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Current Perspective

# Current perspectives of epothilones in breast cancer

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ABSTRACT

Taxanes have been broadly used in the treatment of breast cancer. However, the majority of initially responsive breast cancer patients eventually develop resistance to taxanes (acquired resistance) and a non-negligible percentage of patients are primarily resistant to these agents (*de novo* resistance). Additionally, taxanes require pre-medication and may cause important side effects such as febrile neutropenia and neuropathy. Hence, new agents with better efficacy and/or a better toxicity profile and/or are easier to administer need to be developed. Epothilones are a novel class of microtubule-targeting agents sharing a similar mechanism of action to the taxanes and having a more potent antiproliferative activity in various tumour cells lines, particularly in cases of taxane-resistant breast cancer. This review will focus on clinical development of epothilones in breast cancer, particularly ixabepilone which is in the late stages of development, their potential impact in clinical practice, advantages and limitations.



## 1. Introduction

Among the various classes of anticancer agents developed in the past two decades, few have achieved the same degree of preclinical and clinical validation in the treatment of breast cancer (BC) as the microtubule stabilisers, exemplified by agents such as paclitaxel[1] and docetaxel.[2] Paclitaxel was the first microtubule-stabilising agent to be developed and interferes with the microtubulin assembly process by binding to polymerised tubulin, thus stabilising the tubulin polymer, leading to cellular apoptosis.[3]

However, despite their excellent clinical results in the treatment of BC, there remains considerable room for improvement, both in terms of efficacy and safety. The majority of initially responsive BC patients eventually develop resistance to taxanes (acquired resistance) and a non-negligible percentage of patients are primarily resistant to these agents (*de novo* resistance). Additionally, an increasing proportion of early BC patients are receiving taxanes as part of their adjuvant treatment, which clearly demands the existence of new agents to offer as first line therapy to these patients in case a relapse occurs. Although less problematic than anthracyclines, regarding long term toxicities such as cardiotoxicity and leukaemia, taxanes may induce neuropathy that in some cases is not completely reversible and that has an important negative impact on the patients' quality of life.

Epothilones are naturally occurring macrolides that constitute a novel class of microtubule-targeting agents, which are cytotoxic metabolites from the myxobacterium *Sorangium cellulosum*. Although the epothilones share a similar mechanism of action to the taxanes, they exhibit more potent antiproliferative activity in various tumour cells lines, particularly in cases of taxane-resistant BC.[4,5] Preclinical studies indicate that epothilones bind to and stabilise microtubules in a

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manner similar but not identical to that of paclitaxel, therefore, being effective in paclitaxel-resistant tumour models.[6] This finding is consistent with the fact that the overexpression of P-glycoprotein (Pgp) present in malignant cells exposed to taxanes has only minimal effects on the cytotoxicity of epothilones *in vitro*.[4,7] Not surprisingly, certain epothilones structural modifications appear to influence susceptibility to Pgp-mediated resistance.[6]

The second-generation semisynthetic epothilone B derivative ixabepilone (BMS 247550) has demonstrated potent cytotoxicity *in vitro*, including MCF-7/ADR, which is an established multidrug resistant BC cell line.[8] The efficacy of ixabepilone in resistant tumours may be explained due to its low susceptibility to important mechanisms of tumour resistance, such as changes in proportions of tubulin isotypes, tubulin mutations, and overexpression of cell membrane transporters.[9] Ixabepilone emerged as the most efficacious epothilone in a battery of *in vivo*preclinical studies, out-performing paclitaxel in Pat-21 human breast carcinoma xenograft, which was the paclitaxel-resistant breast tumour model tested.[7]

The promising antitumour activity and improved biopharmaceutical properties of the epothilones have prompted further evaluation of these compounds in the clinical setting.[7] This review will focus on clinical development of epothilones in BC, particularly ixabepilone which is in the late stages of development, their potential impact in clinical practice, advantages and limitations.

## 2. Phase I trials of epothilones

Table 1 summarises phase I trials testing epothilones in solid tumours. Regarding BC the main messages to retain are a) the objective responses and clinical benefit obtained even in taxane-resistant patients; b) the most common toxicities were haematological, mainly neutropenia, peripheral neuropathy and fatigue; c) two possible regimens and respective maximal tolerated dose (MTDs) were defined: 40 mg/m$^2$ given as 1h-infusion every 21 days[10] and 6 mg/m$^2$/day for 5 days given as 1h-infusion every 21 days.[11]

## 3. Ixabepilone (BMS 247550)

Ixabepilone is a second-generation semisynthetic epothilone B derivative, which is in late phases of development in breast and other tumours. Table 2 summarises the main clinical findings of ixabepilone.

The majority of the patients from phase II trials (222 out of 312 patients) had been previously treated with taxanes. The definition for taxane resistance described in phase II trials was disease progression while receiving therapy in the metastatic setting (within 8 weeks of last treatment) or recurrence within 6 months of adjuvant or neoadjuvant taxane chemotherapy-based[12] or disease progression during therapy or within 4 months of their last dose immediately before study enrolment.[10,12–17]

### 3.1. *Phase II single agent trials*

Results are available for several phase II trials in metastatic breast cancer (MBC) evaluating administration of 6 to 8 mg/m$^2$/day over 3 to 5 days or the schedule of 40 mg/m$^2$ over 3 h every 21 days. Almost all studies[12–15] included patients with at least two previous chemotherapeutic regimens, mainly anthracyclines and taxanes. In this population, the overall response rate was generally low (around 12%) ,[12,13] except for one phase II trial using the 5-day schedule that obtained about 20% of objective responses and one complete response among 37 advanced pre-treated BC patients.[15] One trial evaluated 65 patients in first-line treatment of MBC, with high response rates (43%) and high median duration of response (8.2 months).[16] For patients previously treated only with anthracyclines, a 50% response rate was obtained with the 5-day schedule of ixabepilone. Interestingly, in this trial, the objective response was also high for the subgroup of patients with hormone-receptor positive BC.[14] In all these trials, the majority of patients had visceral measurable disease and HER-2 negative tumours. (see Table 3).

### 3.2. *Phase II combination trials*

Recently the results of the combination of weekly ixabepilone, carboplatin and trastuzumab have been presented as first-line therapy in HER-2 positive MBC. The results were quite promising with an overall response rate of 40%, including two complete responses among 59 patients.[17]

Another randomised phase II trial of ixabepilone plus trastuzumab as first-line therapy in patients with HER-2 positive locally advanced and/or MBC is planned, which will compare this regimen to the standard docetaxel plus trastuzumab in 80 patients not pre-treated and not resistant (defined as relapse less than 12 months from taxane therapy) to taxanes and has objective response rate as primary endpoint.[18] Together, these two trials will determine if the combination of ixabepilone with trastuzumab is a valid option for HER-2 positive patients pre-treated with a taxane, and if this regimen merits further evaluation in a large, randomised phase III trial, which would establish it as a new standard of care.

For the HER-2 negative disease, an ongoing phase II, open label, 3-arm, randomised trial is comparing the combination of two schedules of ixabepilone with bevacizumab to paclitaxel plus bevacizumab as first line therapy in 120 patients with locally recurrent or MBC not resistant to taxanes.[19]

### 3.3. *Phase III trials*

Only one phase III trial of ixabepilone has been published, which compared the combination ixabepilone plus capecitabine with capecitabine alone in 752 patients with MBC previously treated or resistant to an anthracycline and to taxanes (see Table 3). The results demonstrated a statistically significant improvement in progression-free survival (PFS) (5.8 versus 4.2 months; $p = 0.0003$) for the combination arm. The subgroup analysis demonstrated a clear benefit for HER-2 positive independently of oestrogen receptor (ER) status.[20,21] However, important information about percentage of crossover is unknown; in the absence of these data, one can only conclude that the combination of ixabepilone with capecitabine is slightly superior (about 1 month gain in PFS) to capecitabine alone but no conclusion can be drawn regarding the sequential use of these agents as monotherapy. In this

**Table 1 – Phase I trials of epothilones**

| Author | Drug | Patients | Dose/schedule | Toxicities (dose limiting or grade 3–4) | Objective responses | Comments |
|---|---|---|---|---|---|---|
| *PHASE I TRIALS – single agents* | | | | | | |
| Abraham J et al., 2003[11] | BMS-247550 | 27 pre-treated solid tumours (4 BC pre-treated with T) | 1.5 to 12 mg/m$^2$/d over 5-days q3w i.v. | Neutropenia in 13 patients, mucositis and anorexia in one patient, fatigue in 4 patients (6 mg/m$^2$/d)<br>Neutropenia in 5 patients, fatigue in 3 patients, mucosite in one patient (8 mg/m$^2$/d) | 5 PR (2 BC) | Lower rate of neuropathy observed, probably because of lower peak concentrations (?)<br>RPTD: 6 mg/m$^2$/d |
| Zhuang SH et al., 2005[50] | BMS-247550 | 26 pre-treated solid tumours, 17 pts pre-treated with T (6 pts < 6 months) (4 BC) | 6 to 18 mg/m$^2$/d over 3-days q3w | Neutropenia in one patient (8 mg/m$^2$)<br>Neutropenia in 6 patients, thrombocytopenia in 2 patient, fatigue in 2 patients, hyponatremia in one patient, ileus in one patient, mucositis in one patient (10 mg/m$^2$)<br>Neutropenia in one patient, fatigue in one patient (12–18 mg/m$^2$) | 3 SD | 17 patients have received previous taxane therapy<br>No grade 3/4 neurotoxicity<br>RPTD: 8 mg/m$^2$/d, with escalation to 10 mg/m$^2$/d if tolerated |
| Mani S et al., 2004[10] | BMS-247550 | 25 pre-treated solid tumours (6 BC; 2 T refractory; one pre-reated with A) | 7.4 to 59.2 mg/m$^2$ over 1-h i.v. q3w | Neutropenia in 2 patients (29.6 mg/m$^2$)<br>Neutropenia in 10 patients, neurotoxicity in one patient, GI discomfort in one patient, diarrhoea in one patient, fatigue in one patient (40 mg/m$^2$)<br>Neutropenia in 6 patients, thombocytopenia in 2 patients, neurotoxicity in one patient, GI discomfort in one patient, fatigue in 4 patients (50 mg/m$^2$) | 2 PR (BC) and 2 SD (one BC) | RPTD: 40 mg/m$^2$<br>Eleven patients received taxane-based treatments previously<br>Lower incidence of neuropathy<br>The vibration perception threshold (VPT) scores may predict clinical neuropathy |
| Gadgell S et al., 2005[24] | BMS-247550 | 17 pre-treated solid tumours (w/o BC) | 7.4 to 56 mg/m$^2$ over 1-h i.v. q3w | Thrombocytopenia in one patient (28.6 mg/m$^2$)<br>Myelotoxicity in 2 patients; fatigue in three patients; myalgia in 2 patients; emesis in one patient (56 mg/m$^2$)<br>Neutropenia in one patient and fatigue in one patient (40 mg/m$^2$)<br>Myalgia in 2 patients | 7 SD | Incidence of neuropathy less than observed in another studies (39% of patients received previous CT known to cause neuropathic symptoms)<br>RPTD: 40 mg/m$^2$<br>DLT:56 mg/m$^2$ |

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**Table 1 – *continued***

| Author | Drug | Patients | Dose/schedule | Toxicities (dose limiting or grade 3–4) | Objective responses | Comments |
|---|---|---|---|---|---|---|
| Aghajanian C et al., 2007[51] | BMS-247550 | 61 (46 with solid tumours) | 40–50 mg/m$^2$ i.v. q3w | Neuropathy (13%), fatigue (13%), myalgia (10%), arthralgia (7%), nausea (5%). | 6 PR, 2 CR | RPTD: 50 mg/m$^2$ over 3-h infusion q3w27 patents had received two previous CT regimens |
| Awada A et al., 2001[52] | BMS-247550 | 20 pre-treated solid tumours | 1, 2.5, 5, 10, 20, and 25 mg/m$^2$/weekly | HSR in 2 patients ($\geqslant$ 10 mg/m$^2$)<br>Sensory neuropathy in one patient (25 mg/m$^2$) and one patient (20 mg/m$^2$) | 5 SD (one BC, 3 pre-treated with T) | |
| Spriggs D et al., 2003[34] | BMS-247550 | 31 pre-treated solid tumours | 7.4, 15, 30, 50, 57 and 65 mg/m$^2$ over 1-h i.v. q3w | Neuropathy in one patient and neutropenia in two patients (65 mg/m$^2$)<br>Arthralgia and myalgia in 3 patients (57 mg/m$^2$)<br>Febrile neutropenia in one patient (50 mg/m$^2$) | 1 CR (pre-treated with T)<br>3 PR (pre-treated with T)<br>11 SD<br>7 PD | MTD: 50 mg/m$^2$<br>DLT: 57 and 65 mg/m$^2$ |
| Hao D et al., 2002[53] | BMS-247550 | 16 pre-treated solid tumours | 2.5, 5, 10, 20, 30 mg/m$^2$/m$^2$ / weekly over 1-h | Fatigue in one patient (20 mg/m$^2$)<br>Neutropenia in 2 patients (30 mg/m$^2$) | No objective responses | DLT: 20 and 30 mg/m$^2$ |
| Burris III HA et al., 2002[54] | BMS-247550 | 24 | 1, 2.5, 5, 10, 20, 25 and 30 mg/m$^2$/ weekly over 30-min | Fatigue in 3 patients (30 mg/m$^2$)<br>Fatigue in 2 patients, nausea in 2 patients, diarrhoea in one patient, myalgia/arthralgia in 2 patients, sensory neuropathy in one patient (25 mg/m$^2$) | 3 PR<br>3 SD | DLT: 30 mg/m$^2$<br>MTD: 25 mg/m$^2$<br>In order to reduce neuropathy, the study was amended to explore a 1-h infusion given weekly for 3 weeks followed by a 1-week break (rates similar of neuropathy, but pts treated > 4months) |
| *PHASE I - combinations* | | | | | | |
| Chuang E et al., 2007[55] | Ixabepilone(I), pegylated liposomal doxorubicin(PLD), | 18 (10 BC) | I: 24–40 mg/m$^2$q3-4w<br>PLD: 30 mg/m$^2$ q3w | Neutropenia < 7 days (1 pt), palmar plantar erythrodysesthesia (PPE) (4pt), mucositis (3 pt), infection (2 pt), fatigue (2 pt), neutropenia (2 pt), thrombocytopenia (2 pt), anemia (1 pt), neuropathy (1 pt), bilirubin (1 pt). | 1 PR, 3 SD, 6 PD (results for BC pts) | PPE and mucositis became problematic when treatment was continued beyond 2 cycles. They are therefore exploring a 4 week PLD schedule, evaluating I given either q4w or weekly (D1, 8, and 15). |
| Cortes J et al., 2006[36] | trastuzumab (T) + KOS-862 (K) | 13 (BC) | T: 4 mg/kg loading dose → 2 mg/kg/weekly<br>K: 70, 85 and 100 mg/m$^2$ as 90-min i.v. infusion weekly × 3 q4 wks after T | Paresthesia grade 3 in one patient, neuropathic pain in two patients | 2 PR (one was not confirmed) | Prior T therapy $n = 9$, prior taxane $n = 11$<br>No DLTs were noted |

| | | | | | | |
|---|---|---|---|---|---|---|
| *OTHER EPOTHILONES* | | | | | | |
| Rubin EH et al., 2005[29] | Patupilone | 91 solid tumours (17 BC) | 0.3 to 3 mg/m$^2$/weekly (6w on/3w off or 3 w on/ one w off schedule) | Anaemia in 7 patients, thrombocytopenia in one patient, neutropenia in one patient, leucopenia in one patient.<br>Diarrhoea in 11 patients, nausea/ vomiting in 6 patients, fatigue in one patient, increased blood bilirubin in one patient (6weeks on/3weeks off)<br>Diarrhoea in 6 patients, nausea/vomiting in 6 patients, abdominal pain in 2 patients, fatigue in one patient, prothrombin time prolonged in 2 patients (3weeks on/1week off) | 3 PR (1BC)25 SD | 41 patients received previous paclitaxel and 12 patients received previous docetaxel<br>Minimal hematologic toxicity<br>DLT > 2.5 mg/m$^2$<br>RPTD: 2.5 mg/m$^2$/ weekly |
| Calvert PM et al., 2001[30] | Patupilone | 42 solid tumours (5 BC) | 0.3 to 8 mg/m$^2$ q3w, 5 to 30 min infusion | Diarrhoea, fatigue in 4 patients and nausea/ vomiting in 2 patients. | 1 PR<br>11 SD | DLT:Diarrhoea (8 mg/m$^2$) |
| Sessa C et al., 2007[32] | BMS-310705 | 59 solid tumours (9 BC) | 5–25 mg/m$^2$/weekly (D1,D8,D15 q4 weeks)<br>20 mg/m$^2$/weekly (D1& D8 q3 w) | Diarrhoea in one patient (15 mg/m$^2$)<br>Diarrhoea in one patient, neutropenia in one patient, vomiting in one patient (20 mg/m$^2$ D1,D8,D15)<br>Diarrhoea in one patient (30 mg/m$^2$D1, D8, D15)<br>Diarrhoea in one patient (20 mg/m$^2$ D1& D8) | 4 PR (one BC in schedule 1, and 2 in schedule 2) | The toxicities were well described for the first cycle<br>Peripheral neurotoxicity was the main reason for treatment discontinuation for 13 of 18 patients (72%).<br>Two BC patients experienced grade 3 ataxia with 20 mg/m$^2$ D1,D8, D15. |
| Piro LD et al., 2003[33] | KOS-862 | 38 pts and14 ptswith solid tumours | 9–185 mg/m$^2$ q3w or 20,40,50 mg/m$^2$/d over 3 days | Impaired gait in two patients, cognitive/ perceptual abnormalities in two patients and atypical chest pain in one patient (185 mg/m$^2$).<br>Sensory neuropathy in one patient, fatigue and nausea | No objective response | DLT: 185 mg/m$^2$ |
| Spriggs DR et al., 2003[34] | KOS-862 | 13 advanced solid tumours | 16 to 100 mg/m$^2$ i.v. infusion for 3 out of every 4 weeks | Not detailed | Not available | |

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**Table 1 – continued**

| Author | Drug | Patients | Dose/schedule | Toxicities (dose limiting or grade 3–4) | Objective responses | Comments |
|---|---|---|---|---|---|---|
| Holen KD et al., 2004[35] | KOS-862 | 17 pts and 7 pts | 1, 2, 4 and 6 mg/hr rates 24-h CI (schedule A) and1 and 1.7 mg/hr up to 72-hr CI (schedule B) q2w | Sensory neuropathy in one patient (6 mg/h) | No objective response | |
| Schmid P et al., 2006[40] | ZK-EPO | 47 advanced solid tumours | 0.6 to 29 mg/m$^2$ over 30-min infusion q3w | Peripheral neuropathy in one patient (16 mg/m$^2$) ataxia in one patient (29 mg/m$^2$) | 2 PR (BC)13 SD | MTD has not been reached |

BC: breast cancer; q3w: every 3 weeks; PR: partial response; SD: stable disease; CR: complete response; RPTD: Recommended phase II dose; pts: patients; T:taxane; A: anthracycline; w/o: without; DLT: dose-limiting toxicity; MTD: maximum-tolerated dose; PPE: hand-foot syndrome.

incurable bad prognosis population (anthracycline and taxane-resistant MBC) quality of life is a crucial issue that needs to be addressed and most probably more toxic combination regimens should be reserved for symptomatic patients where a fast response is needed. The same controversy exists regarding the use of taxanes alone or in combination with an anti-metabolite (i.e. docetaxel plus capecitabine[22] and paclitaxel plus gemcitabine[23]; in these studies the percentage of crossover was also quite low (<30%) and hence the question of combination versus sequential monotherapy use remains open even for a bigger benefit (gain of 3 months in overall survival) than the one seen in the ixabepilone trial.

### 3.4. *Toxicity profile in MBC*

Phase I and phase II trials including MBC patients evaluated ixabepilone in different schedules using a cremophor-based formulation.

Ixabepilone seems to have a similar toxicity profile to the taxanes. Dose-limiting toxicities (DLTs) were mainly neutropenia and peripheral neuropathy, with recommended phase II doses of 40–50 mg/m$^2$ (for every 21-day schedule), 6 mg/m$^2$/d (for daily-times-five every 21-days schedule), 8 mg/m$^2$/d (for daily-times-three schedule given every 21 days), and 20–25 mg/m$^2$/d (for weekly schedule).

Peripheral sensory neuropathy is the main side effect of ixabepilone and seems to be schedule-dependent with higher incidence with the single-dose every 21-day administration schedule[12,13,16] than with the three- and five-times daily schedules.[10,11,14,24] Additionally, it seems to be clinically significant, with grade 2/3 symptoms usually manifesting after a median of six cycles,[16] and slowly reversible in the majority of patients with dose adjustment or discontinuation.[25] No grade 3/4 sensory neuropathy was observed in taxane-naïve MBC patients.[14] The cause for this neuropathy may be, at least in part, the use of a formulation of ixabepilone in polyosyethylated caster oil, similar to the one used for the taxanes.[26,27]

Haematological toxicity, mainly neutropenia and thrombocytopenia, are also frequent with ixabepilone, as is diarrhoea particularly important with the three- and five-times daily schedules, and fatigue.

Of importance, ixabepilone causes less alopecia and can be administered with or without steroid pre-medication[26] since hypersensitivity reactions seem to be prevented by the routine administration of oral H1/H2 blockers prior to therapy.

In the phase III clinical trial of ixabepilone and capecitabine in 752 patients, between 96 and 98% of patients had been previously treated with taxanes, and all were considered taxane-resistant. The taxane and anthracycline resistance was defined as tumour progression during treatment or within 3 months of last dose in the metastatic setting, or recurrence within 6 months in the neoadjuvant or adjuvant setting. The definition of taxane resistance was reviewed, after 377 patients were enrolled, to align entry criteria with clinical practice, and it was decided to include recurrence within 4 months of the last dose in the metastatic setting or within 12 months in the adjuvant setting.[28] An important information to retain from these phase III trials[20,21,28] is the increased rate of toxic deaths (1.9% versus 0.9%) for the combination in

patients with liver dysfunction, which were not evident from earlier phase studies of ixabepilone, suggesting that in patients with liver dysfunction the use of this combination should perhaps be avoided or cautiously used.

## 4. Other epothilones in breast cancer

### 4.1. *Patupilone (EPO906)*

Patupilone (EPO906) is an epothilone analogue in the early stages of clinical development, with two completed phase I studies. The DLT was diarrhoea at doses > 2.5 mg/m$^2$/weekly[29] and 8 mg/m$^2$ every 21 days[30]; fatigue and peripheral neuropathy were also seen. The recommended phase II dose was 2.5 mg/m$^2$, using either a 6 weeks on/3 weeks off or a 3 weeks on/1 week off weekly schedule.[29] In the Rubin trial there was one partial response in a BC patient previously treated with taxanes.[29]

An ongoing phase II trial of patupilone is evaluating the CNS progression-free survival in 55 patients with advanced BC.[31]

### 4.2. *BMS-310705*

BMS-310705 is a semisynthetic analogue of epothilone B that does not require cremophor-based formulation. It has been evaluated in phase I trials, one of them demonstrating objective responses in BC patients (three out of four partial responses), however, with grade 3/4 toxicities at 20 mg/m$^2$/weekly dose level, including neuropathy and diarrhoea.[32] Further evaluation was suggested with 15 mg/m$^2$ per day dose and a modified 2-weekly every 21 days regimen.

### 4.3. *KOS-862*

The epothilone D analogue KOS-862 was evaluated as a single agent in three phase I trials presented,[33–35] and in combination with trastuzumab in one phase I trial in advanced BC.[36] The dose schedules were different in single-agent trials, and the most important toxicity described was neurological.[33,35] The combination of KOS-862 with trastuzumab was evaluated in 13 patients in a weekly schedule. Most patients have been previously treated with taxanes and trastuzumab. No DLTs were noted and the main toxicity was sensory neuropathy. Two patients had a partial response. The good toxicity profile and hints of response prompted the launch of an open-label phase II study to evaluate this combination in patients with HER-2 overexpressing locally advanced or MBC[37]; this trial is now completed with pending results.

One phase II trial evaluated epothilone D at 100 mg/m$^2$ in weekly schedule with results available for 29 evaluable patients treated previously with taxane and anthracycline.[38] There were five partial responses, and the toxicity was mainly neurological and acceptable.

### 4.4. *ZK-EPO*

ZK-EPO is a tubulin stabiliser that induces cell cycle arrest in G2/M, and preclinical data indicate that this fully synthetic epothilone has significantly greater antiproliferative activity against MDR-sensitive and -resistant BC cell lines tested, when compared to paclitaxel and ixabepilone.[39] In a phase I trial[40] ZK-EPO (0.6 to 29 mg/m$^2$ over 30-min infusion) was administered to 47 patients with advanced solid tumours. The MTD has not been reached, main toxicity was neuropathy, and two partial responses were seen in BC patients. One phase II study is currently recruiting patients with pretreated MBC to evaluate the antitumour activity of the single agent ZK-EPO.[41] There is also one phase II trial ongoing to evaluate the response rate of CNS metastases in patients with advanced BC.[42]

## 5. Predictive markers of response to epothilones

Three studies have tried to develop predictive markers of response to ixabepilone. Baselga et al. have presented a study designed to discover a candidate gene or expression profile able to predict complete pathological response (pCR) to ixabepilone as neoadjuvant therapy for BC .[43] A total of 164 women, with invasive stage IIA–IIIB breast tumours $\geqslant$ 3 cm, received 40 mg/m$^2$ ixabepilone over 3-h on day 1 for up to four 21-day cycles followed by surgery. In 56 patients gene expression data was available, and a six-gene model was selected using the training set. The prediction error for pCR in the validation set was 28%, sensitivity 50%, specificity 94%, positive predictive value 66% and negative predictive value 89%. The neoadjuvant approach is very interesting to discover new biological markers with predictive value. However, before they can be applied to clinical practice a thorough technical and clinical validation is needed, which must include a large prospective trial.

Pre-treatment gene expression profiles were generated from 62 ER negative patients treated with ixabepilone in the clinical study CA163080 and from 51 ER negative patients treated with T/FAC (paclitaxel and fluorouracil-doxorubicin-cyclophosphamide) in the clinical study MDA133.[44] Four candidate models that differentiate response to ixabepilone and paclitaxel-containing therapies were identified, two of them based on expression levels for single microtubule-related genes: transforming acidic coiled-coil containing protein 3 (TACC3) and chromosome condensation protein G (HCAP-G). A randomised phase II biomarker neoadjuvant study of sequential AC followed by ixabepilone compared to sequential AC followed by paclitaxel will include 300 early stage HER-2 and hormonal receptors negative BC patients. The main objectives are to estimate the pCR and to validate the gene expression profile described above.[45]

One phase II trial found increased levels of glu-terminated and acetylated $\alpha$-tubulin after treatment with ixabepilone as single agent in MBC. Interestingly, the authors found that acetylated -$\alpha$-tubulin levels were higher at baseline in the tumour cells of patients whose tumours responded or in patients with stable disease than in the patient whose tumour did not respond.[15] On the contrary, increased levels of tumour $\alpha$-tubulin acetylation, tau-1, and p53 expression did not correlate with clinical response in six patients treated with ixabepilone in a study by Denduluri et al.[14]

**Table 2 – Phase II trials of epothilones in breast cancer**

| Author | Drug | Patients | Dose and schedule | Endpoints | Comments |
|---|---|---|---|---|---|
| Low JA et al., 2005[15] | Ixabepilone (BMS-247550) | 37 Previously treatedmetastatic or advanced BC | 6 mg/m$^2$/d for 5-days q3w | OR: 8 (one CR, 7PR)<br>SD:13; PD:16<br>Median TTP: 80 days | All patients previously treated with taxanes<br>Abraham schedule<br>Four pts excluded : one ineligible, one severe toxicity, two early progression<br>Toxicities: 12 pts required dose reduction; fatigue, myalgia and peripheral sensory neuropathy ↑ levels of glu-terminated and acetylated α-tubulin after treatment |
| Denduluri N et al., 2007[56] | Ixabepilone | 12 Previously treated with T | 8 mg/m$^2$/d for 3-days (first cycle)→<br>10 mg/m$^2$/d for 3-days | SD:10<br>No CR or PR | Main toxicities: leucopenia, neutropenia (grades 3–4), neuropathy, ↑transaminases (grades 1–2) |
| Denduluri N et al., 2007[14] | Ixabepilone | 23 Previously untreated with T | 6 mg/m$^2$/d for 5-days | PR:13<br>SD: 6<br>Median TTP: 5.5 mo | Other previous therapies were allowed (16 out of 23 pts)>50% RR for pts treated previously with anthracyclines and with HR+ disease<br>Dose reductions to 5 or 4 mg/m2/d for grade 3–4 non hem toxicities<br>Main toxicities (grade 3–4): neutropenia, thrombocytopenia, arthralgia, fatigue, motor neuropathy, nausea↑ tumour α-tubulin acetylation after treatment; tau-1, p53 expression did not correlate with clinical response ($n$ = 6) |
| Thomas E et al., 2007[13] | Ixabepilone | 49 Previously treated with T | 40 mg/m$^2$ 3-h infusion q3w | PR:6<br>SD:20<br>PD:21<br>Median TTP: 2.2 mo<br>Median survival: 7.9 mo | Mainly with visceral disease, HER2 neg and 2 prior CT regimens<br>First patients received 50 mg/m$^2$ (not described here)<br>Main toxicities (grade 3–4): fatigue, sensory neuropathy, constitutional symptoms, pain, myalgia, arthralgia, dermatology, rash, nail changes, febrile neutropenia, cardiovascular, blood/haemoglobin, hepatic. |
| Perez E et al., 2007[12] | Ixabepilone | 126 Previously treated with A, T, capecitabine | 40 mg/m$^2$ 3-h infusion q3w | ORR: 11.5% (independent radiology facility)<br>PR:13<br>SD:15<br>Median duration of response: 5.7 mo | Mainly with visceral disease, HER2 neg BC, and 3 prior CT regimen in metastatic setting.<br>The majority of patients who responded to ixabepilone failed to respond to their prior CT<br>Main toxicities (grade 3–4): sensor neuropathy, fatigue, asthenia, myalgia, arthralgia, mucositis, alopecia, nausea, anorexia, constipation, pain, HFS, motor neuropathy |

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|---|---|---|---|---|---|
| Rochè H et al., 2007[16] | Ixabepilone | 65 First line MBC | 40 mg/m$^2$ 3-h infusion q3w | PR:27<br>SD:23<br>PD:13<br>Median duration of response: 8.2 mo<br>Median TTP: 4.8 mo<br>Median survival: 22 mo | First patients received 50 mg/m$^2$ (not described here)<br>The majority of patients were pre-menopausal, with HR+, with one prior anthracycline regimen, and at least 2 involved disease sites.<br>Main toxicities (grade 3–4): Pain (myalgia, arthralgia, neuropathy), GI (nausea, stomatitis, diarrhoea, vomiting), fatigue, sensory and neuropathy, infection, neutropenia, anaemia |
| *COMBINATIONS* | | | | | |
| Moulder SL et al., 2007[17] | Ixabepilone (I), trastuzumab (T), carboplatin (C) | 59 First line therapy (MBC)<br>No data regarding previous use of taxanes | I (15 mg/m$^2$ i.v.), C (AUC = 2 i.v.) on D1, 8 and 15 of a 28-day cycle (maximum of 6 cycles). T (4 mg/kg loading dose then 2 mg/kg i.v. qw) during CT then q3w (6 mg/kg i.v.) until disease progression | CR:2<br>PR: 22<br>SD:13<br>Median PFS: 8 mo | Main toxicities (grade 3 or 4): anaemia (7%, 5%), neutropenia (29%, 19%), thrombocytopenia (12%, 2%), non-neutropenic infection (3%, 0), fatigue (12%, 0), nausea (7%, 0), neuropathy (7%, 0). |
| Buzdar A et al., 2005[38] | KOS-862 | 37 patients previously treated with T and A (29 evaluable) | 100 mg/m$^2$ 90 min i.v. infusion weekly × 3 q4 w | PR:5 (one not confirmed) | Main toxicities: 3 grade 3 neuropathy, dizziness, ataxia, nausea, fatigue, diarrhoea |

BC: breast cancer; q4w: every 4 weeks; q3w: every three weeks; qw: every week; OR: overall response; PR: partial response; SD: stable disease; CR: complete response; PD: progression disease; TTP: time to progression; pts: patients; T: taxane; A: anthracycline; GI: gastrointestinal; CT: chemotherapy.

**Table 3 – Phase III trials of ixabepilone in breast cancer**

| Author | Drugs | Patients | Dose and schedule | Endpoints | Comments |
|---|---|---|---|---|---|
| Lerzo GL et al.; Pivot XB et al., 2007[20,21,28] | Ixabepilone (I), capecitabine (C) | 752 (112 HER2+) previously treated with A and defined resistant to T | I (40 mg/m$^2$ i.v. over 3h on d1 q3wk) + C (1,000 mg/m$^2$ po d1-14 q3w), or C alone (1250 mg/m$^2$ on the same schedule) | Median PFS: 5.8 versus 4.2 mo ($p = 0.0003$)<br>ORR: 35% versus 14% ($p < 0.0001$) | 60% of pts HER2+ received prior trastuzumab Significant improvement in PFS for pts with ER-neg, PR-neg, HER-2-negative breast cancerGrade 3/4 treatment-elated sensory neuropathy (21%), fatigue (9%), and neutropenia (68%) were more frequent with combination therapy.<br>Toxic death rate was 1.9% versus 0.9% (pts with liver dysfunction were at greater risk). |

A: anthracycline; T: taxane; q3w: every 3 weeks; mo: months; PFS: progression-free survival; ORR: overall response rate; ER: oestrogen receptor; PR; progesterone receptor; pts: patients.

## 6. Conclusions and future directions

Clinical evidence so far has proven that epothilones are a new class of cytotoxic agents with manageable toxicity profile and interesting activity in BC even in the difficult setting of anthracycline and taxane-resistance.

Their exact place in the cascade of advanced BC treatment, however, remains to be established, as is their potential role in the adjuvant setting. Large phase III trials are now needed to compare the efficacy of ixabepilone, the epothilone in the most advanced stages of development, to the efficacy of the established standard after anthracycline and taxane treatment, i.e. capecitabine monotherapy. Additionally, several 'new taxanes' are emerging as new treatment options particularly for first line options for patients who have received either paclitaxel or docetaxel as part of their adjuvant chemotherapy. One of these agents, abraxane (ABI-007),[46–48] has the advantage of not needing pre-medication and has already proven its efficacy when compared to docetaxel as first line therapy of MBC.[49] How epothilones compare to abraxane is an interesting but also crucial question to establish the most efficacious sequence of use of these different anti-microtubules agents in clinical practice. It will also be essential to determine if one these agents, or both, should challenge the role of the 'traditional' taxanes in the adjuvant setting, based on their potentially better efficacy and no need for steroid pre-medication. Since very large, and hence expensive, prospective adjuvant trials would be needed, the best option would be to join efforts in one large, well designed, prospective phase III trial, with a strong biomarker component, to enable us to achieve a definite conclusion regarding the relative role of docetaxel/paclitaxel, ixabepilone and abraxane in the adjuvant setting. Whether all the hurdles (e.g. economic, intellectual property rights) mounted by this type of trial can be surpassed is currently unknown.

Some of the new taxanes are being developed trying to explore the advantages of an oral formulation (i.e. tocosol from Sonus Pharmaceuticals, Inc). Interestingly, an oral formulation of ixabepilone was studied in preclinical models and found to be equally effective to the intravenous formulation.[7] The bioavailability with the oral formulation was 31% in mice for pH 8.0 buffered solution and 27% in rats following intraduodenal administration of unbuffered solution. Due to the labile nature of ixabepilone at low pH, an enteric-coated oral formulation was develop which could be given daily to maintain steady state plasma levels around 15 ng/mL over several weeks, minimising toxicity and maximising efficacy.[24]

A somewhat disappointing feature of both epothilones and abraxane is the lack of improvement in terms of neuro and haematological toxicities in relation to taxanes. An important issue is the peripheral neuropathy, which is of great concern particularly when moving to the adjuvant setting. Nevertheless, ixabepilone-associated neuropathy seems to be reversible and re-treatment possible. Efforts must however continue to be made to develop new drugs and/or formulations non-inducing this quite limiting toxicity.

Epothilones are definitely a new tool in our armamentarium against BC in particular for patients pre-treated with

taxanes. It is however indispensable to clearly define the subgroup of patients who are likely to benefit from these drugs and also those who are more likely to experience severe side effects and for whom other options should be found. Well designed pharmacodynamics, pharmacogenetics and biomarker studies will undoubtedly lead the way.

## Conflict of interest statement

None declared.

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