Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Ixabepilone and eribulin mesylate: two novel agents approved for the chemotherapeutic treatment of metastatic breast cancer

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While the majority of breast cancer patients present with early stage disease, 40% of these patients will eventually progress to metastatic disease. Resistance to existing chemotherapeutic agents continues to pose a challenge in the management of these patients. This review will analyze the two most recently approved chemotherapy drugs for the treatment of breast cancer; ixabepilone and eribulin mesylate. Ixabepilone is a semisynthetic analog of epothilone B, and is thought to overcome taxane resistance via disruption to microtubule homeostasis. Two Phase III studies, one by Rugo *et al.* and the other by Thomas *et al.*, showed improvement in progression-free survival with the combination of ixabepilone and capecitabine to approximately 6 months compared with 4.2 months in the capecitabine-alone group in both trials. These resulted in ixabepilone being approved for use alone or in combination with capecitabine for the treatment of locally advanced or metastatic breast cancer after failure of an anthracycline and a taxane in either the adjuvant or the metastatic setting. The drug has been shown to have activity even in heavily pretreated patients who have received at least two prior chemotherapy regimens for the treatments of metastatic disease. The main adverse events were noted to be fatigue, cytopenias and peripheral sensory neuropathy, all of which were manageable and reversible. Eribulin mesylate is another novel agent that has been approved for the treatment of metastatic breast cancer. It functions by inhibiting mitotic-spindle formation and has demonstrated efficacy against various taxane-resistant tumor cell lines. Median progression-free survival was approximately 3 months and overall survival ranged from 9 to 13 months amongst the various trials. Eribulin mesylate is approved to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for metastatic disease, including both anthracycline- and taxane-based chemotherapy regimens. The most common toxicities observed were fatigue, nausea, cytopenias and peripheral neuropathy. In conclusion, both drugs provide additional options for patients who have progressed on other agents.

Keywords: advanced breast cancer • eribulin • halaven • ixabepilone • ixempra

Breast cancer is the most prevalent malignancy among women in the USA and, according to the National Cancer Institute estimates, there were 227,000 new cases and close to 40,000 deaths from breast cancer in 2012 [101]. Approximately half of the women with metastatic breast cancer will succumb to the disease within

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24 months of diagnosis of metastasis. Breast cancer mortality rates have been declining annually but it is unclear whether this trend is due to increased rates of early diagnosis or improvements in treatment [1].

There have been tremendous advances in the treatment options for metastatic breast cancer that have improved the survival of these patients over the past decade; however, resistance to existing chemotherapeutic agents continues to pose an ongoing challenge in the management of these patients. Anthracyclines and taxanes have been the mainstay of treatment for breast cancer in the adjuvant, as well as in the metastatic setting. Nevertheless, their use can be limited mostly by resistance and, less frequently, by toxicity. Therefore the exploration of new agents is required. In this review we will analyze the two most recently US FDA-approved drugs for the treatment of breast cancer; ixabepilone and eribulin mesylate.

Epothilones

Epothilones are a novel class of antineoplastic agents, originating from the myxobacterium *Sorangium cellulosum*. They are cytotoxic macrolides that have a mechanism similar to that of the taxanes in that they stabilize microtubules, subsequently leading to mitotic arrest at the G2–M transition from interference with the mitotic spindle, resulting ultimately in apoptosis. However, they have been shown in preclinical as well as multiple Phase I and II studies to be efficacious even in tumors that have been previously treated and have developed resistance to the taxanes.

Ixabepilone is a semisynthetic analog of epothilone B. It binds to β-tubulin, stabilizes tubulin, disrupts microtubule homeostasis and induces cell-cycle arrest and apoptosis. It is thought to overcome taxane resistance that has developed in tumor cells via changes in tubulin-isotype ratios, tubulin mutations and overexpression of cell membrane transporters. Specifically, there are two main pathways that allow the drug to overcome taxane resistance: first, the drug is not a substrate for the p-glycoprotein efflux pump, which is thought to confer resistance to taxanes in particular [2] and, second, the drug has particular inhibition of the β-III class of tubulin, which is known to be overexpressed in taxane-resistant tumors [3]. In fact, *in vitro*, it was shown to be twice as potent as paclitaxel in inducing tubulin polymerization [2]. The drug's efficacy has been illustrated in taxane-naive and taxane-resistant tumors [2–6]. Ixabepilone has been demonstrated to have significant antitumor activity in multiple breast cancer disease settings. Ixabepilone is cleared via hepatic metabolism and has a half-life of ranging from 20–72 h, indicating a variability in metabolism [7,8].

Phase II studies of ixabepilone

Low *et al.* evaluated the role of ixabepilone in metastatic or locally advanced breast cancer patients in a Phase II trial (n = 37). All patients had received at least one prior neoadjuvant, adjuvant, or metastatic regimen that contained docetaxel or paclitaxel. The objective response rate (ORR) was 22% (95% CI: 9.8–38.2%), with one complete response, seven partial responses, and stable disease for 13 patients. The median time to progression was 80 days. In this study, five patients also underwent biopsies of their tumors at baseline and then again during the second cycle of ixabepilone. While this was a small sample size, it did demonstrate increased levels of both Glu-terminated and acetylated α-tubulin after treatment, indicating that ixabepilone stabilized microtubules in the target tissue. These levels were also higher at baseline in the patients who responded to treatment, introducing an interesting hypothesis that a tumor with inherent microtubule stability might be more likely to respond to a stabilizing agent with additional microtubule stabilization and decreased proliferation [9].

Thomas *et al.* conducted another Phase II clinical trial of ixabepilone in 49 patients with taxane-resistant metastatic breast cancer. All the women had received between one and three prior taxane-containing regimens, had progressed on a taxane immediately prior to enrollment in the study, and were then enrolled to receive ixabepilone 40 mg/m^2 every 3 weeks. Time to progression for all patients was 2.2 months (95% CI: 1.4–3.2 months). The median survival was 7.9 months (95% CI: 6.1–14.5 months). Of the six patients (12.2%) who achieved a partial response to ixabepilone, five had not responded to prior taxane treatment, showing that ixabepilone can overcome resistance to taxanes [4].

Ixabepilone was shown to have efficacy in patients without prior taxane treatment in a trial performed by Denduluri *et al.* on 23 patients. Patients received a median of eight cycles of ixabepilone administered as 6 mg/m^2/d for 5 consecutive days every 3 weeks. The ORR was 57% (95% CI: 34.5–76.8%) – a partial response was observed in 13 out of 23 patients, with a median duration of response being 5.6 months. Six out of 23 patients (26%) experienced stable disease for at least 6 weeks [6].

This was followed by another single-arm Phase II study looking at the efficacy of ixabepilone in previously treated patients with metastatic breast cancer who had developed resistance to anthracyclines, taxanes and capecitabine. Among 113 response-assessable patients, the overall response rate was 11.5% (13 patients had a partial response; 95% CI: 6.3–18.9%). Another 15 patients (13.3%) were observed to have stable disease for 6 months or longer. Median

progression-free and overall survivals (OS) were 3.1 months and 8.6 months, respectively [5].

Ixabepilone has activity as first-line therapy in patients with metastatic breast cancer, as demonstrated in the Phase II trial conducted by Roche *et al.* in those previously treated with anthracycline chemotherapy. Amongst 65 patients who received ixabepilone 40 mg/m^2 as an intravenous (iv.) infusion over 3 h every 3 weeks, the overall response rate was 41.5% (95% CI: 29.4–54.4%), all of which were partial responses, with a median duration of response being 8.2 months. Another 35% of patients experienced stable disease. Median survival amongst all patients was 22 months (95% CI: 15.6–27 months) [10].

Phase III studies of ixabepilone in the metastatic setting

There are two large trials (BMS046 and BMS048) completed in the refractory setting. The first trial (BMS 046) was an international Phase III study conducted by Thomas *et al.,* in which 752 patients were randomized to receive ixabepilone plus capecitabine, or capecitabine alone [11,12]. This study illustrated that the combination has superior efficacy to capecitabine alone in patients with metastatic breast cancer pretreated and resistant to anthracyclines and taxanes. While later analysis revealed no statistically significant improvement in OS, progression-free survival (PFS) was superior in the combination group with a hazard ratio (HR) of 0.75 (95% CI: 0.64–0.88; p = 0.0003), with the duration prolonged to 5.8 months (95% CI: 5.45–6.97 months) compared with 4.2 months (95% CI: 3.81–4.50 months) in the capecitabine-alone group. This improvement was seen across subgroups irrespective of performance status, estrogen receptor (ER) status and HER-2 status [11].

These findings were supported in a second large trial, BMS048, by Sparano *et al.*, in which 1221 patients were randomized to receive ixabepilone plus capecitabine versus capecitabine alone. Again, in this study there was no statistically significant improvement in OS for the combination of ixabepilone and capecitabine over capecitabine alone. However, in a secondary Cox regression analysis accounting for performance status (as the combination group had a higher prevalence of impaired performance status), OS was indeed improved in the combination group (HR: 0.85; p = 0.02). Moreover, the combination therapy did improve PFS, with a median of 6.2 months (95% CI: 5.59–6.97 months) compared with 4.4 months (95% CI: 4.14–5.42 months) in the capecitabine alone control arm (HR: 0.79; 95% CI: 0.69–0.90 months; p = 0.0005) [13]. As discussed below and as expected, combination therapy does have more associated toxicity, so perhaps can be considered for use in more urgent need of response.

Another Phase III study conducted by Rugo *et al.* randomized patients to weekly paclitaxel, weekly nab-paclitaxel, or ixabepilone with or without bevacizumab as first-line therapy in the metastatic setting. The dosing of ixabepilone in this study was at the nonapproved weekly dose of 16 mg/m^2 as opposed to the FDA-approved dose of 40 mg/m^2 every 3 weeks. At the first interim analysis, the comparison of ixabepilone with paclitaxel crossed the futility boundary and there was no further accrual to the ixabepilone arm. At the second interim analysis, accrual was closed to the nab-paclitaxel arm for the same reason. PFS remained superior in the paclitaxel group compared with the two experimental arms and the toxicity profile was similarly superior in the paclitaxel group as well [14].

Adjuvant study of ixabepilone

In the adjuvant setting, Campone *et al.* presented at the San Antonio Breast Cancer Symposium in 2011 the results from their Phase III trial evaluating combined fluorouracil, epirubicin and cyclophosphamide chemotherapy followed by ixabepilone or docetaxel in poor prognosis early breast cancer [102]. The study was closed as ixabepilone was found to have higher rates of hematologic and sensory neuropathy toxicities and its development in the adjuvant setting was halted [15]. Another study that has closed to accrual was evaluating ixabepilone versus paclitaxel as adjuvant therapy of triple negative breast cancer (TITAN) [103]. Both of these studies were halted by Bristol-Myers Squibb in light of neoadjuvant data that showed no significant difference in response rates between ixabepilone and paclitaxel (see below) [16]. Currently, ixabepilone is only approved for the treatment of locally advanced and metastatic breast cancer that has progressed on at least two prior therapies including anthracyclines and taxanes.

Neoadjuvant study of ixabepilone

Ixabepilone was studied in the neoadjuvant setting by Baselga *et al.* in a single-arm Phase II study conducted in 161 patients with localized invasive breast cancer not amenable to breast-conservation surgery. Clinical complete response, partial response and stable disease were achieved in 21.1, 55.9 and 16.8%, respectively. Pathologic complete response (pCR) was 18% in the breast mass, and 11% in the lymph nodes. The pCR rate was 29% for ER-negative tumors, 33% for ER/progesterone receptor-negative tumors and 26% for ER/progesterone receptor/HER2-negative tumors. After completing four cycles of ixabepilone, 154 out of 161 patients underwent surgery – 50 patients (32%) were able to undergo breast-conservation surgery and 104 patients (68%) underwent mastectomy. In this study, the authors also conducted a gene-expression analysis based on preclinical analysis that revealed that expression patterns of ER and the microtubule-associated protein tau, which is regulated by ER,

were highly correlated with resistance to ixabepilone. In the clinical study, ER and tau expression were inversely related to a pCR in the breast tumor with exposure to ixabepilone [17]. In preclinical studies evaluating the role of tau, it was found to have an inhibitory effect on paclitaxel binding and, therefore, a diminished amount of paclitaxel-induced microtubule polymerization [18], which may suggest a similar mechanism underlying its negative correlation with tumor sensitivity to ixabepilone.

Another study, by Horak *et al.,* evaluated patients with early-stage breast cancer in a randomized Phase II trial [104]. A total of 313 women received neoadjuvant chemotherapy with doxorubicin and cyclophosphamide and were then randomized to receive ixabepilone or paclitaxel. There was no significant difference in the rate of pCR between the two treatment arms, with 24.3 and 25.2% achieving pCR in the ixabepilone- and paclitaxel-treated groups, respectively (p = 0.8921). Molecular marker analysis was also conducted in order to evaluate the predictive value of certain biomarkers that could differentiate response to ixabepilone. There were higher rates of pCR among patients who were positive for β-III tubulin (which, as mentioned earlier, has previously been shown to correlate with resistance to taxanes) as opposed to those who were β-III tubulin negative, but this was found in patients receiving either taxol or ixabepilone, and therefore could not be used as a predictive marker for differentiating treatment benefit between these agents [19].

Safety of ixabepilone

Ixabepilone is rarely (<1%) associated with hypersensitivity reactions and therefore does not require corticosteroid premedication, although H1 and H2 antagonists are routinely recommended.

Hematologic

Hematologic events, specifically grade 3/4 neutropenia, ranged from 2–73% as shown in Table 1. The incidence of febrile neutropenia ranged from 3–14%. In general, it is considered manageable and dose reductions or discontinuations of the drug due to neutropenia are rare [5,10]. In fact, in the Phase II study looking at ixabepilone in taxane-naive patients, there were no incidents of febrile neutropenia. In combination with capecitabine, there was a higher rate of neutropenia and neutropenia-related deaths, though these were seen in patients with liver dysfunction and once these patients were excluded after the study criteria were amended, the incidence of death as a result of toxicity was reduced to <2% [11]. Safety data presented from the TITAN study showed that the incidence and spectrum of toxicity produced by ixabepilone and weekly paclitaxel were similar.

Peripheral neuropathy

Peripheral neuropathy, while noted to be common among patients receiving ixabepilone, is cumulative, predominantly sensory, usually reversible, and manageable with dose delays and reductions [5,10,20]. According to an in-depth analysis conducted by Vahdat *et al.* across all the Phase II and III clinical trials involving more than 2000 patients who had received ixabepilone, the rate for all grades of peripheral sensory neuropathy in the neoadjuvant setting was 15% when administered for four cycles. Across the monotherapy studies the incidence of all grades of sensory neuropathy was 64%; this rate was similar at 66% in the combination studies of ixabepilone plus capecitabine. In all of the studies, the rates of motor neuropathy were much lower, ranging between 5–10%. In this paper, a risk-factor analysis was performed as well. There was no apparent significant association between development of grade 3/4 peripheral neuropathy and age, prior therapy, or specifically prior taxane treatment. Pre-existing neuropathy did correlate with a greater risk of grade 3/4 neuropathy developing with ixabepilone treatment. Moreover, it was the cumulative dose of ixabepilone, rather than the individual dose level, that correlated with development of peripheral neuropathy. Whereas the incidence of grade 3/4 peripheral neuropathy was 12% at a median-cumulative dose of 120 mg/m^2, the incidence was double at 23% with a cumulative dose of 206.5 mg/m^2. With these factors under consideration, the data analyses elucidated that the majority of patients were able to continue treatment with ixabepilone after the dose was reduced, and the neuropathy was reversible after 4–6 weeks [20].

A summary of the results of the completed clinical trials for ixabepilone can be found in Table 2.

Ongoing studies

There are several ongoing clinical trials that have completed accrual, and are continuing to assess the efficacy and toxicity of ixabepilone in a variety of settings. One such current study across the USA and Europe is evaluating the role of ixabepilone in the in the adjuvant setting is a Phase III randomized study of adjuvant combination chemotherapy with fluorouracil, epirubicin and cyclophosphamide, followed by docetaxel versus ixabepilone in women with completely resected nonmetastatic, poor-prognosis breast cancer [102]. Another study is evaluating ixabepilone versus paclitaxel as adjuvant therapy of triple-negative breast cancer (TITAN) [103].

Eribulin mesylate

Eribulin mesylate is another novel agent that has recently been approved by the US regulatory agencies and others for the treatment of metastatic breast cancer. It is a

synthetic analog of halichondrin B, a natural product isolated from the rare marine sponge *Halichondria-okadai* [21]. It functions by inhibiting the mitotic spindle formation via suppression of microtubule polymerization and sequestration of tubulin into nonfunctional aggregates, with subsequent cell-cycle arrest in the G2–M phase and apoptosis. Preclinical studies have shown that the drug has efficacy against various taxane-resistant tumor cell lines.

Eribulin mesylate's pharmacokinetics are linear and dose-proportional; the drug undergoes rapid distribution and has a mean distribution half-life of 0.4 h followed by a slower elimination phase with a half-life of 38.7 h, as demonstrated in a Phase I study. Urinary excretion was noted to be minimal [22].

Eribulin mesylate was first clinically studied in a Phase I trial conducted by Goel *et al.* using 32 patients with solid tumor malignancies. The maximum tolerated dose was established as a weekly 1 h iv. infusion of 1.0 mg/m^2. Stable disease as a best response was observed in 10 patients, lasting from 39 to 234 days. There was one unconfirmed partial response lasting 79 days. The most common adverse events were fatigue (53%), nausea (41%) and anorexia (38%) [22].

Table 1. Common adverse events reported in ixabepilone studies.

Phase	Patients (n)	Fatigue (%)	Neutropenia (%)	Febrile neutropenia (%)	Sensory neuropathy (%)	Ref.
II	161	Grade 1: 15 Grade 2: 4 Grade 3: 1 Grade 4: 0	Grade 1: 2 Grade 2: 5 Grade 3: 10 Grade 4: 4	3	Grade 1: 26 Grade 2: 14 Grade 3: 3 Grade 4: 0	[17]
II	37	Grade 1: 29 Grade 2: 22 Grade 3: 8 Grade 4: 5	Grade 1: 8 Grade 2: 24 Grade 3: 16 Grade 4: 19	14	Grade 1: 29 Grade 2: 22 Grade 3: 3 Grade 4: 0	[9]
II	49	Grade 1: 16 Grade 2: 33 Grade 3: 27 Grade 4: 0	Grade 1: 0 Grade 2: 4 Grade 3: 2 Grade 4: 0	6	Grade 1: 18 Grade 2: 33 Grade 3: 12 Grade 4: 0	[4]
II	23	Grade 1: 39 Grade 2: 26 Grade 3: 13 Grade 4: 0	Grade 1: 9 Grade 2: 57 Grade 3: 9 Grade 4: 13	0	Grade 1: 39 Grade 2: 13 Grade 3: 0 Grade 4: 0	[6]
II	126	Grade 1: Grade 2: 21 Grade 3: 13 Grade 4: 1	Grade 1: Grade 2: 17 Grade 3: 31 Grade 4: 23	3	Grade 1: Grade 2: 30 Grade 3: 13 Grade 4: 1	[5]
II	65	Grade 1: Grade 2: Grade 3: 6 Grade 4: 0	Grade 1: Grade 2: Grade 3: 27 Grade 4: 31		Grade 1: Grade 2: Grade 3: 20 Grade 4:	[10]
III	752	Grade 1: 12 Grade 2: 19 Grade 3: 9 Grade 4: 0	Grade 1: 6 Grade 2: 14 Grade 3: 32 Grade 4: 36	4	Grade 1: 17 Grade 2: 27 Grade 3: 20 Grade 4: 0.8	[11]
III	1221	Grade 1: 16 Grade 2: 14 Grade 3: 11 Grade 4: 0.8	Grade 1: 6 Grade 2: 13 Grade 3: 34 Grade 4: 39	7	Grade 1: 16 Grade 2: 26 Grade 3: 22 Grade 4: 0.7	[13]

■ Phase II trials of eribulin mesylate in metastatic breast cancer

Evibulin mesylate was then studied in two Phase II clinical trials. Vahdat *et al.* studied two cohorts of metastatic breast cancer patients, one comprising 59 women receiving eribulin mesylate 1.4 mg/m^2 administered as an iv. infusion over 2–5 min on days 1, 8 and 15 of a 28-day cycle, and the second cohort comprised of 28 women receiving eribulin mesylate 1.4 mg/m^2 administered as an iv. infusion over 2–5 min on days 1 and 8 of a 21-day cycle. Median PFS was 79 days (2.6 months; range from 1–453 days). The 6-month PFS rate was 25.9% (95% CI: 15.5–36.3). Median OS was 275 days (9 months; range from 15–826 days). The 6-month and 1-year survival rates were 67.8% and 45.7%, respectively. There was better tolerability in the cohort receiving eribulin mesylate on the 21-day schedule compared with the 28-day schedule. The most frequently reported adverse events were neutropenia, fatigue, leucopenia, anemia, and nausea – all occurring at lower rates in the 21-day schedule cohort; the rate of reported neuropathy was low [23].

The second Phase II trial by Cortes *et al.* evaluated the ORR in 291 women with locally advanced or metastatic breast cancer who had received prior treatment with an anthracycline, a taxane and capecitabine. In total, 21% of these women had triple-negative tumors. Patients received eribulin mesylate at a dose of 1.4 mg/m^2 over 2–5 min iv. infusion on days 1 and 8 of a 21-day cycle. The median number of cycles was four per patient. The ORR was 9.3% (95% CI: 6.1–13.4%) all of which were partial responses. The clinical benefit rate was 17.1% (95% CI: 12.8–22.1%). Median PFS was 2.6 months, and the 6-month PFS rate was 15.6%

Table 2. Summary of results from ixabepilone studies.

Study (year)	Setting	Patients (n)	Response rates (%)	Median time to progression	Overall survival	Ref.
As a single agent						
Baselga *et al.* (2009)	Neoadjuvant	161	Clinical: 21.1 CR 55.9 PR 16.8 SD Radiological: 11.8 CR 37.9 PR 38.5 SD	NR	NR	[17]
Low *et al.* (2005)	Metastatic and locally advanced	37	3 CR 19 PR 35 SD	80 days (2.7 months)	NR	[9]
Thomas *et al.* (2007)	Taxane-resistant metastatic disease	49	12 PR 41 SD	2.2 months	7.9 months (6.1–14.5)	[4]
Denduluri *et al.* (2007)	Metastatic with no prior taxane tx	23	57 PR 26 SD	5.5 months	NR	[6]
Perez *et al.* (2007)	Metastatic with resistance to anthracylcine, taxane and capecitabine	126 (of which 113 were assessable for response)	11.5 PR 50.0 SD	5.7 months	8.6	[5]
Roche *et al.* (2007)	First line in metastatic disease, with prior anthracycline tx	65	41.5 PR 35.0 SD	4.8 months	22 months (15.6–27)	[10]
In combination with capecitabine						
Thomas *et al.* (2007)	Metastatic with resistance to anthracycline and taxane	752	ORR 35 vs 14% ($p < 0.0001$; IR assessment)	PFS 5.8 vs 4.2 months ($p = 0.0003$); ORR 35 vs 14% ($p < 0.0001$)	12.9 vs 11.1 months for patients receiving capecitabine alone (HR: 0.9; 95% CI: 0.77–1.05; $p = 0.19$)	[11]
Sparano *et al.* (2010)	Metastatic with resistance to anthracycline and taxane	1221	43% (95% CI: 39–48%) vs 29% (95% CI: 25–33%)	PFS 6.2 vs 4.2 months ($p = 0.0005$)	16.4 months; in secondary analysis adjusted for KPS; HR: 0.85 ($p = 0.0231$)	[13]

CR: Complete response; HR: Hazard ratio; IR: Independent review; KPS: Karnofsky performance score; NR: Not reported: ORR: Objective response rate; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; tx: Treatment.

(range 0.6–19.9 months). Median OS was 10.4 months and the 6-month OS rate was 72.3%.

Upon conducting subgroup analyses, it was found that while there was activity across all subgroups, responses were higher in patients with hormone receptor-positive tumors and lower in those with triple-negative tumors. There was also better response in patients with previously less refractory disease.

The most common treatment-related adverse events were fatigue, alopecia, nausea, anemia and neutropenia, although the incidence of febrile neutropenia was low (5.5%). The incidence of neuropathy, especially grade 3 neuropathy, was low (6.9%); there were no reports of grade 4 neuropathy [24].

■ Phase III study of eribulin in the metastatic setting

Most recently, eribulin was studied in a Phase III open-label, randomized study conducted by Cortes *et al.* (EMBRACE; study 305), in which 762 women with metastatic breast cancer were randomly assigned to receive either eribulin 1.4 mg/m^2 iv. over 2–5 min on days 1 and 8 of a 21-day cycle or treatment of

the physician's choice. Interestingly, although there was no difference in PFS, OS was significantly improved in the eribulin group, reaching a median of 13.1 months (95% CI: 11.8–14.3 months) compared with 10.6 months (95% CI: 9.3–12.5 months) in the control arm. The most common adverse events observed in this study were also fatigue (54% in the eribulin group vs 40% in the control arm) and neutropenia (52% receiving eribulin vs 30% receiving the treatment of the physician's choice). Peripheral neuropathy was noted in 5% of women receiving eribulin [25,26].

A summary of the results of the Phase II and III clinical studies evaluating the efficacy of eribulin can be found in Table 3.

■ Safety of Eribulin

Eribulin has a manageable safety profile, with neutropenia, fatigue, peripheral neuropathy, and anemia being the most common adverse effects. Fatigue was in fact mild, with 41–55% of patients affected by grade 1–2 fatigue and only 6–13% having grade 3–4 fatigue (in the 21-day cohort, which is the currently accepted schedule). Grade 3–4 neutropenia in all the trials was observed in 19–61% of patients although febrile neutropenia was seen in only 1–5% of patients. The 21-day schedule has been shown to be associated with a better tolerability profile than the 28-day schedule [22–25]. Please refer to Table 4 for the delineation of adverse events reported in the eribulin studies.

Other studies

■ E 209 study

In a multicenter, randomized, Phase II open-label trial, Vahdat *et al.* studied 104 patients, a third of whom had received six or more prior therapies, and randomized them equally to receive either ixabepilone or eribulin. The primary end point was the incidence of peripheral neuropathy. Dose delays (34.0 vs 56.9%), omissions (6.0 vs 17.6%) and interruptions (2.0 vs 11.8%) were lower in the ixabepilone group compared with the eribulin group. However, the incidence of treatment-associated neuropathy was numerically lower in the eribulin group than the ixabepilone group, although the difference was not statistically significant (p = 0.1284). Moreover, the severity of peripheral neuropathy as assessed by the incidence of >grade 3 events was lower in patients treated with eribulin compared with ixabepilone (9.8 vs 20.0%). The median time to onset of neuropathy was longer in the eribulin group compared with the ixabepilone group (11.6 vs 35.9 weeks). These results were controlled for pre-existing neuropathy and prior chemotherapy treatments [28].

■ Study 301

In this randomized Phase III study, eribulin is being compared with capecitabine monotherapy in over 1100 patients, in terms of OS and PFS. Accrual has completed and while the full results are yet to be published, a press release stated that the trial failed to meet coprimary end points of disease-free survival and OS [105].

Conclusion & future perspective

While there have been major steps forward in the treatment of metastatic breast cancer, there are still significant challenges remaining with current available agents. The development of the two novel agents, ixabepilone and eribulin, have provided additional treatment options in management of patients with pretreated, advanced breast cancer. We are awaiting results of ongoing trials that will hopefully confirm the utility of these drugs in various breast cancer settings, namely in neoadjuvant and adjuvant therapies. Moreover, we have yet to systematically study these

Table 3. Summary of results from eribulin studies.

Study (year)	Phase	Setting	Patients (n)	Response rates	Median time to progression (months)	Overall survival (months)	Ref.
Goel *et al.* (2009)	I	Advanced solid malignancies	32	SD: 39–234 days	–	–	[22]
Vahdat *et al.* (2009)	II	Metastatic with resistance to anthracycline and taxane	103	11.5% PR	2.6	9	[23]
Cortes *et al.* (2010)	II	Metastatic with median of four prior therapies	299	9.3% PR	2.6	10.4	[24]
Cortes *et al.* (2011)	III	Metastatic with resistance to anthracycline and taxane	762	<1% CR 13% PR 47% SD	3.6 vs 2.2*	13.1 vs 10.6 in the control TPC group**	[25]

*p = 0.002; **p = 0.009.

CR: Complete response; PR: Partial response; SD: Stable disease; TPC: Treatment of physician's choice.

Table 4. Common adverse events reported in eribulin studies.

Study (year)	Phase	Setting	Patients (n)	Fatigue (%)	Neutropenia (%)	Febrile Neutropenia (%)	Sensory Neuropathy (%)	Ref.
Goel *et al.* (2009)	I	Advanced solid malignancies	32	Grade 1/2: 41 Grade 3/4: 13	Grade 1/2: 6 Grade 3/4: 19	–	25	[22]
Vahdat *et al.* (2009)	II	Metastatic with resistance to anthracycline and taxane	103	Grade 1/2: 48 Grade 3/4: 5	Grade 1/2: 11 Grade 3/4: 64	4	Grade 1/2: 26 Grade 3/4: 5	[23]
Cortes *et al.* (2010)	II	Metastatic with median of four prior therapies	299	–	Grade 1/2: 5.8 Grade 3/4: 54	5.5	Grade 1/2: 26.8 Grade 3/4: 5.8	[24]
Cortes *et al.* (2011)	III	Metastatic with resistance to anthracycline and taxane	762	Grade 3: 8 Grade 4: 1	Grade 3: 21 Grade 4: 24	–	Grade 3: 8 Grade 4: <1	[25]

drugs in combinations with different biologic agents. While there is great need for further exploration of therapeutic options for breast cancer, these two novel agents have certainly contributed to the expansion of available possibilities allowing for increased quantity and quality of life for our patients. Both drugs require dose adjustment for liver enzyme abnormalities, whereas eribulin also needs to be adjusted for renal insufficiency. There are no data to suggest that there is a superior sequence between the two agents. Seeing as how the cost per cycle is similar for both agents, there is no financial rationale for starting with one agent versus the other. Just as multiple other chemotherapeutic agents are used in a variety of sequences in the management of metastatic breast cancer patients, clinicians can add these two agents to the armament of options with the goal of maximizing disease control and increasing survival for these patients.

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Executive summary

Ixabepilone

- Ixabepilone is in the epothilone class of drugs. These agents are cytotoxic macrolides that stabilize microtubules leading to cell-cycle arrest at G2–M transition with subsequent apoptosis.
- Ixabepilone overcomes taxane resistance by not being a substrate for the p-glycoprotein efflux pump that is overexpressed in tumor cells that have developed resistance to the taxanes.
- Multiple Phase II studies have illustrated that ixabepilone has efficacy in taxane-naive and taxane-resistant patients with advanced and metastatic breast cancer, as well as in patients with prior exposure to anthracyclines and capecitabine.
- Two large Phase III studies have shown an improvement in progression free survival with the use of ixabepilone in combination with capecitabine over capecitabine alone.
- Toxicities of ixabepilone, including cytopenias and peripheral neuropathy, are generally manageable with dose delays and reductions.
- Ixabepilone alone or in combination with capecitabine is approved for the treatment of locally advanced or metastatic breast cancer after failure of treatment with an anthracyline and taxane.

Eribulin mesylate

- A synthetic analog of halichondrin B, a natural product isolated from the rare marine sponge *Halichondriaokadai,* eribulin functions by inhibiting the mitotic-spindle formation via suppression of microtubule polymerization and sequestration of tubulin into nonfunctional aggregates, with subsequent cell-cycle arrest in the G2–M phase and apoptosis.
- Two Phase II studies have shown that eribulin at a dose of 1.4 mg/m^2 given every 3 weeks resulted in a median progression-free survival of 2.6 months.
- A Phase III study – EMBRACE – showed significant improvement in overall survival to 13.1 months compared with 10.6 months in the control arm that received treatment of the physician's choice.
- Fatigue and neutropenia are the most common side effects of eribulin.
- Eribulin is approved for the treatment of metastatic breast cancer that has previously been treated with an anthracycline and taxane.

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