The Epothilones: Translating from the Laboratory to the Clinic

James J. Lee and Sandra M. Swain

Abstract The epothilones are macrolide compounds that have been shown to stabilize microtubules. The epothilones are strong promoters of tubulin polymerization in vitro and have significant antitumor activity against human cancer cells that are taxane resistant, express the multidrug resistance gene MDR-1 (ABCB1), and have acquired tubulin mutations. Several epothilones have been evaluated in clinical trials in a variety of tumor types. Ixabepilone (aza-epothilone B) has significant antitumor activity in breast cancer resistant to an anthracycline and a taxane, and has been approved by the U.S. Food and Drug Administration for the treatment of patients with metastatic or locally advanced breast cancer. There have been sustained efforts to develop pharmacodynamic markers to monitor the pharmacologic effect of the epothilones on tumors and normal tissues. The development of predictive markers for epothilone chemotherapy is highly desired to provide more tailored therapy for patients with cancer.

The taxanes are among the most effective cytotoxic chemotherapeutic agents having a broad spectrum of antitumor activity in several types of solid tumors, including breast cancer. Since the introduction of paclitaxel, there has been a continuous effort to develop novel agents with similar properties but improved efficacy and safety profiles, leading to the development of the epothilones.

The epothilones are macrolide compounds. Epothilone A and epothilone B were originally isolated in 1987 from culture broth of the myxobacterium Sorangium cellulosum (1). Both epothilone A and epothilone B have nearly identical structures, with the exception that epothilone B has an additional methyl group at the C12 position (Fig. 1). The epothilones have strong antitumor activity against several human cancer cells in cell culture and in mouse xenograft models (2). Although the epothilones share some similarities with the taxanes, the epothilones have significant antitumor activity against taxane-resistant human cancer cells (3–6). This characteristic has generated strong interest in the clinical development of the epothilones (7–10). Several epothilones have been evaluated in clinical trials and these are discussed below. This review will summarize key issues related to the clinical development of the epothilones, focusing on the translational aspects of published clinical studies.

Mechanism of Action

Microtubules play a critical role in multiple cellular functions, including cell division and the directional transport of proteins and organelles. Microtubules are polymers composed of αβ-tubulin dimers, and the biological function of microtubules depends on the unique microtubule dynamics. Several chemotherapeutic agents, including taxanes, target the microtubule dynamics (11). Taxanes promote tubulin polymerization in vitro, and thus exert cytotoxicity by stabilizing microtubules.

Soon after their isolation, epothilone A and epothilone B were also found to be strong promoters of tubulin polymerization in vitro with kinetics similar to paclitaxel (12). Epothilone A induces tubulin polymerization with potency similar to paclitaxel whereas epothilone B is a more potent inducer than epothilone A and paclitaxel.

Both epothilone A and epothilone B competitively inhibit binding of paclitaxel to tubulin polymers in vitro, suggesting that binding sites for epothilones and paclitaxel on microtubules are overlapping (12, 13). Epothilones and paclitaxel exhibit differential activity against microtubules isolated from yeast, however, suggesting that, despite their similarities, they may have different characteristics for microtubule binding (13). This difference was further shown by a structural analysis of epothilone A bound to αβ-tubulins in zinc-stabilized sheets, which showed that epothilone A shares only one polar contact point (C7-OH) with paclitaxel, whereas the thiazole side chain of epothilone A occupies a region of β-tubulin not occupied by paclitaxel (14).

The epothilones enhance microtubule stability and induce microtubule bundling in cultured cells as do the taxanes (12). In cell culture systems, epothilone B suppresses microtubule dynamics in a concentration-dependent manner similar to paclitaxel. At the IC50, epothilone B induces near-complete stabilization of microtubule dynamics in 80% of cells (15). Furthermore, the epothilones cause the formation of abnormal mitotic spindles, inducing G2-M cell cycle arrest in mitosis and apoptotic cell death as do taxanes. Epothilone B at a low concentration does not induce mitotic cell cycle arrest, however, but transforms proliferating cells into large aneuploid cells, which undergo apoptotic cell death in G1 phase of cell
This observation suggests that protracted mitotic arrest may not be essential for apoptotic cell death induced by the epothilones (16).

**Mechanism of Resistance**

Although microtubule-stabilizing agents are effective chemotherapeutic agents for various cancers, the majority of patients treated with these agents ultimately develop resistance to these agents (Table 1). Overexpression of P-glycoprotein is one mechanism of taxane resistance that has been identified in vitro and confirmed in two meta-analyses of studies correlating the expression of P-glycoprotein and drug sensitivity in patients with breast cancer (17, 18).

Epothilone A and epothilone B have strong antiproliferative activity in paclitaxel-sensitive human cancer cells (19). The major strength of the epothilones, however, is potent antiproliferative activity in human cancer cells with taxane resistance. Epothilone A and epothilone B have strong antiproliferative activity in human cancer cells with high expression of P-glycoprotein (ABCB1), such as SW620AD-300 cancer cells, which are resistant to paclitaxel. The IC_{50} of epothilone B for SW620AD-300 cells is 0.3 nmol/L, that of paclitaxel is 250 nmol/L (19). Consistent with these preclinical observations, tumor samples obtained from a patient whose tumor had a partial response to ixabepilone chemotherapy showed significant expression of both MDR1 and MRP1 mRNA, suggesting that the expression of MDR1 and MRP1 may not confer resistance to ixabepilone in the clinical setting (20).

There has been strong interest in examining the correlation between h-tubulin mutations and resistance to taxanes in tumor samples from patients treated with taxanes (Table 1; refs. 6, 21, 22). To date, however, no correlation between the presence of h-tubulin mutations and clinical response to taxanes has been reported (21, 22). Both epothilone A and epothilone B also have strong antiproliferative activity in human cancer cells.
exhibiting paclitaxel resistance due to acquired β-tubulin mutations such as 1A9-PTX22 (19). McDaid et al. (20) explored the presence of β-tubulin mutations in patients treated with ixabepilone chemotherapy. Analysis of cDNA and genomic DNA of tumor samples from a patient whose tumor exhibited a partial response to ixabepilone chemotherapy revealed a unique polymorphism of the β-tubulin gene at the COOH terminus of β-tubulin (20). Human cancer cells resistant to the epothilones in vitro carry single point mutations of β-tubulin near the M loop, at the nucleotide binding site, and at the COOH terminus, which is critical for the stabilization of microtubules (23, 24). These mutations were detected only in cell lines selected in vitro, however, and to date have not been detected in clinical samples.

Preclinical data suggest that mutations in the α-tubulin gene may have a role in taxane resistance (25). In addition, there is in vitro data regarding the role of altered α-tubulin isotype expression in taxane resistance (6). The significance of β-tubulin isotype expression in patients treated with taxanes, however, is not yet clear due to conflicting reports (6). This may be another direction for further study of resistance in patients treated with epothilone chemotherapy (Table 1).

Preclinical Development of Epothilones

The promising antitumor activity of epothilone A and epothilone B led to extensive studies on the structure-activity relationship to improve the activity and decrease toxicity. The initial effort was the modification of the epoxide moiety of the macrolactone ring at C12-C13, generating desoxyepothilone B (epothilone D, KOS-862; Fig. 1). Epothilone D has potent antitumor activity against multidrug-resistant CCRF-CEM/VBL100 cancer cells similar to epothilone B (IC50s for epothilone B and D are 2 and 17 nmol/L, respectively; refs. 26, 27). In mouse models, epothilone D showed less toxicity to mice and higher antitumor activity than epothilone B. In mouse xenograft models, epothilone D showed less toxicity to mice and higher antitumor activity than epothilone B. In mouse xenograft models, epothilone D showed potent antitumor activity in paclitaxel-sensitive cancer cells (MX-1 breast and HT-29 colon cancer) as well as paclitaxel-resistant cancer cells activity in paclitaxel-refractory human tumors (Pat-7 ovarian, A2780Tax ovarian, HCT116/VG46 colon, Pat-21 breast, and Pat-26 pancreatic cancer) as well as paclitaxel-sensitive human tumors (A2780 ovarian, HCT116 colon, and LS174T colon cancer; ref. 4).

The side chain of epothilones contains an unsaturated heterocycle, which has been a major target for structural alteration to modify the physicochemical and pharmacokinetic properties of parental compounds (29). Among epothilones with a modified heterocycle side chain, BMS-310705 (C21-aminooepothilone B) and ABJ879 (20-desmethy-20-methylsulfonyl-epothilone B) have been evaluated in early clinical trials (27, 30). ZK-EPO has strong antiproliferative activity in several tumor types, including breast, ovarian, small-cell lung, non–small cell lung, prostate, colorectal, pancreatic, cholangiocarcinoma, renal cell, melanoma, hepatocellular, and brain tumors (31).

Clinical Development of Epothilones

Ixabepilone (aza-epothilone B) has been evaluated in patients with breast cancer (32–38). Ixabepilone showed meaningful durable responses in patients with metastatic breast cancer who had not been previously treated with a taxane: response rate, 57%; progression-free survival, 5.5 months (36). Ixabepilone also showed significant activity as a single agent in the first-line treatment of patients with metastatic breast cancer resistant to anthracyclines with a response rate of 41.5% (35). In the setting of breast cancer patients with prior exposure to taxane treatment as neoadjuvant, adjuvant, or metastatic regimen, the response rate (RR) to ixabepilone was 22% (32). The RR to ixabepilone treatment was 12% to 18.3% in patients with breast cancer of taxane resistance, which was defined as disease progression while receiving treatment or recurrence within 4 to 6 months of adjuvant or neoadjuvant taxane chemotherapy (33, 34). These results are consistent with preclinical observations that ixabepilone has antitumor activity in mouse xenograft models bearing taxane-resistant or taxane-refractory human cancer cells (4). Not surprisingly, neurotoxicity, a common toxicity with microtuble-targeting agents such as taxanes, has also been reported with ixabepilone (32, 39–41).

The enhanced expression of thymidine phosphorylase that results from microtubule occupation by taxanes has been

<table>
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<tr>
<th>Table 1. Potential mechanisms of resistance to the epothilones in preclinical models</th>
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<tr>
<td>Increased drug efflux</td>
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<tr>
<td>• MDR-1/P-glycoprotein (6)</td>
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<td>Point mutations of tubulins</td>
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<tr>
<td>• β-Tubulin mutations (23, 24, 93, 94)</td>
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<td>• α-Tubulin mutations (93)</td>
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<tr>
<td>Altered interaction with MAPs</td>
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<tr>
<td>• Altered level of stathmin and MAP4 (93, 94)</td>
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<tr>
<td>• Alteration of MAP4 phosphorylation</td>
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<td>• Alteration of posttranslational tubulin modification (6)</td>
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<tr>
<td>Altered expression of tubulin isotypes</td>
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<tr>
<td>• Increased level of class III (94)</td>
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<td>Altered tubulin synthesis (6)</td>
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Ixabepilone in combination with capecitabine was evaluated in a randomized phase III study (n = 752) in patients with metastatic breast cancer who received anthracyclines and were taxane resistant (46). Patients were randomized to either the combination arm (ixabepilone plus capecitabine) or capecitabine monotherapy arm. There was a significant increase of progression-free survival in the combination arm (5.8 versus 4.2 months, P = 0.0003). This result led to the approval of ixabepilone by the U.S. Food and Drug Administration for the treatment of patients with breast cancer.

Ixabepilone has been also evaluated in other tumor types, including non–small cell lung cancer (RR, 11.6-14.3%; ref. 47), prostate cancer (≥50% prostate-specific antigen decline, 33-48%; refs. 48, 49), renal cell cancer (RR, 10% in clear cell cancer; ref. 50), urothelial carcinoma (RR, 11.9%; ref. 51), gastric cancer (RR, 9%; ref. 52), pancreatic cancer (RR, 21%; ref. 53), hepatobiliary cancer (RR, 17%; ref. 54), and sarcoma (RR, 6%; ref. 55). Ixabepilone has not shown a significant antitumor activity as a single agent in colorectal cancer (56) and melanoma (57). Ixabepilone has been evaluated in combination with gemcitabine (58), carboplatin (59), and pegylated liposomal doxorubicin (60) in phase I clinical trials in patients with solid tumors. Ixabepilone is currently in active phase II clinical trials in patients with metastatic breast cancer in combination with trastuzumab (NCT00490646) or bevacizumab (NCT00370352).

Patupilone (epothilone B; EPO906) has been evaluated in phase II trials in prostate cancer (≥50% prostate-specific antigen decline, 22%; ref. 61), hepatocellular cancer (RR, 4%; ref. 62), gastric cancer (RR, 9%; ref. 63), non–small cell lung cancer (RR, 11%; ref. 64), colorectal cancer (RR, 2-7%; ref. 65), ovarian cancer (RR, 11%; ref. 66), and renal cell cancer (RR, 4%; ref. 67). Patupilone has not shown a significant activity in neuroendocrine tumors (68). Patupilone is currently in active phase III clinical trial compared with pegylated liposomal doxorubicin in patients with ovarian, primary fallopian, or peritoneal cancer (NCT00262990).

Epothilone D has a significant activity in patients with breast cancer (RR, 20%; ref. 69), but failed to show any activity in patients with non–small cell lung cancer (70). ZK-EPO has activity in patients with ovarian cancer (RR, 17%; ref. 71). Other epothilones in phase I clinical trials are BMS-310705, ABJ879, and KOS-1584 (9,10-dehydro-epothilone D; refs. 30, 72).

It is unlikely that all the epothilones derivatives currently in clinical development will achieve U.S. Food and Drug Administration approval. Considering that four different anthracyclines, three different Vinca alkaloids, three taxanes, and three platinum are in clinical use, however, each with a somewhat different spectrum of activity and toxicity, it can be reasonably predicted that one or more of these epothilones in development will succeed.

**Pharmacodynamic Markers and Predictive Markers**

Significant effort has been focused on the development of pharmacodynamic markers to monitor the pharmacologic effect of the epothilones on tumors and normal tissues. Another aspect of translational research has focused on the development of predictive markers for epothilone chemotherapy to develop more tailored therapy for patients with cancer.

**Tubulin polymerization in peripheral blood mononuclear cells.** As noted previously, the epothilones are a strong promoter of tubulin polymerization in vitro. Consequently, alterations of tubulin polymerization in tumor tissues or peripheral blood mononuclear cells (PBMC) after epothilone treatment have been examined as a pharmacodynamic marker of the effect of the epothilones on microtubules.

Aghajanian et al. analyzed the extent of tubulin polymerization in PBMCs from patients receiving ixabepilone chemotherapy. The amount of tubulin in the unpolymerized fraction versus that in the polymerized fraction was measured in total cell lysates of PBMCs by Western immunoblot (73). The percentage of polymerized tubulin was higher in PBMCs collected at 1 hour after ixabepilone infusion than those collected before ixabepilone treatment (73). This observation provided direct evidence showing that ixabepilone enhances tubulin polymerization in vitro and is consistent with preclinical data in vitro.

The key question is whether the alteration of tubulin polymerization in PBMCs with ixabepilone treatment is significantly correlated with tubulin polymerization in tumor tissues and tumor response to ixabepilone chemotherapy. If such a correlation could be established, then the extent of tubulin polymerization in PBMCs could be a convenient and reliable pharmacodynamic marker for epothilone chemotherapy. This assay needs to be validated further in other clinical trials as a pharmacodynamic marker for clinical response and toxicity.

**Microtubule bundle formation in PBMCs.** Other efforts to define reliable pharmacodynamic markers indicating the effect of the epothilones on the stabilization of microtubules in vivo have examined microtubule bundle formation. Alteration of microtubule bundle formation in peripheral tissues may be a reliable pharmacodynamic marker. McDaid et al. evaluated microtubule bundle formation in PBMCs from patients undergoing ixabepilone chemotherapy. Microtubule bundle formation in PBMCs increased at 1 hour after infusion of ixabepilone and was sustained at 24 hours: 75% of PBMCs showed microtubule bundle formation at 1 hour, and 25% at 24 hours (20). Microtubule bundle formation was also observed in tumor biopsy samples from one patient: 54% at 1 hour and 40% at 24 hours after the infusion of ixabepilone. The kinetics of microtubule bundle formation showed different response patterns between PBMCs and tumor cells, suggesting a difference in drug uptake and clearance kinetics between these two compartments (74).

The degree of microtubule bundle formation in PBMCs at 1 hour was positively correlated with plasma drug exposure (AUC1-24) for cycles 1 and 2 (20). In a follow-up study, the investigators showed that the percentage of PBMCs with microtubule bundle formation at the end of infusion was significantly correlated with the severity of neutropenia and plasma ixabepilone concentration (P = 0.05; ref. 75).

An assay of microtubule bundle formation may have limitations, however, for direct application as a pharmacodynamic marker. The epothilones have significant cytotoxicity at low concentrations without noticeable microtubule bundle formation,
most likely mediated by interruption of microtubule dynamics (76). Therefore, the extent of microtubule bundle formation in PBMCs may not be directly correlated with the extent of epothilone-induced cytotoxicity in tumor tissues.

**Posttranslational modification of α-tubulin.** Tubulins undergo several posttranslational modifications, including acetylation and detyrosination (Table 2; ref. 77). Some of these posttranslational modifications occur exclusively in tubulins in microtubules and have been used as surrogates for the extent of microtubule stabilization. Acetylation of the lysine 40 of α-tubulin occurs after microtubule assembly, and acetylated α-tubulin is a marker for microtubule stabilization in vivo. Similarly, removal of the COOH-terminal tyrosine residues by tubulin carboxypeptidase yields a tubulin with a glutamic acid as the COOH-terminal residue, sometimes referred to as detyrosinated or glu-terminated α-tubulin.

The extent of tubulin acetylation has been studied in tumor biopsy samples obtained from patients receiving ixabepilone chemotherapy (32, 36). Tubulin acetylation was measured by immunohistochemical staining and Western immunoblot. An increased level of α-tubulin acetylation in tumor tissues was found following the administration of ixabepilone, supporting the thesis that ixabepilone enhances microtubule stabilization in vivo. One interesting observation from this analysis was that there was a striking difference in the level of acetylated α-tubulin between tumor cells and surrounding stromal cells (32). The sample from one patient whose tumor was deemed to have a clinical response to ixabepilone showed an increased level of acetylated α-tubulin in both tumor cells and stromal cells, whereas the sample from a second patient whose tumor did not exhibit a clinical response showed an increased level of acetylated α-tubulin only in stromal cells. This observation leads to the interesting hypothesis that differences in the extent of α-tubulin acetylation between tumor cells and surrounding stromal cells may be correlated with tumor response to ixabepilone chemotherapy.

Low et al. found increased levels of glu-terminated tubulin levels in tumor biopsy samples obtained from patients after ixabepilone treatment. Similarly, in renal cell carcinoma patients treated with ixabepilone, target engagement by ixabepilone could be shown by assessing the levels of detyrosinated and/or acetylated α-tubulin (78). These suggest that the level of glutermminated tubulin may reflect the extent of tubulin stabilization by ixabepilone (32).

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<tr>
<th>Modification/deacetylation</th>
<th>Characteristics</th>
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<tr>
<td>Acetylation/deacetylation</td>
<td>Acetylation of the lysine 40 Deletion of the tyrosine at the COOH terminus</td>
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<tr>
<td>Tyrosination/detyrosination</td>
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<tr>
<td>Polyglycilation</td>
<td>Addition of a chain of multiple glycines</td>
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<tr>
<td>Polyglutamylation</td>
<td>Addition of a chain of multiple glutamates</td>
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<tr>
<td>Formation of Δ2-tubulin</td>
<td>Deletion of two amino acids at the COOH terminus</td>
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**Gene expression.** The status of microtubule stability is regulated in part by microtubule-associated proteins (MAP). There are numerous MAPs, including stathmin, MAP4, and tau. Stathmin destabilizes microtubules whereas MAP4 increases the stability of microtubules (79, 80). There are preclinical data suggesting that stathmin and MAP4 modulate sensitivity to taxanes in human cancer cells (81). Tau also interacts with microtubules and modulates microtubule stability (82, 83).

High expression of tau determined by immunohistochemistry predicts improved progression-free survival and overall survival in patients with metastatic HER-2–negative breast cancer treated with docetaxel and vinorelbine (84). On the contrary, tumors with low levels of tau mRNA expression were reported to be sensitive to paclitaxel-containing neoadjuvant chemotherapy in patients with estrogen receptor–positive breast cancer (85). The level of tau protein expression measured by immunohistochemistry in tumor biopsy samples was not correlated with clinical response to ixabepilone chemotherapy in patients with metastatic breast cancer (36, 86).

Potential biomarkers identified from preclinical models were validated in a neoadjuvant breast cancer clinical study with ixabepilone chemotherapy (CA163080; ref. 86). In a preclinical model, 200 genes were identified to be correlated with sensitivity or resistance to ixabepilone by in vitro screening using 18 human breast cancer cell lines. The expression of estrogen receptor showed an inverse correlation with sensitivity to ixabepilone treatment in vitro. These potential predictive biomarkers were validated by gene expression profiling using core needle biopsy samples from the CA163080 study. This analysis showed that estrogen receptor had the best predictive value for pathologic complete response to ixabepilone chemotherapy, and tau had less predictive value than estrogen receptor (86).

Another approach that has been reported involved the identification of biomarkers that could differentially predict the pathologic complete response to ixabepilone-containing chemotherapy versus taxane-containing chemotherapy regimens in patients with breast cancer using gene set enrichment analysis and classification by threshold gradient descent (87). Gene set enrichment analysis showed that transforming, acidic coiled-coil containing protein 3 (TACC3) and chromosome condensation protein G (HCAP-G) had predictive power. Threshold gradient descent analysis showed that two sets of gene expression profiles (26-gene and 20-gene) were correlated with preferential response to ixabepilone chemotherapy, and tau had less predictive value than estrogen receptor (87).

Development of predictive biomarkers is critical for individualized or tailored treatment strategy for patients with cancer.

**Conclusion**

As observed in the companion articles in this issue of CCR Focus, the distinction between cytotoxic and targeted therapeutics has blurred, as we understand the biology underlying cytotoxicity (88–92). Thus, the epothilones form a new class of anticancer agents that is both targeted and cytotoxic. There have been continuous efforts on translational studies in the clinical development of the epothilones. Several pharmacodynamic markers have been evaluated for the correlation with the pharmacologic effect of the epothilones. The extent of tubulin...
polymerization and microtubule bundle formation in PBMCs has been measured in patients receiving epothilone chemotherapy. Although this measurement has some correlation with the toxicity profile of the epothilone chemotherapy, including neutropenia, there is no evidence showing that this measurement reflects the extent of epothilone-induced cytotoxicity in tumor cells. The measurement of acetylated tubulin and glu-terminated tubulin by immunohistochemistry is a potential pharmacodynamic marker for epothilone effect.

The possibility remains that the extent of these modifications before epothilone treatment might be correlated with tumor sensitivity to epothilone in vivo. The study of predictive markers is in its very early stages and will require more effort to identify reliable markers. Although mechanisms of resistance to microtubule-stabilizing agents have been studied extensively, especially as regards the taxane resistance, much work remains to be done to study the mechanism of resistance to the epothilones in vivo.

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bine in patients with metastatic breast cancer previously


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