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Ixabepilone

Rec INN; USAN

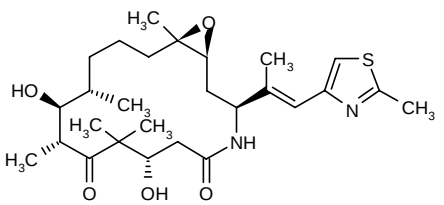
Antimitotic Drug
Microtubule-Stabilizing Agent
Epothilone

BMS 247550-01
BMS-247550
NSC-710428
16-Aza-epothilone B
Ixempra™

(4*S*,7*R*,8*S*,9*S*,13*R*,14*S*,16*S*)-13,14-Epoxy-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2(*E*)-(2-methylthiazol-4-yl)vinyl]-1-azacyclohexadecane-2,6-dione

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione

InChI=1/C27H42N2O5S/c1-15-9-8-10-27(7)22(34-27)12-20(16(2)11-19-14-35-18(4)28-19)29-23(31)13-21(30)26(5,6)25(33)17(3)24(15)32/h11,14-15,17,20-22,24,30,32H,8-10,12-13H2,1-7H3,(H,29,31)/b16-11+/t15-,17+,20-,21-,22-,24-,27+/m0/s1



$C_{27}H_{42}N_2O_5S$
Mol wt: 506.6989

CAS: 219989-84-1
EN: 293356

Abstract

Ixabepilone (BMS-247550, Ixempra™) is an analogue of epothilone B that exerts antitumor activity by stabilizing microtubules. The epothilones were originally isolated from a fermentation of a myxobacteria, *Sorangium cellulosum*, and later synthesized. These natural products were shown to bind to tubulin, stabilize microtubules and induce mitotic arrest at the G2/M transition, resulting in potent anticancer activity, especially against taxane-resistant tumors. Ixabepilone was recently approved by the FDA as monotherapy for resistant or refractory metastatic or locally advanced breast cancer. Phase III clinical development for the treatment of breast cancer continues, as well as earlier clinical trials for many other types of solid tumors and hematological malignancies.

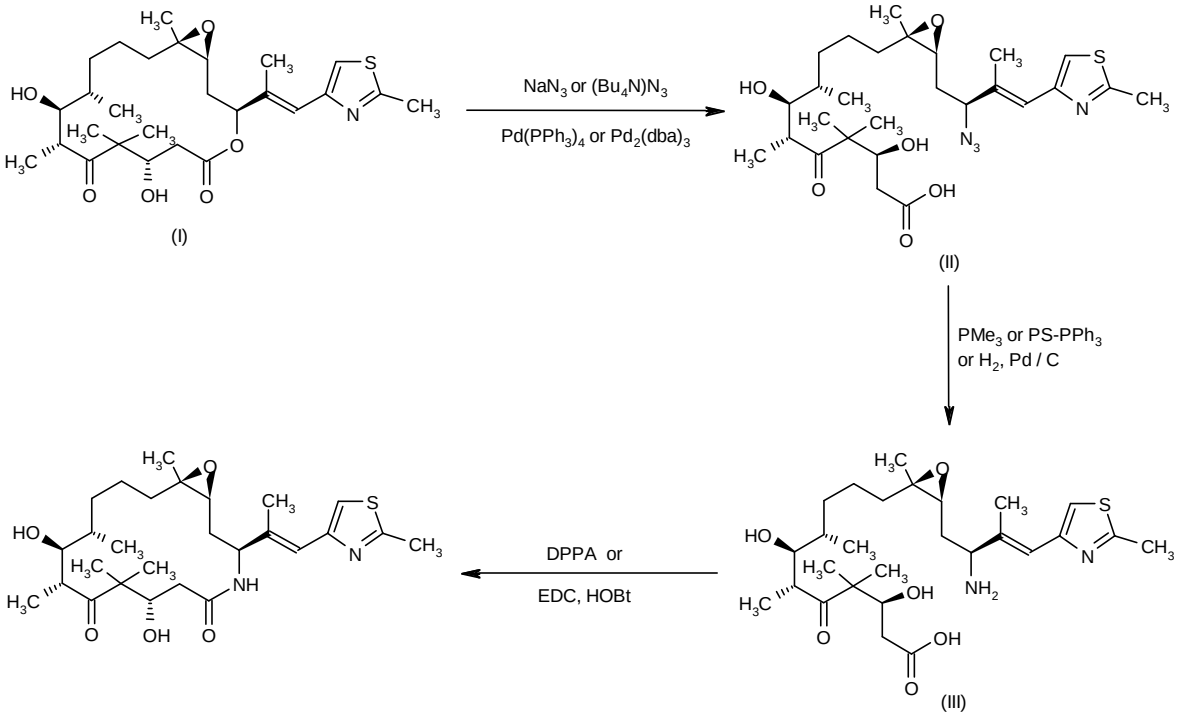
Synthesis[+]

Ixabepilone can be prepared by lactone ring opening in epothilone B (I) with either sodium azide or tetrabutylammonium azide in the presence of a catalytic amount of palladium compounds (to stabilize the allylic cation) to produce the azido carboxylic acid (II), which is reduced to the corresponding aminoacid (III) by treatment with trimethylphosphine, polymer-supported triphenylphosphine or by catalytic hydrogenation over Pd/C. Subsequent macrolactamization of the linear aminoacid (III) by means of DPPA or EDC/HOBt furnishes ixabepilone (1-7). Scheme 1.

The total synthesis of ixabepilone has also been reported. Deprotection of the known silyl ether (IV) using AcOH in THF/H_2O followed by treatment of the liberated allyl alcohol (V) with diphenylphosphoryl azide affords the alkyl azide (VI). Staudinger reduction of azide (VI) with triphenylphosphine in moist THF then produces the amine (VII), which is further protected as the *tert*-butyl carbamate (VIII) by means of Boc_2O. The borane compound generated from the dioxo undecenoate fragment (IX) and 9-borabicyclononane then undergoes *B*-alkyl Suzuki coupling with the vinyl iodide (VIII) to furnish the *N*-Boc amino ester (X), albeit in low yield. In an improved

Sridhar Mani*, Mohammed Ghalib, Sanjay Goel. Albert Einstein Cancer Center, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, USA. *Correspondence: smani@montefiore.org. [+]Synthesis prepared by N. Serradell, J. Bolós, E. Rosa. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Ixabepilone



procedure, the azido fragment (VI) is coupled with the undecenoate derivative (XI) with the β-keto ester masked as the corresponding enol ether to give adduct (XII). Staudinger reduction of azide (XII), followed by treatment with Boc_2O then yields the Boc-protected amine (XIII). Selective deprotection of the enol ether function of (XIII) by transfer hydrolysis with *p*-TsOH in acetone furnishes the key dioxo ester (X). Ruthenium-mediated asymmetric hydrogenation of the β-keto ester (X) using a modified Noyori catalyst produces the corresponding (*S*)-alcohol, which is subjected to acidic *N*-Boc group and *tert*-butyl ester cleavage to give (XIV). Subsequent HATU-mediated cyclization of (XIV) followed by reductive cleavage of the trichloroethoxycarbonyl group leads to the desoxy azaepothilone B (XV), which is finally epoxidized by using dimethyldioxirane in cold CH_2Cl_2 to furnish the title compound (8, 9). Scheme 2.

Background

The epothilones (the name being derived from molecular features: epoxide, thiazole, ketone) were originally isolated by Holfe and Reichenbach in 1992 from the fermentation broth of the myxobacterium *Sorangium cellulosum* (10). Subsequently, Bollag *et al.* demonstrated that epothilones A and B, two related natural products, induced microtubule stabilization similar to taxanes (11). Although taxanes are widely used in oncology, paclitaxel (Taxol®) resistance is becoming a major problem and is frequently associated with treatment failures and poor response rates. The epothilones represent an alternative to the taxanes, as they have been shown to be active against various paclitaxel-resistant cancer cell lines that retain either a multidrug resistance (MDR) and/or tubulin mutation phenotype (12).

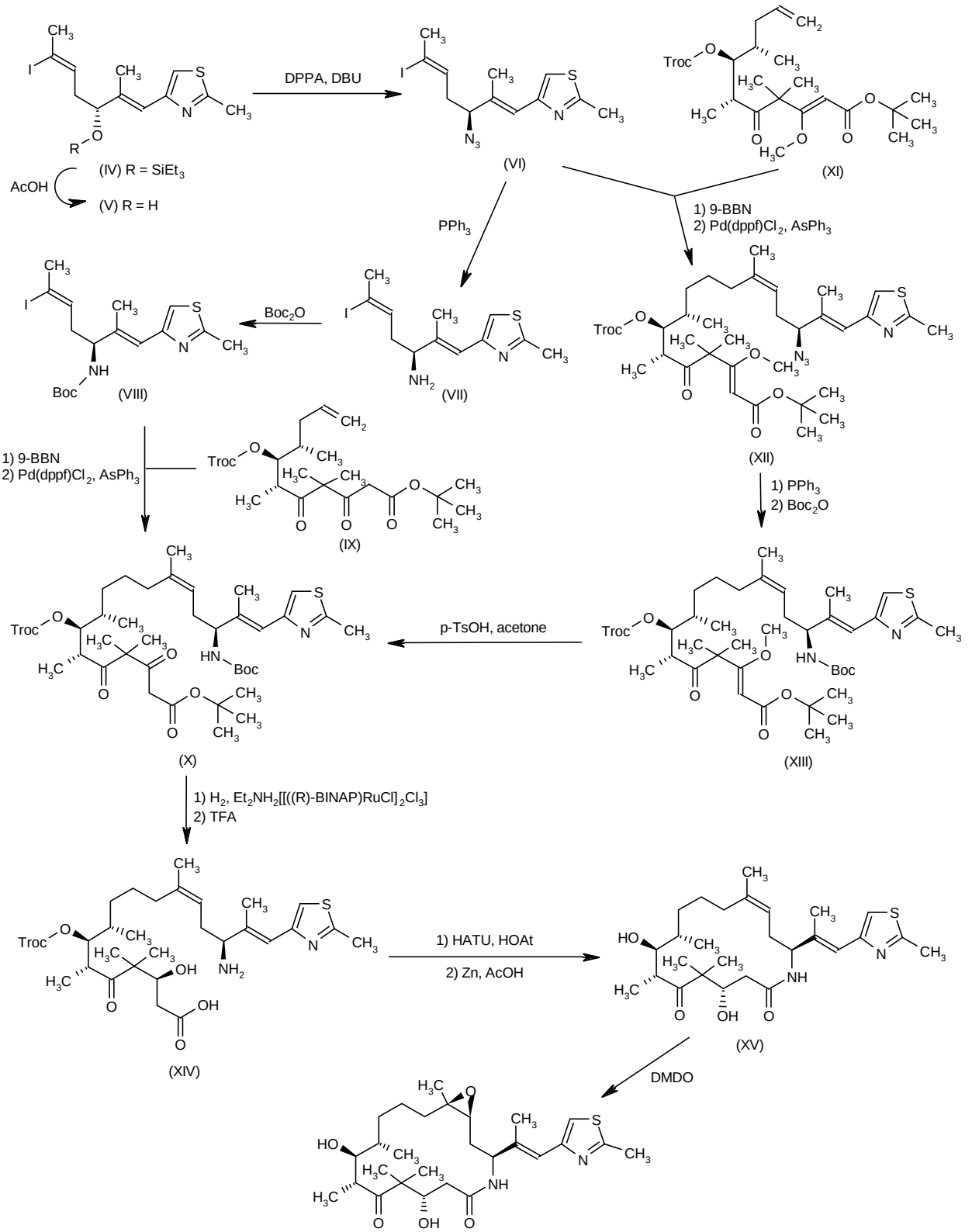
Preliminary preclinical studies with epothilones A and B yielded modest *in vivo* antitumor activity, partly due to their poor metabolic stability, unfavorable pharmacokinetic characteristics and narrow therapeutic window (12). Therefore, Bristol-Myers Squibb developed a synthetic method to produce epothilone analogues (1, 12, 13). One such analogue, ixabepilone (BMS-247550, Ixempra™), thought to be more esterase-resistant than the parent compound epothilone B, emerged as the most effective epothilone in *in vitro* and *in vivo* testing (12).

Pharmacological Actions

Ixabepilone binds tubulin and induces tubulin polymerization with a potency similar to that of paclitaxel, epothilone A and epothilone B, resulting in mitotic arrest at the G2/M transition and cell death (13-16). Cancer cells are susceptible to ixabepilone regardless of MDR-1 protein status. Ixabepilone also induces caspase-dependent apoptosis in tumor cells (17, 18).

Based on the described pharmacological actions of tubulin binders (stabilizers), several important translational projects have demonstrated that target effect (*i.e.*,

Scheme 2: Total Synthesis of Ixabepilone



tubulin stabilization) can be measured and correlated with toxicity. We and others have described that ixabepilone's effect on tubulin (*i.e.*, tubulin bundle formation and post-translational modification, such as acetylation) can be measured (quantitated) in both tumor and peripheral blood mononuclear cells (PBMCs) (19-22). We have shown that quantitation of tubulin bundles in PBMCs correlates with ixabepilone blood concentrations and toxicity (*i.e.*, neutropenia) (19).

Preclinical *in vivo* efficacy for ixabepilone has been demonstrated in several adult and pediatric tumor models both as a single agent and in combination with other drugs (*e.g.*, capecitabine, cetuximab, trastuzumab) (12, 18, 23, 24). Furthermore, ixabepilone is a potential radiosensitizer (25). Importantly, ixabepilone exerts cytotoxicity against tumor types that have developed resistance to paclitaxel (12, 18, 26).

Pharmacokinetics and Metabolism

The limited published data on ixabepilone pharmacokinetics in humans are characterized by linear kinetics which are derived from consistent total body clearance and apparent terminal half-life across doses from 10 to 60 mg/m^2. The plasma concentration-time profile of ixabepilone is characterized by a steep log decline during the first hour after the completion of a 1-h infusion. The rapid distribution phase is followed by a more prolonged terminal elimination phase with a mean half-life of 16.8 ± 6.0 to 35 ± 14.5 h (14, 27, 28). This is similar to the profile of other tubulin-binding agents, such as the vinca alkaloids and taxanes. The mean end-of-infusion plasma concentration of ixabepilone after the first dose of 6 mg/m^2/day x 5 days was 93.7 ± 40.3 ng/ml. Over the 5-day treatment course, there was minimal accumulation of drug (28). Total body clearance is rapid (712 ± 247 ml/min/m^2) and does not appear to be dose-dependent (27-29). The large steady-state volume of distribution (mean Vd_{ss}: 798 ± 375 l) is consistent with extensive tissue binding of the drug. There was also no correlation between Vd_{ss} and body weight or surface area (28). On the clinically relevant schedule of 1-3-h infusion every 3 weeks, the same pharmacokinetic parameters were observed. Importantly, there is no obvious dependence on body surface area for accurate dosing (flat dosing may perform equally well) (27-29).

Moderate to severely altered liver function may affect ixabepilone pharmacokinetics and toxicity, thereby necessitating dose modifications for such patients; however, formal recommendations have not been published (personal communication, Dr. Angela Davies, University of California at Davis, CA).

A human mass balance study with ixabepilone has been published, where 8 cancer patients received an i.v. dose of 70 mg (80 nCi of [^{14}C]-ixabepilone) over 3 h. The mean recovery of radioactivity was 77.3% of dose, 52.2% and 25.1%, respectively, in the feces and urine. Unchanged ixabepilone accounted for only a minor part of the total radioactivity in both plasma and urine (30). This indicates that metabolism is an important elimination mechanism for this drug (14, 30). Future studies should focus on structural elucidation of ixabepilone metabolites and characterization of their activities.

We and others have also demonstrated that ixabepilone has variable interpatient pharmacokinetics (coefficient of variation [CV] > 50%) (27). In order to determine the effect of cytochrome P-450 on ixabepilone biotransformation *in vitro*, a series of studies with liver microsomes were performed together with computational docking studies for ixabepilone using molecular dynamic simulations of CYP3A4, as well as data derived from published crystal structures. The results show that ixabepilone is a good substrate for CYP3A4 catalysis and that inhibition of CYP3A4 by ketoconazole in humans can significantly increase the exposure to ixabepilone, suggesting that inhibition of its metabolism directly alters its blood exposure and toxicity (21). The implications of the results of these studies are significant and directly relevant to drug development in the clinic.

Clinical Studies

Several schedules have been evaluated in phase I testing and include but are not limited to once every 21 days, daily x 5 and weekly administration, and combination studies have been performed with a variety of agents, including but not limited to capecitabine, gemcitabine, trastuzumab, carboplatin and estramustine (13, 20, 26-29, 31, 32). The list of studies currently ongoing and approved by Bristol-Myers Squibb and/or the National Cancer Institute (NCI) is long, but only published (peer-reviewed) articles on the clinical application of ixabepilone will be considered here.

Its early clinical development included two separate 21-day phase I studies, results from which indicated that the maximum tolerated dose (MTD) was 40-50 mg/m^2 as a 1-h infusion every 21 days (27, 32). However, based on further safety results, the recommended dose was amended to 40 mg/m^2 or less over 3 h (33), and this dose was used in subsequent trials. At 40 mg/m^2, significant neutropenia was still observed in one study, suggesting a very steep dose-toxicity relationship (19).

Early in its development, responses were demonstrated in heavily pretreated patients with lung, taxane-refractory breast, melanoma, ovarian and other malignancies (13, 22, 34-43). Taxane-refractory tumors (*e.g.*, prior taxane-treated breast cancer) have responded to this drug. A broad phase II development plan in virtually all solid tumor malignancies was therefore launched by the NCI and Bristol-Myers Squibb.

Furthermore, *in vivo* pharmacodynamic proof of mechanism of action was demonstrated by investigators at the Albert Einstein College of Medicine. Further explorations of pharmacokinetic/pharmacodynamic relationships are ongoing there and elsewhere (14, 19, 20, 27, 44). Based on an overall assessment of schedule-dependent toxicities in phase I, it was thought that the incidence of neuropathy could be associated with high peak plasma levels of ixabepilone. Therefore, clinical trials are now

focusing on the following alternate schedules: 3-h infusion every 21 days, 1-h infusion weekly and 1-h infusion on days 1-5 or days 1-3 every 21 days.

In phase II studies, impressive response rates have been obtained in previously treated non-small cell lung cancer (NSCLC; 14%) and taxane-refractory and taxane-naïve metastatic breast cancer (12% and 57%, respectively; responses may be greater in estrogen receptor-negative patients). The results from several of the published studies reporting phase II response rates and/or toxicity parameters are summarized below.

A multicenter phase II study evaluated the efficacy and safety of ixabepilone in patients with resistant (anthracylines, taxanes, capecitabine) metastatic breast cancer. In 126 patients treated with 40 mg/m^2 by 3-h i.v. infusion every 21 days, an investigator-assessed objective response rate (ORR) of 18.3% was obtained, half of the patients having stable disease; median duration of response, progression-free survival and median overall survival were 5.7, 3.1 and 8.6 months, respectively. Treatment-related adverse events were generally manageable, with grade 3/4 neutropenia being reported in 54% of patients and grade 3/4 peripheral neuropathy in 13% of patients (36).

Sixty-five patients with breast cancer were evaluable for response in a phase II trial of ixabepilone (50 mg/m^2 as 1-h infusion every 3 weeks initially, and then 40 mg/m^2 by 3-h i.v. infusion every 3 weeks) as first-line metastatic chemotherapy. The ORR was 41.5%, with a median duration of response of 8.2 months. Adverse events were generally manageable, the most frequent being grade 1/2 neuropathy, alopecia, fatigue and myalgia (38).

Another phase II trial involved administration of ixabepilone at a dose of 6 mg/m^2/day by 1-h i.v. infusion for 5 days every 3 weeks to 23 patients with metastatic breast cancer not previously treated with taxanes. A partial response rate of 57% was obtained and 6 patients (26%) had stable disease, with a duration of response and a median time to progression of 5.6 and 5.5 months, respectively. The most frequent grade 3/4 adverse events consisted of neutropenia (22%), fatigue (13%), anorexia (9%) and motor neuropathy (4%), but no cases of grade 3/4 sensory neuropathy were reported (45).

Further phase II studies in breast cancer demonstrated a response rate of 12% in patients with disease progression on prior taxane therapy treated with ixabepilone (50 mg/m^2 by 1- or 3-h infusion, and then 40 mg/m^2 over 3 h every 3 weeks), including 5 of 6 patients not responding to taxanes. Toxicity was manageable and generally mild to moderate (35). Combination therapy with trastuzumab (loading dose of 4 mg/kg i.v. followed by 2 mg/kg i.v. weekly), ixabepilone (15 mg/m^2 i.v. on days 1, 8 and 15 every 28 days) and carboplatin (AUC2 i.v. on days 1, 8 and 15 every 28 days) in patients with HER2+ metastatic breast cancer was also associated with significant activity (3.5% complete responses, 38.6% partial responses, 22.8% stable disease) and acceptable toxicity (46).

Clinically relevant activity was seen in a phase II trial in patients with NSCLC progressing after cisplatin- or carboplatin-based chemotherapy and treated with second-line ixabepilone (32 mg/m^2 by 3-h infusion or 6 mg/m^2 by 1-h infusion for 5 days every 3 weeks). Objective response rates in the intent-to-treat population were 14.3% on the first regimen and 11.6% on the second regimen, with responses obtained in taxane-pretreated and platinum-refractory patients. Toxicity was acceptable and, as in the above studies, neuropathy was mostly mild to moderate and generally sensory (37).

Ixabepilone, recently approved by the FDA for use as monotherapy for the treatment of resistant or refractory metastatic or locally advanced breast cancer, continues to be evaluated in phase III clinical trials in breast cancer (47, 48), as well as earlier stage clinical studies for other malignancies (see clinicaltrials.gov). Abstracts presented at the 2007 ASCO meeting reported results from one of these phase III trials evaluating ixabepilone (40 mg/m^2 i.v. over 3 h every 3 weeks) plus capecitabine (2000 mg/m^2 p.o. on days 1-14 every 3 weeks) in comparison to capecitabine alone (2500 mg/m^2 on the same schedule) in 752 patients with metastatic breast cancer progressing after anthracycline and taxane chemotherapy. The combination proved to be superior to capecitabine alone in both the entire study population and poor-prognosis HER2+ patients, and independent of estrogen receptor (ER) status (49-51).

Source

Bristol-Myers Squibb Co. (US).

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