neutropenia and leukopenia were the most common grade 3 or 4 adverse events in ixabepilone plus capecitabine recipients (figure 3a). Deaths related to neutropenia occurred in both treatment groups; in patients with liver function grade 0 or 1 at baseline, the incidences were 2% in the combination group and 0.9% in the capecitabine group and, in patients with liver function grade ≥2, the corresponding incidences were 31% (5 of 16 patients) and 19% (5 of 26 patients). Exclusion criteria were amended during the trial to exclude patients with pre-existing hepatic dysfunction.[25]
- Peripheral neuropathy (primarily sensory but also motor) occurred in 67% of patients in the combination group and in 16% of patients in the capecitabine group.[25]
- Grade 3 or 4 peripheral neuropathy (sensory and/or motor) was experienced by 23% of ixabepilone plus capecitabine recipients, but was not experienced by any capecitabine monotherapy recipients (figure 3a). Neuropathy was generally reversible and was managed with dose reductions or delay in treatment. Grade 3 or 4 neuropathy had a median time to onset of four treatment cycles and, after dosage reduction, resolved to baseline or grade 1 levels with a median of 6 weeks.[25]
- Hand-foot syndrome, an adverse event associated with capecitabine therapy, was experienced by a high proportion of patients in both the combination and capecitabine monotherapy groups (64% vs 62%).[25]

Monotherapy

- Most ixabepilone recipients (94%) in the phase II trial experienced at least one treatment-related adverse event, although most adverse events (55%) were mild or moderate (grade 1 or 2) in severity.[26]
- Ixabepilone treatment was discontinued because of adverse events in 11% of patients in the study; for 6% of patients, this was due to peripheral neuropathy.[26]
- Haematological adverse events were the most common adverse events experienced by ixabepilone recipients overall; the most common events were leukopenia (90% of patients), anaemia (84%) and neutropenia (79%).[26]
- Neutropenia and leukopenia were also the most common grade 3 or 4 adverse events (figure 3b). These adverse events were considered manageable.[26] There was one treatment-related death due to septic shock in association with grade 4 neutropenia in a patient with grade 4 cardiac failure at baseline.[26]
- Peripheral sensory neuropathy (60%) was the most common treatment-related nonhaematological adverse event overall (all grades), followed by fatigue/asthenia (50%), myalgia/arthralgia (49%) and alopecia (48%).[26] The incidence (all grades) of peripheral motor neuropathy was 10%.
- Peripheral sensory neuropathy and fatigue/asthenia were also the most common nonhaematological grade 3 or 4 adverse events (figure 3b). Peripheral neuropathy was generally reversible and improved or remained stable in most of the patients following a dose reduction. The median time to resolution of grade 3 or 4 neuropathy to baseline or grade 1 levels was 5.4 weeks.[26]

5. Dosage and Administration

The recommended dosage of ixabepilone in patients with locally advanced or metastatic breast cancer is 40 mg/m^2 (to a maximum of 88 mg) administered as a 3-hour intravenous infusion every 3 weeks.[8] Dosage reductions (as specified in the manufacturer's prescribing information[8]) may be required based on toxicities including neuropathy or haematological events. Treatment should be

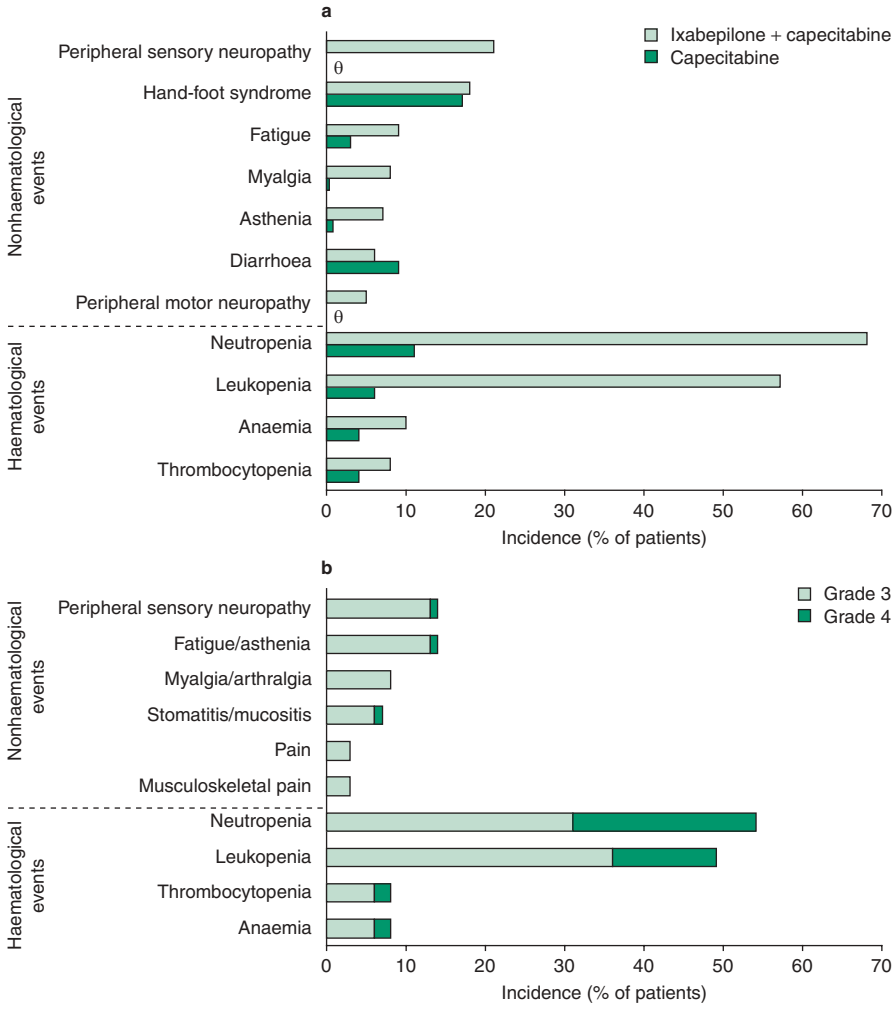


Fig. 3. Tolerability of ixabepilone in combination with capecitabine or as monotherapy in women with locally advanced or metastatic breast cancer.[25,26] Grade 3 or 4 (National Cancer Institute Common Terminology Criteria for Adverse Events version 3 criteria) incidences of haematological and nonhaematological treatment-related adverse events occurring in (**a**) ≥5% of patients who received ixabepilone 40 mg/m^2 administered as a 3-h intravenous infusion on d 1 of a 3-wk cycle plus oral capecitabine 2000 mg/m^2 on d 1–14 of a 3-wk cycle (n = 369), or oral capecitabine 2500 mg/m^2 on d 1–14 of a 3-wk cycle (n = 368) in a randomized, nonblind, multicentre, phase III trial,[25] and (**b**) ≥3% of patients receiving ixabepilone 40 mg/m^2 as a 3-h intravenous infusion on d 1 of a 3-wk cycle in a noncomparative, multicentre, phase II trial (n = 126).[26] Patients received treatment until disease progression or unacceptable toxicity, with a maximum ≤18 cycles in the phase II trial.[26] θ = 0% of patients.

discontinued for grade 3 neuropathy that has lasted ≥7 days or is disabling, and for any disabling grade 4 toxicity.

Patients should be premedicated with an H_1 and an H_2 receptor antagonist ≈1 hour before starting the ixabepilone infusion to reduce the chance of experiencing a hypersensitivity reaction.[8] For patients who have previously experienced a hypersensitivity reaction to ixabepilone, premedication with corticosteroids is required in addition to premedication with H_1 and H_2 receptor antagonists.[8]

Ixabepilone in combination with capecitabine is contraindicated (with a boxed warning in the

manufacturer's prescribing information[8]) in patients with hepatic impairment measured as AST or ALT >2.5×ULN or bilirubin >1×ULN, as there is an increased risk of toxicity and neutropenia-related death in these patients. Patients with AST and ALT ≤2.5×ULN and bilirubin ≤1×ULN may receive the standard ixabepilone dosage in combination with capecitabine.

Ixabepilone may be administered as monotherapy at a reduced starting dosage in patients with mild or moderate hepatic impairment; recommended starting dosages are 20–30 mg/m^2 for those with AST and ALT ≤10×ULN and bilirubin >1.5 and ≤3×ULN, and 32 mg/m^2 for those with AST and ALT ≤10×ULN and bilirubin ≤1.5×ULN. Use of ixabepilone as monotherapy is not recommended in patients with AST or ALT >10×ULN or bilirubin >3×ULN.[8]

Concomitant use of strong CYP3A4 inhibitors should be avoided if possible during treatment with ixabepilone, as these drugs may increase exposure to ixabepilone (see section 2).[8] If concomitant administration cannot be avoided, the ixabepilone dosage should be reduced to 20 mg/m^2. The use of mild or moderate CYP3A4 inhibitors (e.g. erythromycin, fluconazole or verapamil) together with ixabepilone has not been studied, and caution is advised if administering these drugs concomitantly.[8]

Local prescribing information should be consulted for other contraindications, warnings and precautions, specific dosage recommendations in special patient populations and drug interactions.

6. Ixabepilone: Current Status

In the US,[8] ixabepilone is approved in combination with capecitabine for the treatment of locally advanced or metastatic breast cancer that is resistant to treatment with a taxane and an anthracycline, or in patients whose cancer is taxane-resistant and for whom further therapy with anthracyclines is contraindicated. As monotherapy, ixabepilone is approved in patients with locally advanced or metastatic breast cancer that is resistant or refractory to anthracyclines, taxanes and capecitabine.

Ixabepilone in combination with capecitabine extended progression-free survival compared with capecitabine monotherapy in women with taxane-resistant and anthracycline-resistant or -pretreated advanced breast cancer in a phase III trial, and antitumour activity was associated with ixabepilone monotherapy in women with locally advanced or metastatic breast cancer resistant or refractory to anthracyclines, taxanes and capecitabine in a phase II trial. Common adverse events in these clinical trials were myelosuppression and peripheral neuropathy. Given the nature of the disease, the tolerability profile of ixabepilone was considered manageable.

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