

## Current State of the Art of New Tubulin Inhibitors in the Clinic

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**Abstract:** For years the microtubule stabilizing agents docetaxel and paclitaxel belong to the most successful clinical chemotherapeutic agents. Several attempts have been made over the years to equal and better these drugs. Both taxanes are associated with the notorious side effect neurotoxicity and are often accompanied with increased drug resistance and cross resistance with other chemotherapeutic agents. In addition their high lipophilicity demands use of co-solvents, which are associated with less favorable side effects such as hypersensitivity. To prevent these disadvantages and improve the clinical application of the taxanes several new agents have entered clinical testing. The agents that are discussed are the drug class of the discodermolides; XAA296A and the epothilones; BMS-247550, BMS-310705, epo906, kos-862 and the agents ABT-751 and D-24851. Here we present an overview of recently performed clinical studies to determine the current state of the art of the tubulin inhibitors which are intended to enlarge and improve the clinical use of the taxanes docetaxel and paclitaxel.

**Keywords:** Taxanes, Tubulin inhibitors, Epothilone, Epo906, Kos-862, BMS-247550.

### INTRODUCTION

The taxanes, docetaxel and paclitaxel are representatives of a class of clinical successful chemotherapeutic agents. Both drugs have been registered in the treatment of a variety of tumors. In Europe docetaxel (Taxotere<sup>®</sup>) single agent is registered for anthracycline resistant breast cancer, second line treatment of non-small-cell lung cancer (NSCLC) and it is registered in combination with cisplatin for first line treatment of advanced NSCLC [1-4]. Paclitaxel (Taxol<sup>®</sup>) has been approved in Europe for ovarian cancer as first line treatment in combination with a platinum drug and for anthracycline resistant breast cancer [5,6]. Furthermore, more recently it has been registered in combination with trastuzumab for metastatic breast cancer in patients for who an anthracycline analogue is not appropriate [6,7]. However, despite their undisputed therapeutic advantages however, both docetaxel and paclitaxel are associated with a number of important clinical drawbacks and disadvantages (see Table 1). An important one, being that treatment failure develops over time due to drug resistance. A well known factor involved in this drug resistance is the up-regulation of the drug transporter P-glycoprotein (P-gp) in several tumor tissues e.g. in colon and kidney cancer [8-10]. This may explain the disappointing response rates (RRs) in these tumor types and limits their clinical activity to a certain range of tumors [11-15]. In addition cross resistance with other chemotherapeutic drugs for example vinblastine [16], etoposide [16] and doxorubicin [17] is an important clinical problem. Besides limiting the penetration of the taxanes in the tumor tissue, P-gp is also held responsible for limiting molecules to reach the brains (blood brain barrier) [13-15]. Another associated disadvantage is that the affinity for this drug transporter and the metabolism by Cytochrome P450 3A4 enzyme (CYP3A4) hinders sufficient systemic exposure after oral administration,

there by hindering monotherapy per os. Both docetaxel and paclitaxel are substrates for P-gp and both are extensively metabolised by CYP3A4. In addition, their physio-chemical property of being very lipophilic agents has resulted in the use of co-solvents which are associated with hypersensitivity reactions [18] (see Table 1). What is more, a clinical significant adverse effect, neuropathy may develop at any time in treatment and is only reversed at cessation of the drug [19,20].

These disadvantages of the taxanes docetaxel and paclitaxel, taken together with their successful application in the treatment of several cancer types have promoted the quest for new active agents. The aim of this review is to present an evaluation of these new clinically tested drugs. However, we will first summarize the methods applied to improve the pharmacology of the taxanes and the mechanism of action that these agents have in common with docetaxel and paclitaxel.

### IMPROVING PROPERTIES OF TUBULIN INHIBITORS

Many tubulin inhibitors have been tested pre-clinically and clinically as possible successors of the taxanes docetaxel and paclitaxel. In general we can distinguish between the agents that are a result of adjustments in formulation or that are part of an improved administration schedule, and in agents that resulted from adjustments in chemical structures and different chemical entities. Examples of adaptations / changes in formulation are the use of co-solvents, emulsions and liposomes (see Table 2) [8,9]. Improvement of the administration schedules by modulation of their biological properties comprises both pharmacodynamic as well as pharmacokinetic modulation. An example of pharmacodynamic modulation is the improvement of the therapeutic index observed when paclitaxel is combined with H1/H2 antagonists to reduce the occurrence and severity of hypersensitivity reactions [21], whereas co-administration of cyclosporin A (CsA) with paclitaxel is an example of pharmacokinetic modulation. It was in this latter concept that

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**Table 1. Summary of Disadvantages of the Taxanes Docetaxel and Paclitaxel**

Agent	Disadvantage	Clinical Implication
Docetaxel	Co-solvent polysorbate 80	Hypersensitivity reactions [18] <sup>1</sup> , peripheral neuropathy [19]
Paclitaxel	Co-solvent Cremophor EL <sup>2</sup>	Hypersensitivity reactions [18], peripheral neuropathy [58,59], dyslipidaemia [60,61] Possible precipitation of the solubilized drug substance upon dilution [62,63]
Both	Drug resistance	Cross resistance against different chemotherapeutic agents e.g. vinblastine [16], etoposide [16] and doxorubicin [17]
Both	Substrate for drug transporter P-gp	No penetration in blood brain barrier [14,15] Low oral bioavailability [22,23]

**Footnotes:**

<sup>1</sup> The relation of hypersensitivity reactions (and neuropathy [19]) and polysorbate 80 is not as well established as with cremophor EL [18].

<sup>2</sup> Cremophor EL is also known as castor oil.

the apparent disadvantages of paclitaxel and docetaxel were turned into advantages. Both, paclitaxel and docetaxel are P-gp substrates and are extensively metabolized by cytochrome P450 3A4 enzyme, which are held responsible for the poor oral bioavailability of the taxanes. Improving oral application of docetaxel and paclitaxel appeared feasible when CsA, a P-gp and CYP3A4 inhibitor was co-administrated, resulting in remarkably improved uptake of the taxanes and increased oral bioavailability [22,23]. These findings are currently investigated in phase II/III studies.

Also the development of new chemical entities has received great interest either by adaptation of the chemical structure of the taxanes, leading to so called second-, and third-generation taxanes e.g. ortataxel [24]<sup>1</sup> NBT-287<sup>2</sup>, MAC-321 [25]<sup>3</sup>, or by the development of complete new chemical entities. Examples are the drug classes of the discodermolides (e.g. XAA296A) [26]<sup>4</sup> and epothilones (e.g. epo906, kos-862) [27,28]<sup>5,6</sup> and other yet unclassified tubulin inhibitors such as ABT-751<sup>7,8</sup> D-24851 [29,30], which are subject of this review. Currently, several of these compounds

are undergoing Phase I/II clinical trials, while others are close to entering phase III trials.

**MECHANISM OF ACTION**

After transcription of genes coding for tubulin to produce mRNA, translation by ribosomes follows leading to formation of the protein tubulin. Alpha and beta tubulin bind one another to form a functional subunit, a heterodimer, consisting of two different gene products. Tubulin heterodimers assemble under certain favorable intracellular conditions into linear protofilaments, which in turn assemble into microtubules. Microtubules are complex structures and are composed of polymerized tubulin heterodimers (see Fig. (1)). They are involved in numerous cellular functions, including the maintenance of cell shape, intracellular transport, secretion, and neurotransmission (axonal transport in neurons) [31]. An important property of the microtubules is that they are highly dynamic and unstable and are constantly incorporating free dimers and releasing dimers into the soluble tubulin pool [39]. During growth heterodimers are added to the end of a microtubule and during shrinkage they come off as intact subunits. Antimitotic agents arrest cells in mitosis and the majority can be classified as tubulin interactive agents [8]. Mitosis is the process in the cell cycle in which the cells divide and ensure the distribution of their chromosomes into two daughter cells [32]. The tubulin interactive agents have been classically divided into those that inhibit polymerization of tubulin to form microtubules (microtubule-stabilizing) e.g. taxanes and those that promote the polymerization of tubulin, i.e. depolymerising microtubules which increase the soluble tubulin pool e.g. vinca alkaloids (Fig. (1)). The aim of this review is to provide a summary of the most recent clinical advances of new tubulin inhibitors that appear to have overlapping clinical indications with the taxanes.

**EPOTHILONES**

Epothilones are derived from a fermenting soil bacteria, *Sorangium cellulosum* and several structural modifications have been made to optimize the microtubule stabilizing activity [33]. However as discussed earlier by others, several variables are important for cytotoxicity, e.g. metabolic stability, cellular accumulation [34]. Epothilones, lack in a

<sup>1</sup> Gurtler JS, Von Pawel J, Spiridonidis CH, *et al.* An uncontrolled phase II study evaluating anti-tumor efficacy and safety of ortataxel (BAY 59-8862) in patients with taxane-resistant non-small cell lung cancer. Proc Am Soc Clin Oncol 2004; 7136 (abstr).

<sup>2</sup> Helson L, Ferrara J, Jones M, *et al.* NBT-287, a third generation taxane analog, and paclitaxel resistance due to MDR-1 and mutant tubulin. Proc Am Soc Clin Oncol 2004; 3114 (abstr).

<sup>3</sup> Zhu AX, Bukowski R, Lockhart AC, *et al.* Phase I trial of oral MAC-321 in subjects with advanced malignant solid tumors. Proc Am Soc Clin Oncol 2004; 2040 (abstr).

<sup>4</sup> Mita A, Lockhart AC, Chen T-L, *et al.* A phase I pharmacokinetic (PK) trial of XAA296A (Discodermolide) administered every 3 wks to adult patients with advanced solid malignancies. Proc Am Soc Clin Oncol 2004; 2025 (abstr).

<sup>5</sup> Piro LD, Rosen LS, Parson M, *et al.* KOS-862 (epothilone D): A comparison of two schedule in patients with advanced malignancies. Proc Am Soc Clin Oncol 2003; 539 (abstr).

<sup>6</sup> Spriggs D, Dupont J, Pezzulli S, *et al.* KOS-862 (epothilone D): Phase I dose-escalating and pharmacokinetic study in patients with advanced malignancies. Proc Am Soc Clin Oncol 2003; 894 (abstr).

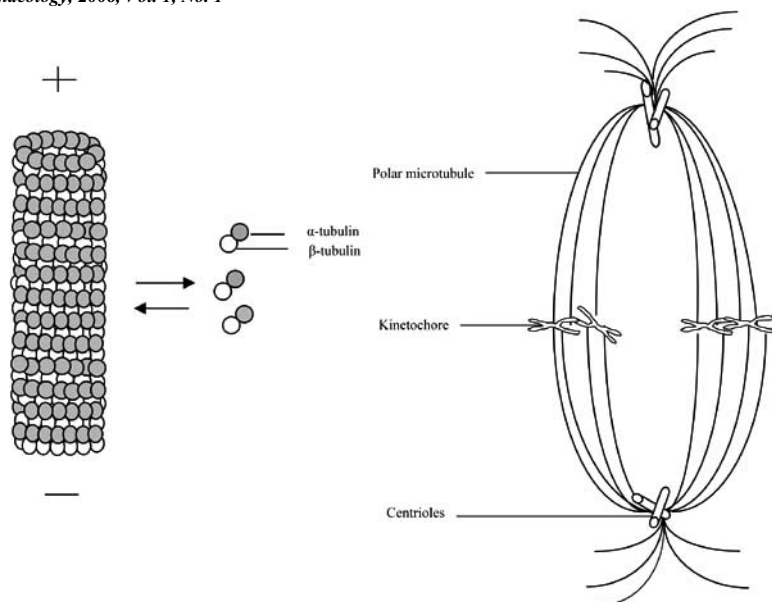
<sup>7</sup> Kobayashi H, Hande KR, Berlin JD, *et al.* Phase I results of ABT-751, a novel microtubulin inhibitor, administered daily \* 7 every 3 weeks. Proc Am Soc Clin Oncol 2004; 2079 (abstr).

<sup>8</sup> Sprague E, Fleming GF, Carr HL, *et al.* Phase I study fo 21-day continuous dosing of the oral antimitotic agent ABT-751. Proc Am Soc Clin Oncol 2003; 518 (abstr).

**Table 2. Examples of Strategies to Improve Properties of the Taxanes Docetaxel and Paclitaxel**

Strategy		Phase	References
<b>Pharmaceutical</b>			
Nanoparticles	ABI-007	Phase II-III	[5,64-66]
Cosolvent	HSA-paclitaxel	Preclinical	[67]
Prodrug	Protaxel	Phase II	[55]
Liposomal paclitaxel	LEP-ETU	Phase I	[68]
Cosolvent	HSA paclitaxel	Preclinical	[68]
Cyclodextrins	PTX-CYD		[5]
Microspheres	Paclimer	Preclinical	[69]
Nanoparticles	TPGS-paclitaxel	Preclinical	[70]
Nanoparticles	NK105 (micel)	Preclinical	[81]
Emulsion	S-8184	Phase I	<sup>62</sup>
Emulsion	LDE-paclitaxel	Preclinical	[71]
<b>Chemical</b>			
Epothilone	KOS-862	Phase II	<sup>5,57</sup>
Epothilone	BMS-247550 (Ixabepilone)	Phase II/III	<sup>13</sup>
Epothilone	BMS-310705	Phase II	<sup>11,63</sup>
Epothilone	Epo 906	Phase II	<sup>41,43</sup>
Discodermolide	XAA 296	Phase I	[69] <sup>44</sup>
Other	MAC-321	Phase I	[25] <sup>3</sup>
Other	Indibulin (D-24851)	Phase I	[29,30]
Other	ABT-751	Phase II	<sup>7,59</sup>
Taxane-analogue	DJ-927	Phase I	[74,75]
Taxane-analogue	Ortataxel	Phase I	[24] <sup>1</sup>
Taxane-analogue	PNU-166945	Phase I discontinued	[76]
Taxane-analogue	RPR-116258A	Phase II	<sup>64</sup>
Taxane-analogue	BMS-184476	Phase II	[77]
Taxane-analogue	MAC-321	Phase I	[25,78] <sup>3</sup>
Taxane-analogue	RPR-109881A	Phase II	[79]
Taxane-analogue	BMS-188797	Phase II	[80]
Taxane-analogue	NBT-287	Preclinical	<sup>2</sup>
<b>Biological</b>			
Biological	Docetaxel + cyclosporin A	Phase II	[23],[73]
Biological	Paclitaxel + cyclosporin A	Phase II	[22]

<sup>62</sup> Spigel SC, Jones SF, Greco FA, *et al.* S-8148 vitamin E paclitaxel emulsion: preclinical and phase I data. Proc Am Soc Clin Oncol 2002; 21; 406.<sup>63</sup> Mekhaill T, Holden S, Pierson S, *et al.* A Phase I pharmacokinetic and biologic study of the novel epothilone BMS-310705 in patients with advanced cancer. Proc Am Soc Clin Oncol 2002; 408 (abstr).<sup>64</sup> Goetz AD, Denis LJ, Rowinsky EK, Ochoa L, *et al.* Phase I and Pharmacokinetic Study of RPR116258A, a novel Taxane Derivative, Administered Intravenously over 1 Hour Every 3 Weeks. Proc Am Soc Clin Oncol 2001; 419 (abstr).



**Fig. (1).** Left: Equilibrium microtubule dynamics; switching between growth (polymerisation) and shortening (depolymerisation). The taxanes shift the equilibrium to the polymerized form thereby stabilizing microtubules. Right: Mitotic spindle.

great extent substrate affinity for P-gp and are active in cells with the MDR phenotype [27]. A clinical consequence of this deviating property compared with the taxanes, is that the epothilones can be administered as single agent per os e.g. ixabepilone<sup>9</sup>. Some of the epothilones however, share overlapping binding sites with Taxol [35]. If mutations in the drug-binding site on tubulin are clinically important then cross-resistance with agents that share the same tubulin-binding region could be a problem. So even though new agents may circumvent P-gp-mediated drug resistance, their efficacy in resistant tumor cells exhibiting alterations in tubulin/microtubule proteins may still hamper the usefulness of some of these drugs. Moreover, *Chou et al.* described that in the development of new epothilones structural modifications have led to increased affinity for P-gp overexpressing sublines, which could be of influence upon their clinical efficacy [36]. However, as was already pointed out by *Goodin et al.* the IC50s of these compounds in P-gp overexpressing cell lines are relatively small compared with the IC50s of paclitaxel in these cell lines [37]. Currently four agents have entered clinical studies: aza-epothilone B (NSC 71028, BMS-247550, ixabepilone); epothilone B (BMS-310705); epothilone B (EPO906); epothilone D (desoxyepothilone B, KOS-862). Noteworthy is that these epothilones are more water-soluble than paclitaxel [38]<sup>10</sup>. Therefore

sometimes other solvents can be used, which are not associated with hypersensitivity e.g. BMS-310705<sup>11,12</sup>.

#### **BMS-247550 (Aza-Epothilone B, NSC 71028, Ixabepilone)**

Several phase I studies have been performed to determine the optimal schedule for ixabepilone; once every 21 days, once every week, daily times 5 every 21 days, daily times 3 every 21 days, see Table 3. In the early studies in which ixabepilone was administered in 30 or in 60 minutes, hypersensitivity reactions were observed<sup>9,13</sup>. In later studies H1 and H2 blockers were administered to prevent hypersensitivity<sup>9,13</sup>. The Dose Limiting Toxicity (DLT) that was reported in all these studies was neutropenia. Additionally, sensory neuropathy and sepsis were also reported to be dose limiting in the 60 minutes iv administration schedules every 3 weeks and additionally in a 30 minutes weekly schedule investigated by *Burris et al.* fatigue was reported to be dose limiting<sup>14</sup>. In this latter study, one patient suffered from sensory neuropathy, which was cumulative. In order to reduce neuropathy the study was amended to explore a 1h iv weekly administration for 3 weeks, followed by a week rest<sup>14</sup>. Preliminary results suggest similar toxicity, except more patients were able to continue treatment for more than 4 months. In a study by *Delbaldo et al.* in patients suffering from NSCLC 50 mg/m<sup>2</sup> was administered in 60 minutes iv every 3 weeks<sup>15</sup>. In order to reduce cumulative neurotoxicity and to improve the therapeutic index, the study was amended

<sup>9</sup> Awada A, Bleiberg H, de Valeriolo D, *et al.* Phase I Clinical and Pharmacology Study of the Epothilone Analog BMS-247550 Given Weekly in Patients (Pts) with Advanced Solid Tumors. Proc Am Soc Clin Oncol 2001; 427 (abstr).

<sup>10</sup> Lee FY, Vite G, Hofle G, *et al.* The discovery of BMS-310705: A water-soluble and chemically stable semisynthetic epothilone possessing potent parenteral and oral antitumor activity against models of taxane-sensitive and -resistant human tumors *in vivo*. Proc Am Assoc Cancer Res 2002; 43(a3928).

<sup>11</sup> Mekhail T, Chung C, Holden S, *et al.* Phase I trial of novel epothilone B analog BMS-310705 IV q21 days. Proc Am Soc Clin Oncol; 2003; 515 (abstr).

<sup>12</sup> Sessa C, Perotti A, Malossi A, *et al.* Phase I and pharmacokinetic study of the novel epothilone BMS-310705 in patients with advanced solid cancer. Proc Am Soc Clin Oncol 2003; 519 (abstr).

<sup>13</sup> Spriggs D, Soignet S, Bienvu B, *et al.* Phase I First-in-Man of the Epothilone B Analog BMS-247550 in Patients with Advanced Cancer. Proc Am Soc Clin Oncol 2001; 428 (abstr).

<sup>14</sup> Burris HA III, Awada A, Jones S, *et al.* Phase I study of the novel epothilone BMS-247550 administered weekly in patients (pts) with advanced malignancies. Proc Am Soc Clin Oncol 2002; 412 (abstr).

<sup>15</sup> Delbaldo C, Lara PN, Vansteenkiste J, *et al.* Phase II study of the novel epothilone BMS-247550 in patients (pts) with recurrent or metastatic non-small cell lung cancer (NSCLC) who have failed first-line platinum-based chemotherapy. Proc Am Soc Clin Oncol 2002; 1211 (abstr).

**Table 3. Phase I Studies with Tubulin Inhibitors, Dose Schedule MTD, DLT and Recommended Dose**

Schedule	N (eval)	Dose mg/m <sup>2</sup>	MTD mg/m <sup>2</sup>	DLT	Recommended Dose mg/m <sup>2</sup>	Reference
<b>BMS-247550 (azaepothilone, ixabepilone)</b>						
60 min iv, every 3 w <sup>1</sup>	31	7.4,15,30,50,57,65	50	Neutropenia, sensory neuropathy	50	<sup>13</sup> (Spriggs, 2001) <sup>65</sup> (Damle, 2001)
60 min iv, every 3 w	12	7.4-59.2	50	Neutropenia, sepsis	40	[40] <sup>66,67</sup> (Mani, 2004)
60 min iv, every 3 w	17	7.4-56	40	Neutropenic sepsis, neutropenia	40	<sup>21</sup> (Tripathi,)
60 min iv, every 3 w	7	7.4-40	NR	NR	NR	<sup>68</sup> (LoRusso)
30 min iv, weekly <sup>2</sup>	24	1,2,5,5,10,20,25,30	25	Neutropenia, sensory neuropathy, fatigue	25	<sup>14</sup> (Burris, 2002)
30 min or 60 min weekly <sup>3</sup>	205	1,2,5,5,10,20,25 <sup>4</sup>	ND	ND	ND	<sup>9</sup> (Awada, 2001)
60 min iv, weekly	16	2.5,5,10,20,30	ND	ND	ND	<sup>69</sup> (Hao, 2002)
60 min iv, weekly	16	2.5,5,10,20,30	30	Neutropenia	20 mg/m <sup>2</sup> /w	<sup>69</sup> (Hao, 2002)
60 min iv, for 5 d, every 3 w	21	1.5, 3, 6, 8 mg/m <sup>2</sup> /d <sup>5</sup>	6 mg/m <sup>2</sup> /d	Neutropenia	6 mg/m <sup>2</sup> /d	<sup>22</sup> (Agrawal, 2002)
60 min iv, for 5 d, every 3 w	27	1.5,3,6,8	8 mg/m <sup>2</sup> /d	Neutropenia	6 mg/m <sup>2</sup> /d	[39] (Abraham, 2003)
Iv, daily * 3, every 3 w	26	8-10	8 mg/m <sup>2</sup> /d	Neutropenia	8 mg/m <sup>2</sup> /d	<sup>18</sup> (Thambi, 2003)
Iv, daily * 5, every 3 w	21	1.5-8 mg/m <sup>2</sup> /d	6 <sup>6</sup>	Neutropenia	NR	<sup>19</sup> (Fojo, 2001)
<b>BMS-310705 (epothilone B)</b>						
15 min iv every 3 w	59	0.6-70	ND	Neutropenia, hyponatremia, sensory neuropathy	40	<sup>11,63</sup> (Mekhail, 2002)
Iv w for 3 w, every 4 w	21	5,10,20,30	30	Diarrhea	NR	<sup>12</sup> (Sessa, 2003)
<b>EPO906 (epothilone B, patupilone)</b>						
5-10 min iv every 3 w <sup>7</sup>	42 (36)	0.3-8	6.0	Diarrhea	NR	<sup>43</sup> (Calvert, 2001)
5 min weekly iv, for 4 w every 6 w <sup>8</sup>	36	0.3-3-6	2.5	Diarrhea	2.5	<sup>41</sup> (Rubin, 2001)
5-7 min iv every 3 w	57	0.3-6.0	6.0	Diarrhea	6.0	<sup>42</sup> (Calvert)
5-7 min iv weekly, 6 w on, 3 w off, q w <sup>9</sup>	86	0.3-2.5	2.5	Diarrhea	2.5 <sup>9</sup>	
<b>KOS-862</b>						
Iv, every 3 w	38	9-185	185	impaired gait, cognitive/perceptual abnormalities, atypical chest pain	NR	<sup>5</sup> (Piro, 2003)
Iv, daily * 3, every 3 w	14	20,40,50	NR			
once daily * 3, every 3 w	5	9,18	ND	ND	ND <sup>10</sup>	<sup>57</sup> (Rosen, 2002)
Iv for 3 w, every 4 w	13	16-100	ND	ND	ND <sup>11</sup>	<sup>6</sup> (Spriggs, 2003)

<sup>65</sup> Damle BD, Letrent S, Duncan G, *et al.* Pharmacokinetics (PK) and Pharmacodynamics (PD) of BMS-247550, an Epothilone Analog, in Patients with Advanced Solid Tumors. Proc Am Soc Clin Oncol 2001; 268 (abstr).

<sup>66</sup> Mani S, McDaid H, Shen H-J, *et al.* Phase I Evaluation of an Epothilone B Analog (BMS-247550): Clinical Findings and Molecular Correlates. Proc Am Soc Clin Oncol 2001; 269 (abstr).

<sup>67</sup> Mani S, McDaid H, Shen HJ, *et al.* Phase I pharmacokinetic and pharmacodynamic study of an epothilone B analog (BMS-247550) administered as a 1-hour infusion every 3 weeks: An update. Proc Am Soc Clin Oncol 2002; 409 (abstr).

<sup>68</sup> LoRusso PM, Wozniak AJ, Flaherty LE, *et al.* Phase I Clinical Trial of BMS-247550 (aka Epothilone B Analog; NSC710428) in Adult Patients with Advanced Solid Tumors. Proc Am Soc Clin Oncol 2001; 2125 (abstr).

<sup>69</sup> Hao E, Hammond LA, deBono JS, *et al.* Continuous weekly administration of the epothilone-B derivative, BMS247550 (NSC710428): a phase I and pharmacokinetic (PK) study. Proc Am Soc Clin Oncol 2002; 411 (abstr).

(Table 3. Contd....)

Schedule	N (eval)	Dose mg/m <sup>2</sup>	MTD mg/m <sup>2</sup>	DLT	Recommended Dose mg/m <sup>2</sup>	Reference
24-h, every 2 w 72-h, every 2 w	17 7	1,2,4,6 1,1.7 mg/h	ND	ND	ND <sup>12</sup>	<sup>58</sup> (Holen, 2004)
<b>XAA296A (Discodermolide)</b>						
Iv, once every 3 w <sup>13</sup>	26	0.6,1.2,2.4,4.8, 9.6,14.4,19.2	ND	ND <sup>13</sup>	ND	<sup>4</sup> (Mita, 2004)
<b>ABT-751</b>						
Po daily * 7 d, every 3 w Po daily * 21 d, every 4 w	22 <sup>14</sup>	100,130,165,200 75	ND	ND <sup>14</sup>	ND	<sup>59</sup> (Cho, 2004)
Po daily * 21 d, every 4 w	29	25,100,200	ND	ND	ND	<sup>8</sup> (Sprague, 2003)
Po daily * 7 d, every 3 w Po twice daily, every 3 w	15 22	300 175 <sup>15</sup>	250 <sup>15</sup>	Abdominal pain and constipation Fatigue, intestinal obstruction abdominal pain, constipation	250 19	<sup>7</sup> (Kobayashi, 2004)
Po daily * 7 d, every 3 w Po twice daily, every 3 w	12 10	NR NR	250 ND	Peripheral neuropathy and intestinal obstruction ND	250 ND	<sup>60</sup> (Hande, 2003)
<b>D-24851 (indibulin)</b>						
Po daily * 14 d, every 3 w	14	20, 40, 80	ND	Nausea and vomiting	ND	<sup>30</sup> (Kuppens, 2004)

Abbreviations: NR= Not Reported; ND= Not Determined; d= days; h= hour; w= weeks; po= per os; iv= intravenous; DLT= dose limiting toxicity; MTD= maximum tolerated dose

**Footnotes:**

- <sup>1</sup> A hypersensitivity reaction was observed at 30 mg/m<sup>2</sup>, subsequent patients were pre-treated with H1/H2 blockers<sup>13</sup>.  
<sup>2</sup> In order to reduce neuropathy study was amended to explore a 1h iv weekly for 3 weeks, followed by a week rest<sup>14</sup>.  
<sup>3</sup> Following 2 cases of hypersensitivity, subsequent patients were pre-medicated with diphenhydramine and ranitidine. Patients were either taxane refractory or taxane naïve<sup>9</sup>.  
<sup>4</sup> Accrual is ongoing at 30 mg/m<sup>29</sup>.  
<sup>5</sup> Inpatient dose escalation was permitted<sup>22</sup>.  
<sup>6</sup> Twenty-one patients received BMS-247550 without filgrastim in the first cycle. Six patients with starting dose of 8 mg/m<sup>2</sup>/day had filgrastim support [60]. In both groups DLT was 8 mg/m<sup>2</sup>/d<sup>39</sup>.  
<sup>7</sup> First 6 dose levels given as a 30 min iv every 21 days and subsequent dose levels as 5-10 min iv every 3 weeks<sup>43</sup>.  
<sup>8</sup> Due to frequent diarrhea during week 3, the schedule was modified to a schedule of 2 weekly doses every 3 weeks with again diarrhea as DLT.  
<sup>9</sup> In the 4 week study a modified regimen of 3 weeks on/one week off had the same DLT (diarrhea) and MTD but better long-term tolerability<sup>42</sup>.  
<sup>10</sup> Toxicities included emesis, anemia<sup>57</sup>.  
<sup>11</sup> Dose dependent toxicities included fatigue and neuropathy<sup>6</sup>.  
<sup>12</sup> One grade 3 neurosensory occurred at 6 mg/h x 24h. other toxicities reported were fatigue, nausea/abdominal pain, dizziness<sup>58</sup>.  
<sup>13</sup> Administered with a fixed infusion rate of 0.77 mg/ml/min once every 3 weeks<sup>4</sup>. Grade 4 anemia occurred in one patient during the fourth cycle, other more frequently reported toxicities were anemia, nausea, vomiting, fatigue, diarrhea<sup>4</sup>.  
<sup>14</sup> Study performed in children<sup>68</sup>. Grade 2 motor neuropathy was seen at 130 mg/m<sup>2</sup>/day in 1/6 patients, grade 3 constipation in 1/6 at 165 mg/m<sup>2</sup>/day. Other toxicities were sensory neuropathy, nausea, constipation and transiently elevated transaminases<sup>59</sup>.  
<sup>15</sup> Dose-limiting toxicities in the twice daily regimen were observed at the 150 mg dose. In patients treated with 175 mg toxic dose in which patients with performance status of 2 and underlying constipation were excluded a dose of at least 175 mg toxic dose was tolerated and only an increase in fatigue (grade 2) was observed<sup>7</sup>.

to compare a schedule of 40 mg/m<sup>2</sup> over 3 h every 21 days with 6 mg/m<sup>2</sup> in 1 h daily for 5 days in an every 3 weeks schedule<sup>15</sup>. Several other phase II studies followed the advice to extend the infusion duration from 1 to 3 hours<sup>16,17</sup>. Increased mucositis and abdominal pain were observed with a dose of 50 mg/m<sup>2</sup> in 3 h every 21 days, therefore a dose reduction followed to 40 mg/m<sup>2</sup> in 3 h every 21 days<sup>17</sup>. Interestingly, both the 1 h daily for 5 days and for 3 days schedules every 3 weeks have not been associated with grade

3 and 4 neuropathy<sup>18,19</sup>. Of note, however also pre-treatment seems to influence development of neuropathy. In a study by *Chen et al.* 19 out of 42 patients developed grade 2 or 3 neuropathy. Ten patients developed new onset grade 2 or 3 after a median of 3 cycles (range 2-8), of which 9 were pre-treated with taxanes or cisplatin, whereas only one chemotherapy naïve patient developed neuropathy after 8 cycles<sup>20</sup>. *Tripathi et al.* reported that the area under the curve

<sup>16</sup> Roche H, Cure H, Bunnell C, *et al.* A phase II study of epothilone analog BMS-247550 in patients with metastatic breast cancer previously treated with an anthracycline. Proc Am Soc Clin Oncol 2003; 69 (abstr).

<sup>17</sup> Thomas E, Taberno J, Fornier M, *et al.* A phase II study of the epothilone B analog BMS-247550 in patients with taxane-resistant metastatic breast cancer. Proc Am Soc Clin Oncol 2003; 30 (abstr).

<sup>18</sup> Thambi PM, Ederly M, Agarwal M, *et al.* A phase I trial of BMS-247550, an epothilone B derivative, given daily for 3 days on a 21 day cycle in patients with refractory neoplasms. Proc Am Soc Clin Oncol 2003; 540 (abstr).

<sup>19</sup> Fojo AT, Kotz H, Abraham J, *et al.* A phase I clinical trial of BMS-247550 (NSC 710428), an epothilone B analogue, in patients with refractory neoplasms. Proc of the 12th NCI-EORTC AACR Symposium 2001; Clin Cancer Res 2001; 774 (abstr).

<sup>20</sup> Chen T, Molina S, Moore S, *et al.* Epothilone B analog (BMS-247550) at the recommended phase II dose (RPTD) in patients (pts) with gynecologic (gyn) and breast cancers. Proc Am Soc Clin Oncol 2004; 2115 (abstr).

and the maximal plasma concentration appear proportional to the dose when administered in 1 hour every 3 weeks, as well as to myelotoxicity and the DLTs which were neutropenic sepsis and prolonged grade 4 neutropenia<sup>21</sup>. They observed that grade 3-4 emesis and fatigue only occurred at a dose of 56 mg/m<sup>2</sup>.

Awada *et al.* investigated the systemic exposure after single oral administration in six patients at a dose of 20 mg/m<sup>2</sup> and reported an oral bioavailability of approximately 53%<sup>9</sup>. Unfortunately, the DLT and MTD with oral administration have not been investigated.

In these phase I studies activity has been reported in different types of tumors that include breast cancer [39]<sup>9,22</sup> [40], ovarian<sup>13,14</sup>, cervical cancer [39]<sup>22</sup>, head and neck cancer<sup>9,14</sup>, basal cell carcinoma<sup>22</sup>, anal tumor<sup>9</sup>, NSCLC<sup>13</sup> and melanoma<sup>13</sup>. Subsequently several phase II studies have been conducted in various types of tumors, see Table 4. All these studies reported the tumor RRs, however only few determined time to progression (TTP) and median survival time (MST). In the majority of these trials patients were pre-treated with chemotherapy, which sometimes included the use of taxanes<sup>17,20,23</sup>. In breast cancer response rates varied from 12 to 53%. In a study by Low *et al.* in taxane pre-treated and naïve patients similar response rates of 18% were seen, whereas Roché *et al.* reported higher response rates in taxane naïve patients of 53% versus 29%<sup>24,25</sup>. However, different schedules were used in these studies, which could be an explanation for these different response rates. In only one study patients with gynaecologic, ovarian and endometrial, tumors were included. In 2002, ixabepilone received the status of orphan drug for the treatment of ovarian cancer [41]. In a study by Eng *et al.* in patients with colorectal cancer, no responses were observed and peripheral neuropathy was dose limiting [42]<sup>26</sup>. In gastric cancer patients, a RR of 10% was reported by Ajani *et al.*<sup>23</sup>. In patients with previously untreated pancreatic cancer, an even higher overall response probability of 16% was seen, indicating activity in pancreatic cancer [69]. The estimated six-month survival was 59% (95% CI 46% to 71%) with a median survival of 6.9 months and a median time to treatment failure of 3.3 months<sup>27</sup>. Furthermore, in patients suffering from hepatobiliary tumors 2 partial responses (PRs) were seen, one in metastatic gallbladder carcinoma and one

PR in a patients with hepatocellular carcinoma<sup>28</sup>. Conflicting results have been observed in metastatic melanoma. Pavlick *et al.* concluded that ixabepilone is inactive when administered in 1 h weekly for 3 weeks, every 4 weeks in untreated and previously treated metastatic melanoma<sup>29</sup>. Spriggs *et al.* on the other hand observed in a dose finding study 2 PRs in patients with melanoma when administered in 1 h once every 3 weeks<sup>13</sup>. In NSCLC three different schedules have been administered. Vansteenkiste *et al.* compared two schedules; 32 mg/m<sup>2</sup> in 3 h, every 3 weeks with 6 mg/m<sup>2</sup> in 1 h, daily for 5 days, every 3 weeks. In both schedules RRs of 13% were found<sup>30</sup>. In a schedule of 50 mg/m<sup>2</sup> in 1 h, every 21 days a RR of 18% was reported by Delbado<sup>15</sup>. Also in prostate cancer responses were seen, of approximately 14% as single agent<sup>31</sup>. These findings have led to combination with estramustine in several phase II studies in prostate cancer patients [43]<sup>32,33</sup>. Estramustine binds to tubulin and combination with ixabepilone is likely to act synergistically [44,45]. In a study by Smaletz *et al.*, a minimum response proportion of 55% in prostate cancer was observed, although the MTD was not defined at that time. So far only one study compared tumor responses for combination therapy and for monotherapy which were respectively 44 and 23%<sup>33</sup>. Currently second line taxane-based therapy after first-line ixabepilone therapy in hormone refractory prostate cancer is investigated<sup>34</sup>. In renal cell cancer 10% of the patients responded when treated with 6 mg/m<sup>2</sup>/day for 5 days every 3 weeks<sup>35</sup>. Ixabepilone has also been investigated in soft tissue sarcomas<sup>36</sup> and is currently investigated in a phase III trial for breast cancer and in phase II studies for colorectal cancer and for treatment of gliomas<sup>37</sup>.

Furthermore, ixabepilone has been combined with irinotecan and activity was shown in two patients with NSCLC, one

<sup>21</sup> Tripathi R, Gadgeel SM, Wozniak AJ, *et al.* Phase I clinical trial of BMS-247550 (epothilone B derivative) in adult patients with advanced solid tumors. Proc Am Soc Clin Oncol 2002; 407 (abstr).

<sup>22</sup> Agrawal M, Kotz H, Abraham J, *et al.* A phase I clinical trial of BMS 247550 (NSC 71028), an epothilone B derivative, in patients with refractory neoplasms. Proc Am Soc Clin Oncol 2002; 410 (abstr).

<sup>23</sup> Ajani JA, Shah MA, Bokemeyer C, *et al.* Phase II study of the novel epothilone BMS-247550 in patients (pts) with metastatic gastric adenocarcinoma previously treated with a taxane. Proc Am Soc Clin Oncol 2002; 619 (abstr).

<sup>24</sup> Low JA, Wedam SB, Brufsky A, *et al.* A phase 2 trial of BMS-247550 (ixabepilone), an epothilone B analog, given daily x 5 in breast cancer. Proc Am Soc Clin Oncol 2004; 545 (abstr).

<sup>25</sup> Roché H, Delord JP, Bunnell CA, *et al.* Phase II studies of the novel epothilone BMS-247550 in patients (pts) with taxane-naïve or taxane-refractory metastatic breast cancer. Proc Am Soc Clin Oncol 2002; 223 (abstr).

<sup>26</sup> Eng C, Kindler HL, Skoog L, *et al.* The epothilone analogue, BMS-247550, in patients with advanced colorectal cancer. Proc Am Soc Clin Oncol 2003; 1134 (abstr).

<sup>27</sup> Whitehead RP, Mccooy SA, Rivkin SE, *et al.* A Phase II trial of epothilone B analogue BMS-247550 (NSC#710428) in patients with advanced pancreas cancer: A Southwest Oncology Group Study. Proc Am Soc Clin Oncol 2004; 4012 (abstr).

<sup>28</sup> Singh DA, Kindler HL, Eng C, *et al.* Phase II trial of the epothilone B analog BMS-247550 in patients with hepatobiliary cancer. Proc Am Soc Clin Oncol 2003; 1127 (abstr).

<sup>29</sup> Pavlick AC, Millward M, Farrell K, Hamilton A, Broseus A, Haas N *et al.* A phase II study of epothilone B analog (EpoB)-BMS 247550 (NSC#710428) in stage IV malignant melanoma (MM). Proc Am Soc Clin Oncol 2004; 7542 (abstr)(174).

<sup>30</sup> Vansteenkiste JF, Breton J-L, Sandler A, *et al.* A randomized phase II study of epothilone analog BMS-247550 in patients with non-small cell lung cancer who have failed first-line platinum-based chemotherapy. Proc Am Soc Clin Oncol 2003; 2519 (abstr).

<sup>31</sup> Hussain, Faulkner J, Vaishampayan P, *et al.* Epothilone (Epo-B) analogue BMS-247550 (NSC#710428) administered every 21 days in patients (pts) with hormone refractory prostate cancer (HRPC). A Southwest Oncology Group Study (S0111). Proc Am Soc Clin Oncol 2004; 4510 (abstr).

<sup>32</sup> Smaletz O, Kelly WK, Horse-Grant D, *et al.* Epothilone B analogue (BMS-247550) with estramustine phosphate (EMP) in patients (pts) with progressive castrate-metastatic prostate cancer (PC). Proc Am Soc Clin Oncol 2002; 732 (abstr).

<sup>33</sup> Kelly WK, Galsky MD, Small E, *et al.* Multi-institutional trial of epothilone B analogue (BMS-247550) with or without estramustine phosphate (EMP) in patients with progressive castrate-metastatic cancer (PCMP). Proc Am Soc Clin Oncol 2003; 1584 (abstr).

<sup>34</sup> Rosenberg JE, Galsky MD, Weinberg V, *et al.* Response to second-line taxane-based therapy after first-line epothilone B analogue BMS-247550 (BMS) therapy in hormone refractory prostate cancer (HRPC). Proc Am Soc Clin Oncol 2004; 4564 (abstr).

<sup>35</sup> Zhuang SH, Menefee M, Kotz H, *et al.* A phase II clinical trial of BMS-247550 (ixabepilone), a microtubule-stabilizing agent in renal cell cancer. Proc Am Soc Clin Oncol 2004; 4550 (abstr).

<sup>36</sup> Okuno SH, Geyer SM, Maples WJ, *et al.* Phase 2 study of epothilone B analog (BMS-247550) in soft tissue sarcomas: an interim report. Proc Am Soc Clin Oncol 2002; 1645 (abstr).

<sup>37</sup> Peereboom K, Carson K, Lawson D, *et al.* A phase I/II trial of BMS-247550 for patients with recurrent high-grade gliomas. Proc Am Soc Clin Oncol 2004; 1546 (abstr).

**Table 4. Phase II/II Dose/Activity Studies**

Cancer Type	Prior CT	Regimen mg/m <sup>2</sup>	N (eval)	Tumor Response (Rate)	TTP (months)	MST (months)	Reference
<b>BMS-247550 (azaepothilone, ixabepilone)</b>							
Breast	Y	40 mg/m <sup>2</sup> in 3h, every 3 w; DR <sup>1</sup>	49	PR 6/49 (12%)	NR	NR	<sup>17</sup> (Thomas, 2003)
Breast	Y	6 mg/m <sup>2</sup> /d 1-5, every 3 w <sup>2</sup>	33	PR 6 (18%)	NR	NR	<sup>24</sup> (Low, 2004)
	N		9	PR 4 (18%)			
Breast	Y	40 mg/m <sup>2</sup> in 3h, every 3 w	65 (44)	PR 15/44 (34%)	NR	NR	<sup>16</sup> (Roche, 2004)
Breast	Y <sup>3</sup>	40 mg/m <sup>2</sup> in 3h, every 3 w	7	PR : 2/7 (29%)	NR	NR	<sup>25</sup> (Roché, 2002)
			19	PR ; 10/19 (53%)			
Breast and gynaecologic <sup>4</sup>	Y	40 mg/m <sup>2</sup> in 1h, every 3 w	40	PR 6 <sup>4</sup>	NR	NR	<sup>20</sup> (Chen, 2004)
CRC	Y	40 mg/m <sup>2</sup> in 3h, every 3 w	25 (25)	0	11 w	36 w	[42] <sup>26</sup> (Eng, 2003)
Gastric	Y	50 mg/m <sup>2</sup> in 1h, every 3 w <sup>5</sup>	23 (21)	PR 2 (10%)	NR	NR	<sup>23</sup> (Ajani, 2002)
Hepatobiliary	NR	40 mg/m <sup>2</sup> in 3h, every 3 w	15 (12)	PR 2 (17%)	5.7	4.3	<sup>28</sup> (Singh, 2003)
Melanoma	Y	20 mg/m <sup>2</sup> in 1h, every w for 3 w,	12 (12)	0	8 w	NR	<sup>29</sup> (Pavlick, 2004)
	N	every 4 w	12 (11)				
NSCLC	Y	32 mg/m <sup>2</sup> in 3h, every 3 w <sup>6</sup>	49	PR : 7/52 (13%)	NR	NR	<sup>30</sup> (Vansteenkiste 2003)
		6 mg/m <sup>2</sup> in 1h, daily * 5, every 3 w	62	CR 1 + PR 6 / 60 (13%)			
NSCLC	Y	50 mg/m <sup>2</sup> in 1h, every 3 w	31 (25)	PR 4 (18%)	NR	NR	<sup>15</sup> (Delbaldo, 2002)
Pancreas	N	40 mg/m <sup>2</sup> in 3h, every 3 w	60 (54)	PR 4 (7%)	3.3	6.9 <sup>7</sup>	<sup>27</sup> (Whitehead, 2004)
Prostate	N	40 mg/m <sup>2</sup> in 3h, every 3 w	48 (41) <sup>8</sup>	CR 1 + PR 2 / 22 (14%)	NR	8 <sup>8</sup>	<sup>31</sup> (Hussain, 2004)
Renal	Y	6 mg/m <sup>2</sup> /d, daily * 5, every 3 w	39	PR 4 (10%)	NR	NR	<sup>35</sup> (Zhuang SH, 2004)
Soft tissue sarcomas	N	50 mg/m <sup>2</sup> in 1h, every 3 w	24	NR	NR	NR	<sup>36</sup> (Okuno, 2002)
<b>EPO906 (Patupilone)</b>							
Carcinoid	NR	2.5 mg/m <sup>2</sup> w, for 3 w, every 4 w	26	PR 0 / 14 (0%)	NR	NR	<sup>46</sup> (Anthony, 2003)
CRC	Y	2.5 mg/m <sup>2</sup> w, for 3 w, every 4 w	47	PR 1	NR	NR	<sup>45</sup> (Poplin, 2003)
CRC	Y	6 mg/m <sup>2</sup> once every 3 w	44	PR 3	NR	NR	<sup>45</sup> (Poplin, 2003)
NSCLC	Y	6.5 mg/m <sup>2</sup> , every 3 w	9	NR	NR	NR	<sup>48</sup> (Oesterlind, 2004 )
Ovarian	Y	6.5-7.0 in 5 min, once every 3 w <sup>9</sup>	(6)	0	NR	NR	<sup>44</sup> (Smit, 2004)
Prostate	Y	2.5 mg/m <sup>2</sup> w, for 3 w, every 4 w	37 <sup>10</sup>	PR 7 (22%)	NR	NR	<sup>47</sup> (Hussain, 2004)
Renal cell	N	w for 3 w, every 4 w	53	PR 2 (4%)	NR	NR	<sup>49</sup> (Thompson, 2003)

Abbreviations; Y= yes; N= no; NR= not reported; h= hour; w= weeks; CR= complete response; DR= dose reduction; PR= partial response; TN= taxane naïve; TR= taxane refractory; TTP= time to tumor progression; RR= response rate; MST= median survival time; iv= intravenous.

**Footnotes:**

<sup>1</sup> An extended infusion and then a lower dose (DR=dose reduction) was used after initial patients experienced neuropathy and mucositis .

<sup>2</sup> Of the 33 pre-treated (30 evaluable) patients; 6 PR (18%). In the 9 taxane-naïve (8 evaluable); 4 (44%) PR; 4 (44%)<sup>17</sup>.

<sup>3</sup> Patients refractory to taxane (TR) or Taxane-naïve with prior adjuvant anthracycline (TN) were included<sup>25</sup>.

<sup>4</sup> 42 patients were enrolled, of which 21 gynaecological , 13 breast, 8 other (unspecified)<sup>20</sup>. Two patients had a hypersensitivity reaction and one patient died off fatal sepsis. Responses were seen in gynaecological PR 2 (1/14 (7%) ovarian, 1/3 (33%) endometrial primaries) and in breast cancer (PR 4/13 (31%) all taxane pre-treated)<sup>20</sup>.

(Legend Table 4. Contd....)

<sup>5</sup> To reduce toxic side effects, study was amended to 6 mg/m<sup>2</sup> iv in 1h \* 5 every 3 weeks<sup>23</sup>.<sup>6</sup> After the first 18 patients were treated with 40 mg/m<sup>2</sup> in 3h, subsequent patients were treated with 32 mg/m<sup>2</sup> in 3h due to mucositis and neutropenia. 7 PRs were seen in patients treated with 32 mg/m<sup>2</sup>, of which 2 confirmed and 1 CR and 6 PRs of which 5 confirmed of patients in the 6 mg/m<sup>2</sup>.<sup>7</sup> Study primary endpoint was six-month survival, with a true six-month survival of 55% or greater judged. Estimated six-month survival is 59% (95% CI 46-71%). MST of 6.9 months, TTP 3.3 months, an overall RR of 16% (95%CI 8%-29%). Furthermore, a 4 confirmed PRs and 5 unconfirmed PRs were seen<sup>27</sup>.<sup>8</sup> Of the 48 patients, 41 were eligible, and for 28 patients complete data were available and 22 had measurable disease<sup>45</sup>. Eleven grade 3 / 4 toxicities occurred, only most frequent were mentioned. Of the 3 responses, all were unconfirmed. Estimated 1-year survival was 75%<sup>31</sup>.<sup>9</sup> Study is ongoing<sup>44</sup>.<sup>10</sup> A total of 37 patients entered, of which 29 received prior chemotherapy<sup>47</sup>.

patient with SCLC and one patient with carcinoma of unknown primary<sup>38</sup>. Others have combined ixabepilone with gemcitabine or with carboplatin<sup>39,40</sup>. With this latter combination, two responses were seen, one in breast cancer and the other in neuroendocrine carcinoma<sup>40</sup>.

Currently the combination of ixabepilone with cisplatin is investigated in patients with metastatic or recurrent head and neck cancer [46].

### BMS-310705 (Epothilone B, Patupilone)

Two dose finding studies have been performed so far (Table 3). The first study evaluated 15 minutes iv administration for 3 weeks. In the second study BMS-310705 was administered weekly for 3 weeks followed by one week rest<sup>11, 12</sup>. In the 3-week schedule neutropenia, hyponatremia and sensory neuropathy was dose-limiting, while in the 4-week schedule diarrhea was dose limiting. At a dose of 20 mg/m<sup>2</sup> in the 4-week schedule 2/3 patients had grade 3 or 4 sensory neuropathy at their 4<sup>th</sup> course which required a dose reduction. In this schedule, one patient experienced a hypersensitivity reaction at 20 mg/m<sup>2</sup>. This has led to evaluation of a 2 weeks on, 1 week off schedule, which is ongoing<sup>12</sup>. In these phase I studies responses have been reported in ovarian, breast, non-small-cell lung, bladder and stomach cancer.

### epo906 (Epothilone B)

In an effort to determine the optimal dosing schedule of epo906 in patients with solid tumors, 4 different administration schedules have been administered; 5 minutes iv bolus weekly for 4 weeks, every 6 weeks<sup>41</sup>; 5-7 minutes iv bolus weekly 6 weeks on, 3 weeks off q weeks<sup>42</sup>; 5-10 min iv bolus every 3 weeks<sup>42,43</sup>. However, this latter schedule was modified into schedule of 2 weekly doses every 3 weeks due to frequent diarrhea<sup>43,44</sup>. In all of these schedules diarrhea

was dose-limiting. It has been speculated that the inactivation of EPO906 by tissue esterases is involved in this toxicity. Interestingly no significant neuropathy and myelosuppression was observed. Other more frequently reported toxicities were fatigue, nausea and vomiting. In these studies responses in breast<sup>41,43</sup> colon<sup>42</sup>, colorectal<sup>43,45</sup>, carcinoid<sup>46</sup>, ovarian<sup>41</sup> and cancer of unknown primary<sup>42</sup> were reported. Currently epo906 is investigated in ovarian cancer<sup>44</sup>, prostate<sup>47</sup>, NSCLC<sup>48</sup>, colorectal cancer<sup>45</sup>, carcinoid cancer<sup>46</sup> and renal cancer<sup>49</sup>. Preliminary results have shown responses in all these studies, except in patients with carcinoid carcinoma and for the ovarian cancer patients. In this latter study only 6 patients have been included so far<sup>44,46</sup>. Further phase II studies are indicated to determine the tumor activity profile of epo906. Meanwhile the combination with carboplatin<sup>50</sup>, gemcitabine<sup>51,52</sup>, capecitabine<sup>53,54</sup>, estramustine<sup>55</sup> is also under investigation. Consistently all these studies reported as DLTs diarrhea. However, surprisingly no apparent relationship was established between the systemic drug exposure at a

<sup>44</sup> Smit WM, Honkoop AH, Spanik S, *et al.* A phase I/II dose-escalation trial of EPO906 every 3 weeks in patients with relapse/refractory ovarian, primary fallopian, or primary peritoneal cancer. Proc Am Soc Clin Oncol 2004; 5102 (abstr).

<sup>45</sup> Poplin EA, Moore M, O'Dwyer P, *et al.* Safety and efficacy of EPO906 in patients with advanced colorectal cancer: A review of 2 phase II trials. Proc Am Soc Clin Oncol 2003; 1135 (abstr).

<sup>46</sup> Anthony LB, Carlisle T, Pommier R, *et al.* An open-label phase IIA trial evaluating the safety and efficacy of EPO906 as therapy in patients with metastatic carcinoid and other neuroendocrine tumors. Proc Am Soc Clin Oncol 2003; 1413 (abstr).

<sup>47</sup> Hussain A, Dipaola RS, Baron AD, *et al.* A Phase IIa trial of weekly EPO906 in patients with hormone-refractory prostate cancer (HPRC). Proc Am Soc Clin Oncol 2004; 4563 (abstr).

<sup>48</sup> Oesterlind K, Sanchez JM, Zatloukal P, *et al.* A phase I/II dose escalation trial of EPO906 every 3 weeks in patients with non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2004; 7248 (abstr).

<sup>49</sup> Thompson JA, Swerdloff J, Escudier B, *et al.* Phase II trial evaluating the safety and efficacy of EPO906 in patients with advanced renal cancer. Proc Am Soc Clin Oncol 2003; 1628 (abstr).

<sup>50</sup> Aisner J, Gore M, Rubin EH, *et al.* Two phase IB trials of EPO906 plus carboplatin in patients with advanced malignancies. Proc Am Soc Clin Oncol 2003; 574 (abstr).

<sup>51</sup> Rinehart JJ, Rothermel JD, Anderson J, *et al.* Phase I dose-escalation trial investigating the safety and tolerability of EPO906 plus gemcitabine in patients with advanced cancer. Proc Am Soc Clin Oncol 2004; 3100 (abstr).

<sup>52</sup> Lorusso P, Rinehart J, Anderson J, *et al.* Phase I dose-escalation trial investigating the safety and tolerability of EPO906 plus gemcitabine in patients with advanced cancer. Proc Am Soc Clin Oncol 2003; 627 (abstr).

<sup>53</sup> Van Oosterom AT, Dumez H, Calvert AH, *et al.* Phase I dose-escalation trial evaluating the safety and tolerability of EPO906 plus capecitabine in patients with advanced cancer. Proc Am Soc Clin Oncol;2003; 624 (abstr).

<sup>54</sup> Dumez H, Van Oosterom AT, Rothermel JD, *et al.* Phase Ib/II dose-escalation trial evaluating the safety and tolerability of EPO906 plus capecitabine in patients with advanced cancer. Proc Am Soc Clin Oncol 2004; 2093 (abstr).

<sup>55</sup> Wojtowicz M, Rothermel JD, Anderson J, *et al.* Phase I dose-escalation trial investigating the safety and tolerability of EPO906 plus estramustine in patients with advanced cancer. Proc Am Soc Clin Oncol 2004; 4623 (abstr).

<sup>38</sup> Faivre SJ, Delbaldo C PP, *et al.* Phase I study of ixabepilone given every other week in combination with irinotecan in patients with advanced malignancies. Proc Am Soc Clin Oncol 2004; 2051 (abstr).

<sup>39</sup> Anderson S, Dizon D, Sabbatini P, *et al.* Phase I trial of BMS-247550 and gemcitabine in patients with advanced solid tumor malignancies. Proc Am Soc Clin Oncol 2004; 2098 (abstr).

<sup>40</sup> Plummer R, Molife R, Verrill M. Phase I and pharmacokinetic study of BMS-247550 in combination with carboplatin in patients with advanced solid malignancies. Proc Am Soc Clin Oncol 2002; 2125 (abstr).

<sup>41</sup> Rubin EH, Siu LL, Beers S, *et al.* A Phase I and Pharmacologic Trial of Weekly Epothilone B in Patients with Advanced Malignancies. Proc Am Soc Clin Oncol 2001; 270 (abstr).

<sup>42</sup> Calvert AH, Rubin EH, Oza AM, *et al.* Weekly and q3weekly epothilone B (EPO906) in combination with carboplatin in patients with advanced malignancies: Two phase I clinical and pharmacokinetic studies.

<sup>43</sup> Calvert PM, O'Neill V, Twelves C, *et al.* A Phase I and pharmacokinetic study of EPO906 (weeks, in patients with advanced solid tumors. Proc Am Soc Clin Oncol 2001; epothilone B), given every three 429 (abstr).[http://www.annonc.oupjournals.org/cgi/reprint/13/suppl\\_5/21.pdf](http://www.annonc.oupjournals.org/cgi/reprint/13/suppl_5/21.pdf) 2004; 760 (abstr).

dose of 0.3-8 mg/m<sup>2</sup> once every 3 weeks, and the development of diarrhea<sup>56</sup>.

### **kos-862 (Epothilone D)**

Several dose-schedule studies have been performed; once every 3 weeks; daily times 3 every 3 weeks; weekly for 3 weeks, every 4 weeks; once for 24-h and once for 72-h, every 2 weeks<sup>5,6,57,58</sup>. Only one study so far reported the DLT which was determined to be at 185 mg/m<sup>2</sup> when administered once every 3 weeks<sup>5</sup>. DLT with this schedule were impaired gait, cognitive/perceptual abnormalities and atypical chest pain, other toxicities that were observed were sensory neuropathy and fatigue. Responses were reported in bladder<sup>58</sup> and prostate<sup>58</sup> cancer. Furthermore antitumor activity, primarily decreases in tumor markers, was observed in patients with testicular, ovarian, pancreatic and breast cancer<sup>5</sup>. Phase II trials in colorectal, metastatic breast and non-small-cell lung cancers have been initiated in December 2003 [47]. Recently a phase II clinical trial in patients suffering from colorectal cancer was discontinued due to unanticipated cumulative drug toxicities in previously treated patients. As a result, also a phase IB trial of kos-862 in combination with capecitabine in colon cancer has been abandoned [48]. Currently several combination regimens are investigated, with gemcitabine, carboplatin and with trastuzumab [49].

## **OTHER TUBULIN INHIBITORS**

### **XAA296A**

XAA296A belongs to the discodermolides, originating from the marine sponge *Discodermia dissolute* [26]<sup>4</sup>. Discodermolides poses additional activity in addition to those overlapping with the taxanes and epothilones *in vitro*; rapid assembly of microtubules and they exhibit synergy with paclitaxel in cultured cell lines [50].

Only one dose finding study was conducted so far and only preliminary results are reported (see Table 3)<sup>4</sup>. In this study by *Mita et al.* one grade 4 anemia was observed during third cycle and furthermore adverse events that were reported to occur more frequently were anemia, nausea, vomiting, fatigue, diarrhea and mucositis. No neuropathy or neutropenia were observed and no responses were reported.

### **ABT-751**

ABT-751 binds to the colchicine site on tubulin [51]. ABT-751 is not an MDR substrate, therefore it can be administered per os<sup>8</sup>. Several dose finding studies have been performed; daily times 7 every 21 days, daily times 21 every 28 days, twice daily every 21 days<sup>7, 8, 59, 60</sup>. Only two studies

have determined the MTD, which was at 250 mg/m<sup>2</sup> daily for 7 days, every 21 days<sup>7, 60</sup>. In these studies different DLT were found. *Kobayashi et al.* found abdominal pain and constipation to be dose limiting, whereas *Hande et al.* found peripheral neuropathy and intestinal obstruction dose limiting<sup>7, 60</sup>. Up to now only one minor response was reported in a patient suffering from colorectal cancer at a dose of 50 mg once daily<sup>8</sup>. So far in these studies no myelosuppression or alopecia has been reported<sup>8</sup>. Phase II studies are being conducted in colorectal, breast and lung cancer, results are awaited<sup>52</sup>. Preliminary results of ABT-751 administered to children, indicate that higher doses than the MTD found in adults are tolerated<sup>59</sup>. The recommended dose in children however, is still under investigation.

### **D-24851 (Indibulin)**

D-24851 is a synthetic small molecule which antitumor activity is based upon destabilization of microtubules. Several properties such as its oral availability, lack of neurotoxicity, efficacy towards drug resistant tumor cell lines and *in vivo* antitumor activity in various cancer types have favored testing in humans<sup>53</sup>. Currently a dose finding study in humans is conducted in the Netherlands Cancer Institute, in which D-24851 is administered once daily for 14 days every 3 weeks<sup>30</sup>. Preliminary results indicate a high variability and the %CV of the AUC<sub>0-72</sub> was 38% between patients and 33% within patients. Indibulin was well tolerated, with the exception of nausea and vomiting. This appeared to be related to the increased dose-volume of indibulin and was considered dose limiting. No signs of neurotoxicity or haematologic toxicity >grade 2 were reported. Furthermore, we have seen stable disease in a patient suffering from oropharynxcarinoma, who is continuing treatment at a dose of 80 mg for over 7 months. To prevent nausea and vomiting, a capsule formulation will be investigated. A future study is planned.

## **DISCUSSION**

The challenge to develop and introduce new tubulin inhibitors with improved properties was founded on the success of the taxanes. A major concern regarding the use of the taxanes has been the side effect neurotoxicity. Unfortunately, neuropathy has also been observed with the epothilones ixabepilone [54,55], BMS-310705<sup>11</sup> and with ABT-751<sup>60</sup>.

It appears that ixabepilone dosed daily times 5, every 21 days shows less neurotoxicity than administered once every 21 days. Indicating the importance of elucidating the optimal dosing schedules. Besides neurotoxicity, hypersensitivity reactions have been observed with the ixabepilone which was as expected since the used co-solvent was cremophor EL [19,20]. Subsequently ixabepilone is now given only after administration of H1/H2 blockers. Interestingly a completely different toxicity profile was observed for epo906 (diarrhea) and ixabepilone (neurotoxicity and myelosuppression), even though these compounds are structurally very similar. These new tubulin inhibitors do not only possess different toxicity

<sup>56</sup> Chen TL, Twelves C, Calvert AH, *et al.* Pharmacokinetics of EPO906 in cancer patients receiving EPO906 by short intravenous infusion once every 3 weeks. *Proc Am Soc Clin Oncol* 2002; 363 (abstr).

<sup>57</sup> Rosen PJ, Rosen LS, Britten C, *et al.* KOS-862 (epothilone D): results of a phase I dose-escalating trial in patients with advanced malignancies. *Proc Am Soc Clin Oncol* 2002; 413 (abstr).

<sup>58</sup> Holen KD, Syed S, Hannah AL, *et al.* Phase I study using continuous intravenous (CI) KOS-862 (Epothilone D) in patients with solid tumors. *Proc Am Soc Clin Oncol* 2004; 101 (abstr).

<sup>59</sup> Cho SY, Adamson PC, Hagey AE, *et al.* Phase I trial and pharmacokinetic (PK) study of ABT-751, an orally bioavailable tubulin binding agent, in pediatric patients with refractory solid tumors. *Proc Am Soc Clin Oncol* 2004; 2080 (abstr).

<sup>60</sup> Hande KR, Meek K, Lockhart AC, *et al.* Pharmacokinetics and safety of ABT-751, a novel microtubulin inhibitor. *Proc Am Soc Clin Oncol* 2003; 520 (abstr).

**Table 5. Combination Regimens with Tubulin Inhibitors, Dose Schedule MTD, DLT and Recommended Dose**

Schedule	Tumor Type	N (eval)	Dose mg/m <sup>2</sup>	MTD mg/m <sup>2</sup>	Tumor Response	Most Severe Toxicities	Reference
<b>Combination</b>							
<b>BMS247550</b>							
<u>BMS247550</u> + <u>irinotecan</u> , on d1+14, every 4 w	Solid	30 (26)	Up to 25 + 180	ND	4 PR <sup>1</sup>	ND	<sup>38</sup> (Faivre, 2004)
<u>BMS247550</u> in 3 h on d8 + <u>gemcitabine</u> in 90 min d1+8 every 3 w	Solid	18	20-30/900	20/900	0 (12 eval)	Neutropenia, thrombocytopenia	<sup>39</sup> (Anderson, 2004)
<u>BMS247550</u> + <u>carboplatin</u> , every 3 w	Solid	24	30-40 + AUC 5-6	40 + 6	2 PR <sup>2</sup>	Febrile-, Neutropenia, thrombocytopenia	<sup>40</sup> (Plummer, 2002)
<u>BMS247550</u> in 3h + <u>Estramustine</u> 3 * d, d1-5 every 3 w	Prostate	13	35 + 280	35 + 280	<sup>3</sup>	Neurotoxicity	[43] (Smaletz, 2003)
<u>BMS247550</u> iv + <u>estramustine</u> tid for 5 d, every 3 w	Prostate	5	35-40 + 280	40	ND	ND	<sup>32</sup> (Smaletz, 2002)
<u>BMS247550</u> iv in 3 h, every 3 w + <u>estramustine</u> po TID d1-5	Prostate	45	35 + 280 <sup>4</sup>	ND <sup>5</sup>	8/18 (44%)	Neuropathy, neutropenia	<sup>33</sup> (Kelly, 2003)
<u>BMS247550</u> iv in 3 h, every 3 w		47	35		6/26 (23%)		
<b>Epo906</b>							
<u>Epo906</u> 5 min iv, weekly for 3-4 w + <u>carboplatin</u> 30 min iv (AUC 2)	Solid	28	0.5-2.5 + AUC2	2.5	1 PR (13 eval)	Diarrhea, paresthesias	<sup>50</sup> (Aisner, 2003)
<u>Epo906</u> 5 min iv, once every 3 w + <u>carboplatin</u> 60 min iv (AUC 6)	Solid	8	3.6-6.0 + AUC5	NR	ND	Diarrhea	<sup>50</sup> (Aisner, 2003)
<u>Epo906</u> 5 min iv, weekly for 3 w + <u>capecitabine</u> TD in w 2+3, every 4 w	Solid	16	0.5-2.5 + 1250	2.0 + 1250 TD	0/11	Diarrhea	<sup>53</sup> (van Oosterom, 2003)
<u>Epo906</u> 5 min iv, weekly for 3 w + <u>capecitabine</u> TD in w 2+3, every 4 w	Solid	24	0.5;1.0; 1.5;2.0	1.5	0/24	Diarrhea, nausea, anorexia, small bowel obstruction	<sup>54</sup> (Dumez, 2004)
<u>Epo906</u> 5 min iv + <u>gemcitabine</u> 30 min iv, for 3 w, every 4 w	Solid	24	0.5,1.0,1.5, 2.0,2.5 + 800	2.0 + 800	1 PR (16 eval)	Diarrhea, nausea, dizziness	<sup>51</sup> (Rinehart, 2004) <sup>52</sup> (Lorusso, 2003)
<u>Epo906</u> 5 min iv weekly, on d2 for 3 w + <u>estramustine</u> TD d1-3	Solid	14	0.5-2.5 + 280	2.5 + 280	1 PR (14 eval)	Diarrhea, fatigue, vomiting, nausea	<sup>55</sup> (Wojtowicz, 2004)

Abbreviations: TD= Twice daily; TID= three times a day; AUC= area under the curve; d= days; h= hours; w= weeks; min= minutes; PR= partial response; eval= evaluable; ND= not determined; iv= intravenous; po= per os; NSCLC= non small cell lung cancer; SCLC= small cell lung cancer

**Footnotes:**

<sup>1</sup> PR were seen in NSCLC (2), SCLC and carcinoma of unknown primary <sup>38</sup>.

<sup>2</sup> Two PRs were seen, one in breast and one in neuroendocrine carcinoma. Carboplatin was dosed based on AUC (Calvert formula) <sup>40</sup>.

<sup>3</sup> A decline in prostate specific antigen of  $\geq 50\%$  was seen in 11 of 12 evaluable patients. There were objective responses in soft tissue (57%) and bone metastasis (40%).

<sup>4</sup> At a median follow-up of 6.5 months, 81 patients are alive and 11 have died <sup>33</sup>.

<sup>5</sup> This was not a dose-finding study <sup>33</sup>.

profiles, but also their mutual responses in different tumor types varies. In phase I/II studies, activity was demonstrated in a wide variety of tumors, including prostate and renal cancer (ixabepilone and patupilone)<sup>31,35,47,49</sup>. Moreover, several of these studies demonstrated activity in patients which were pre-treated with taxanes. This could be of clinical benefit. It is yet to be decided whether these

observed activities lead to clinical efficacy in terms of overall survival, TTP and MST. However, most studies have aimed to investigate the optimal treatment schedule and several of them are currently ongoing. A point of interest for future studies is to investigate the joined bonus value of the tubulin inhibitors either with other chemotherapeutic agents or with drugs also acting upon tubulin. *Martello et al.* have

suggested possible synergy when taxol and discodermolide were combined in human cell lines [56]. Furthermore the possibility of oral administration of several of these agents has not received much attention of investigators. Since only in one study ixabepilone was administered per os and none of the other epothilones was given orally<sup>9</sup>. Recently, insights in dosing of the taxanes have been refined. In a study by Seidman *et al.* enhanced response rates (40% versus 28%,  $P < 0.001$ ) and time to progression (9 versus 5 months,  $P < 0.001$ ) was observed in breast cancer patients who were treated with an one hour weekly infusion of paclitaxel versus patients treated with a 3 hour infusion every 3 weeks<sup>61</sup>. This stresses the importance of protracted dosing of tubulin inhibitors and stimulates our curiosity to oral administration of these new agents. In addition, several of these compounds e.g. paclitaxel, 5-methylpyridine-epothilone B, ixabepilone and epothilone B have shown suppression of angiogenesis and certain endothelial cell functions relevant to angiogenesis such as migration and protease production occurs at significant lower concentrations than that are necessary for antiproliferative effects against endothelial cells [57]. In summary, several new tubulin inhibitors have shown promising response rates in a variety of schedules. Future studies are required to determine their optimal administration mode and schedule in relation to their efficacy and safety profile, either by administration as single agent or in combination regimen.

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