

**A Phase II Clinical Trial of Ixabepilone (Ixempra®, BMS–247550, NSC 710428), an  
Epothilone B Analog, in Cervical Cancer  
NCI Protocol Number 6620**

National Cancer Institute  
Center for Cancer Research  
Medical Oncology Branch

Drugs used: IXABEPILONE (Bristol-Myers Squibb)/(NSC 710428)

Sponsor: CTEP (Cancer Treatment Evaluation Program, NCI)

Short Title: Ixabepilone in Cervical Carcinoma

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## Précis:

### Background

- Ixabepilone (Ixempra®, BMS-247550, NSC 710428) is a semi-synthetic analog of the natural product epothilone B.
- The epothilones are a novel class of non-taxane microtubule-stabilizing agents obtained from the fermentation of the cellulose degrading myxobacteria, *Sorangium cellulosum*.
- Ixabepilone is active against cancer models that are naturally insensitive to paclitaxel or have developed resistance to paclitaxel, both *in-vitro* and *in-vivo*.

### Objectives

#### Primary-

- Establish the efficacy of the investigational agent ixabepilone in patients with cervical carcinoma when administered as a daily one hour infusion on day 1 to 5 every three weeks, as measured by overall response (PR+CR).

#### Secondary-

- Assess pharmacodynamic endpoints to determine the extent of tubulin polymerization and whether or not there has been activation of cellular death pathways “distal” to the target.
- Estimate progression free survival and duration of response.

### Eligibility

- Age > 18
- Histologic or cytologic confirmation of cervical carcinoma; either squamous cell or non-squamous consisting of cervical adenocarcinoma, cervical adenosquamous carcinoma or cervical carcinoma, non-squamous type.

### Design

- Phase II study, open, non-randomized
- Ixabepilone will be administered at a dose of 6mg/m<sup>2</sup> daily on days 1 through 5, every three weeks.
- Restaging will be done every two cycles using RECIST
- Planned maximum enrollment 76 persons

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## 1 INTRODUCTION

### 1.1 STUDY OBJECTIVES

#### 1.1.1 Primary:

- Establish the activity of ixabepilone administered daily as a one-hour infusion on five successive days (daily x 5), every three weeks in patients with cervical carcinoma previously treated with chemotherapy, as determined by overall response (PR+CR). Activity will be measured using standard RECIST guidelines.

#### 1.1.2 Secondary:

- Assess pharmacodynamic endpoints after ixabepilone administration to determine the extent of tubulin polymerization and whether or not there has been activation of cellular death pathways “distal” to the target.
- Determine progression free survival and duration of response

### 1.2 BACKGROUND, TRANSLATIONAL STUDIES AND RATIONALE

#### 1.2.1 Cervical Carcinoma

Cervical cancer is the second most common cancer among women worldwide [1]. The proportion and absolute incidence of the adenocarcinoma subtype has increased relative to the more common squamous cell subtype of cervical cancer [2, 3]. Although a recent study found that the adenocarcinoma subtype had only a minor prognostic importance for survival, the prognostic significance of the adenocarcinoma subtype remains controversial [4, 5]. Consequently, there has been no attempt to sub classify recurrent adenocarcinoma in therapeutic trials. In the United States cervical cancer there were an estimated 9710 new cases in 2006 (NCI SEER CACJC 2006) with an estimated 3700 estimated deaths.

Table 1: Epidemiology of Cervical Cancer

Stage at Presentation:	
Localized	55%
Regional	31%
Distant	8%
Unstaged	6%
Histopathology:	
Squamous cell carcinoma	75 - 80 %
Large cell, keratinizing	
Large cell, nonkeratinizing	
Small cell (not neuroendocrine)	
Verrucous carcinoma	
Adenocarcinomas	15 - 20 %
Adenous malignum	
Mucinous	
Papillary	
Endometrial	
Clear cell	
Adenoid cystic	

Adenosquamous	Rare
Glassy cell carcinoma	Rare
Neuroendocrine small cell carcinoma	Rare

### **Metastatic Cervical Carcinoma**

#### **Systemic chemotherapy in metastatic squamous carcinoma of the cervix**

Squamous cell carcinoma (SCC) of the cervix (80%) is much more common than adenocarcinoma of cervix (15%). Several single chemotherapy agents and combination regimens are active in patients who present with metastatic disease or suffer a recurrences of SCC of cervix that are not amenable to potentially curative treatment with surgery and/or radiation therapy. The most active single agents are cisplatin (RR 20-32%) [6], ifosfamide (RR 22 %) [7], paclitaxel (RR 17 %) [8], vinorelbine (RR 15 %) [9] and topotecan (RR 19 %) [10].

While combination regimens (cisplatin/ifosfamide, cisplatin/paclitaxel, cisplatin/topotecan, or carboplatin/paclitaxel) have demonstrated higher response rates than the single agent platinum compounds, the only trial to show a survival benefit to multiagent therapy with advanced disease was cisplatin (50 mg/m<sup>2</sup> every three weeks) with topotecan (0.75 mg/m<sup>2</sup> days 1 to 3 every three weeks). Compared to cisplatin alone, the topotecan/cisplatin group had a median survival 9.4 versus 6.5 months (p = 0.017), but significantly more toxicity [11].

#### **Systemic chemotherapy in metastatic adenocarcinoma of the cervix:**

Systemic chemotherapy is the recommended treatment for metastatic or recurrent adenocarcinoma of the cervix not amenable to irradiation or surgery. However, there is limited data on the treatment of recurrent cervical adenocarcinoma because of its infrequent occurrence and the paucity of active chemotherapeutic agents. The available data on the use of chemotherapy in cervical adenocarcinoma comes from clinical trials, many of which have been conducted by the Gynecologic Oncology Group (GOG) [12-24]. Single agent trials in patients who had received prior irradiation and/or chemotherapy demonstrated evidence of activity for six chemotherapeutic agents: cisplatin, piperazinedione, ifosfamide gallium nitrate, 5-FU plus leucovorin and paclitaxel (Table 1). Agents that have been tested and deemed ineffective include: CCNU, methyl-CCNU, mitoxantrone, etoposide (VP-16), teniposide (VM-26), vinblastine, aminothiadiazole, echinomycin, ICRF-159 (Razoxane), dianhydrogalactitol, diaziquone (AZQ) and tamoxifen.

Several studies have noted the activity of paclitaxel in cervical adenocarcinoma. The first published suggestion that paclitaxel may be active in cervical adenocarcinoma came from a study in which paclitaxel was used as part of a combination chemotherapy regimen principally in the neoadjuvant setting [23]. Whereas a prior study had noted an overall pathologic response rate of 47% with weekly cisplatin and epirubicin as neoadjuvant therapy [22], Lissoni and colleagues reported that the addition of paclitaxel to this neoadjuvant regimen resulted in a pathologic response rate of 65% [23]. Subsequent to this, single agent activity was reported in a phase 2 GOG study of 46 patients treated with 170 mg/m<sup>2</sup> paclitaxel (or 130 mg/m<sup>2</sup> for patients with prior pelvic irradiation) given as a 24 hour infusion every three weeks [16]. The overall response rate for the 42 assessable patients was 31% (4 CRs and 9 PRs). In addition, Ota et al



reported a single case of metastatic cervical adenocarcinoma with a complete response after twenty cycles of weekly paclitaxel [17].

**Table 1: Chemotherapy for Adenocarcinoma of the Cervix**

Single Agent Chemotherapy				
Author (Year)	Agent	Pts	RR <sup>1</sup>	Comments
Thigpen (86) <sup>12</sup>	Cisplatin	12 <sup>2</sup>	25%	Only 50 mg/m <sup>2</sup> q3wks; lowest WBC: 1600/mL
Thigpen (86) <sup>12</sup>	Piperazinedione	6 <sup>2</sup>	17%	9 mg/m <sup>2</sup> q 3wks; drug not available
Sutton (93) <sup>13</sup>	Ifosfamide	41 <sup>2</sup>	15%	1.5 g/m <sup>2</sup> /d x 5d (1.2 if prior RT); 28 pts with adenocarcinoma
Malfetano (95) <sup>14</sup>	Gallium Nitrate	26 <sup>2</sup>	11%	750 mg/m <sup>2</sup> q3wks; 21 pts with adenocarcinoma
Look (97) <sup>15</sup>	5-FU + High Dose Leucovorin	43	13%	370 mg/m <sup>2</sup> qd x 5d q4wks; G3/4 ANC: 53%
Curtin (01) <sup>16</sup>	Paclitaxel (24h infusion q3 weeks)	42 <sup>2</sup>	31%	170 mg/m <sup>2</sup> ; 130 mg/m <sup>2</sup> if prior pelvic RT; G3/4 ANC: 74%
Ota (01) <sup>17</sup>	Paclitaxel (weekly)	1	1/1	Case report. 70 mg/m <sup>2</sup> by 1h infusion
Combination Chemotherapy Regimens				
Author (Year)	Agent	Pts	RR	Comments
Kavanagh (87) <sup>18</sup>	Cisplatin/5-FU/Doxorubicin	24	42%	Cis: 50-60mg/m <sup>2</sup> ; 5-FU: 500-800mg/m <sup>2</sup> ; Dox: 40-50mg/m <sup>2</sup> G3/4ANC: 38%
Bates (91) <sup>19</sup>	Cisplatin/Mitomycin C	1	1/1	Case report. Cis: 50 mg/m <sup>2</sup> q3wks; MMC: 10 mg/m <sup>2</sup> /q6wks
Fanning (95) <sup>20</sup>	Cisplatin/5-FU/Ifosfamide	9 <sup>2</sup>	78%	Cis: 90 mg/m <sup>2</sup> /5-FU: 1500 mg/m <sup>2</sup> ; Ifos: 3 g/m <sup>2</sup> ; G4ANC:6%
Umesaki (99) <sup>21</sup>	Cisplatin/Mitomycin/Etoposide	31	16%	Cis: 50 mg/m <sup>2</sup> ; MMC: 10 mg/m <sup>2</sup> ; E: 100 mg/m <sup>2</sup> x3; G3/4ANC: 45%
Zanetta (97) <sup>22</sup>	Cisplatin/Epirubicin	22	50%	Neoadjuvant. Cis: 50 mg/m <sup>2</sup> qwk; Epi: 70 mg/m <sup>2</sup> q3wks; +GF; G3/4ANC: 45%
Lissoni (97) <sup>23</sup>	Cisplatin/Epirubicin/Paclitaxel	19	53%	17 neoadjuvant. Cis: 50 mg/m <sup>2</sup> ; Epi: 70 mg/m <sup>2</sup> Pac: 135-175 mg/m <sup>2</sup> ; G3/4 ANC: 60%
Saito (04) <sup>24</sup>	Cisplatin/Aclacinomycin A/Mitomycin C	16	75%	IV or Intra-arterial for localized disease

<sup>1</sup>Some responses have been recalculated from that reported based on currently accepted criteria and histologic breakdown

<sup>2</sup>Data reported for "Nonsquamous Carcinoma". Insufficient information given to determine activity in adenocarcinoma subtype

**Abbreviations:** Pts: patients; RR: response rate; RT: radiation therapy; G: toxicity grade; ANC: neutropenia; +GF: growth factor (GCSF or GMCSF)

### 1.2.2 Drugs targeting microtubules

Vincristine, first used in clinical oncology in the 1950's, was the first drug to target the microtubules (MTs). Since then, the successful introduction of similar agents has established the MT as an effective target [24]. While most microtubule-targeting agents (MTAs) initially used in clinical oncology resulted in depolymerization of microtubules, the success of the taxanes demonstrated that stabilization of microtubules was an equally or more efficacious mechanism of action [26,27].

### 1.2.3 Epothilones

The activity of the taxanes, evidenced by their widespread use, led to the search for additional agents with similar mechanisms of action. Several classes of MTAs were identified, and these are at various stages of development [28-36]. Among these, are the epothilones, a novel class of non-taxane MT-stabilizing agents obtained from the fermentation of the cellulose degrading myxobacteria, *Sorangium cellulosum*, that have received special attention [28-31]. As a group the epothilones are more potent than the taxanes and are active against tumors refractory to taxanes, especially those expressing P-glycoprotein (Pgp). ***These two properties have driven the development of the epothilones and it is because of their ability to overcome tumor resistance mechanisms that this class of agents has been of great interest to our groups in the Medical Oncology Branch whose focus of research and clinical investigations are mechanisms of drug resistance and ways to overcome drug resistance clinically.*** Finally the epothilones are also more soluble than the taxanes and have enhanced oral bioavailability. These properties make these agents desirable candidates for clinical development. This phase II study is designed to examine activity of the epothilone B analog, ixabepilone (Ixempra®) against cervical carcinoma [37].

### 1.2.4 Ixabepilone [Ixempra®]

General comments: Ixabepilone (Ixempra®) is a member of the novel class of non-taxane MT-stabilizing compounds known as epothilones obtained from the fermentation of the cellulose degrading myxobacteria, *Sorangium cellulosum* [28-31]. Similar to paclitaxel and other taxanes, epothilones block cells in mitosis, resulting in cell death [28-30]. Ixabepilone is being developed by Bristol-Myers Squibb for the treatment of cancer [37].

Chemistry: The epothilones are a new class of agents that like the taxanes, promote the polymerization of tubulin. The epothilones are obtained from the fermentation of the myxobacterium, *Sorangium cellulosum*. The chief components of the fermentation process are epothilones A and B. These natural products are polyketide derived, sixteen-membered ring macrolides. Ixabepilone, [1S-[1R\*, 3R\*(E), 7R\*, 10S\*, 12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione, is a semisynthetic derivative of epothilone B that has improved *in vivo* metabolic stability when compared to its natural precursor. The key difference between ixabepilone and epothilone B is the replacement of the macrolide ring oxygen atom with a nitrogen atom to give the corresponding macrolactam. Ixabepilone has a molecular formula of C<sub>27</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub>S and a molecular weight of 506.7 grams/mole.

Preclinical pharmacology studies: In preclinical pharmacology studies ixabepilone demonstrated significant improvement over paclitaxel in several critical aspects. [A] Ixabepilone is active against cancer models that are naturally insensitive to paclitaxel or have developed resistance to paclitaxel, both *in-vitro* and *in-vivo*, most notably efflux transporters (eg, P-glycoprotein and multidrug-resistance protein-1) and in preliminary studies, models with relative insensitivity mediated by the expression of the class III isoform of beta-tubulin [38, 39]. Ixabepilone exhibits a very impressive and broad spectrum of antitumor activity against paclitaxel-sensitive (A-2780, HCT 116 and LS 174T) tumors as well as paclitaxel-resistant human colon tumors (HCT116/VM46), ovarian carcinoma (Pat-7 and A2780Tax) and breast carcinoma (Pat-21) models. [B] Ixabepilone is orally efficacious; the antitumor activity produced after oral administration is comparable to that produced by parenteral administration of the drug. [C] Synergistic activity of ixabepilone with a number of antineoplastic agents has been demonstrated *in vitro*. These preclinical efficacy data suggest that ixabepilone has the potential to demonstrate improved clinical efficacy in paclitaxel-insensitive and sensitive disease types.

Clinical Information: Ixabepilone has undergone phase I/II/III testing in humans. The NCI has had extensive experience with ixabepilone dating to the initial phase I trials. Several intravenous infusion schedules were evaluated in the phase I setting, including a single dose every 3 weeks, a daily dose for 3 days every 3 weeks, a weekly schedule, and a daily dose for five consecutive days every 21 days. Both the daily dose for 3 days every 3 weeks and a daily dose for five consecutive days every 21 days were developed in the Medical Oncology Branch of the NCI. A bolus regimen every three weeks established 50 mg/m<sup>2</sup> as the MTD, with neurotoxicity and neutropenia as dose limiting toxicities – although subsequent trials eventually established lower doses of 30 to 40 mg/m<sup>2</sup> as the recommended doses [40-42]. In these three studies ixabepilone was administered every 21 days to sixty-three patients with the schedule at several dose levels in the range of 7.4–65 mg/m<sup>2</sup>. After observing a hypersensitivity reaction in one patient on the 30-mg/m<sup>2</sup> dose, oral H1/H2 blockers were administered in all three studies [39]. Responses were observed in patients with melanoma, non-small cell lung cancer (prior docetaxel), ovarian cancer (prior paclitaxel), and breast cancers (taxane naïve and taxane refractory). Although both 40 and 50 mg/m<sup>2</sup> doses emerged as the recommended doses for phase II trials subsequent experience found 50 mg/m<sup>2</sup> ixabepilone every three weeks intolerable and identified 40 mg/m<sup>2</sup> as the better recommendation. DLTs included prolonged grade 4 neutropenia, peripheral neuropathy, gastrointestinal discomfort, fatigue, and emesis.

Phase I studies were also designed to establish the MTD for ixabepilone administered as a 1-hour infusion on five consecutive days every 3 weeks - the schedule pursued in the Medical Oncology Branch of the NCI. In the initial phase I study 27 patients were enrolled. Twenty-one of these 27 patients had received prior taxane therapy including five who had received prior Taxol® or Taxotere® less than six months prior to receiving ixabepilone. Dose levels included 1.5, 3, 6 and 8 mg/m<sup>2</sup>/d administered on each of five successive days. Intra-patient dose escalation without/with GCSF was permitted if dose-limiting toxicity (DLT) was not observed in the previous cycle. All three patients receiving 8 mg/m<sup>2</sup>/d without GCSF in cycle 1 experienced grade 4 neutropenia as the DLT. Accordingly 6 mg/m<sup>2</sup>/d was identified as the maximum tolerated dose (MTD)

without GCSF, and the recommended phase II dose. A dose  $\geq 8 \text{ mg/m}^2/\text{d}$  was administered in 48 cycles to 20 pts. All patients received a dose  $\geq 6 \text{ mg/m}^2/\text{d}$  either initially or after intra-patient dose escalation. A total of 102 cycles were administered (median of 3 per patient; with 13 patients receiving  $\geq 4$  cycles). Ninety-nine of the 102 cycles were given at a dose  $\geq 6 \text{ mg/m}^2/\text{d}$ . Non-hematologic grade 3 toxicities included: fatigue (7 cycles), stomatitis (2 cycles) and anorexia (1 cycle). All other non-hematologic toxicities were grade 2 or less including neurotoxicity in 17 patients. Pharmacokinetic studies indicated steady state is reached by day 3, with  $C_{\text{max}}$  and  $C_{\text{min}}$  values suggesting no accumulation (day 5 vs. day 1). Additional parameters include: a  $t_{1/2a}$  of  $.115 \pm .062$  hours, a  $t_{1/2b}$  of  $12.7 \pm 4.4$  hours, a  $V_{d_{ss}}$  of  $8.08 \pm 3.99 \text{ L/kg}$ , and a clearance of  $419 \pm 123 \text{ ml/min/m}^2$ . A partial response was observed in 5 patients including two patients with breast cancer, two patients with cervical cancer and one patient with basal cell carcinoma; with  $> 50\%$  reduction in CA125 in two of 12 patients with advanced ovarian cancer (all breast, cervical and ovarian cancer patients had prior taxane therapy). Hypersensitivity reactions were not observed using a pre-medication regimen consisting of H1 and H2 antagonists without steroids prior to each dose of ixabepilone. We concluded that a dose of  $6 \text{ mg/m}^2/\text{d} \times 5\text{d}$  of ixabepilone was well tolerated, and clinically active in patients with cancer who have previously received taxane therapy [43]. In addition, twenty-six patients were enrolled in a phase I trial in which ixabepilone was administered as a 1-hour infusion on three consecutive days every 3 weeks [44]. The DLT was, once again, grade 4 neutropenia and again there was no grade 3 or 4 peripheral neuropathy. Interestingly, the recommended dose of ixabepilone administered on a daily for three consecutive days schedule every 21 days was  $8 \text{ mg/m}^2$  per day ( $24 \text{ mg/m}^2$  per cycle) a total dose that was less the  $30 \text{ mg/m}^2$  of the daily for five consecutive days. Ixabepilone was also evaluated on a weekly schedule.

Finally, in trials with weekly administration investigators were able to administer weekly doses of  $30 \text{ mg/m}^2$ , with neurotoxicity noted as the DLT. However, because of a lack of significant advantages, this schedule has not been aggressively pursued [45-47].

Phase I trials also demonstrated the feasibility of combining ixabepilone with other cytotoxic agents much like the taxanes. Combinations included: (a) ixabepilone  $40 \text{ mg/m}^2$  plus carboplatin AUC 5 [48] (b) ixabepilone at  $40 \text{ mg/m}^2$  initially with  $2,000 \text{ mg/m}^2$  capecitabine per day for 14 days with a 1-week rest every 21 days and subsequently with lower capecitabine doses [49,50] (c) ixabepilone on day 1 of a cycle with gemcitabine on days 1 and 8 of a 21-day cycle with ixabepilone at a dose of  $20 \text{ mg/m}^2$  and gemcitabine at a dose of  $900 \text{ mg/m}^2$  the recommended doses [51].

In phase II studies, single-agent ixabepilone showed very encouraging clinical activity in metastatic breast cancer, with objective response rates ranging from 12% in patients that had been "heavily pretreated" and whose disease was deemed refractory to anthracyclines, taxanes, and capecitabine to 42% in patients with metastatic disease whose prior therapy had been limited to adjuvant anthracycline-based chemotherapy [52-55]. In the first trial, conducted in the Medical Oncology Branch, ixabepilone was administered at  $6 \text{ mg/m}^2$  per day on days 1–5 every 3 weeks to 37 patients with advanced breast cancer with measurable disease who had received at least one prior regimen that contained paclitaxel or docetaxel [52]. An overall response rate of 21% in

these patients who had received at least one prior regimen that contained paclitaxel or docetaxel was noteworthy. Grade 3 and 4 toxicities included neutropenia (35%), febrile neutropenia (14%), fatigue (14%), diarrhea (11%), nausea/vomiting (5%), myalgia/arthralgia (3%), and sensory neuropathy (3%). A second study was also conducted to determine the efficacy and safety of ixabepilone in patients with taxane-refractory or taxane-naïve metastatic breast cancer [53]. Patients who had experienced disease progression while receiving or within 4 months of taxane therapy (6 months if adjuvant taxane only), and who had a taxane as their last regimen, received ixabepilone (1- or 3-hour infusion of 50 mg/m<sup>2</sup> or 3-hour infusion of 40 mg/m<sup>2</sup> every 3 weeks). Of 49 patients treated with 40 mg/m<sup>2</sup> ixabepilone during 3 hours, 35 (73%) had experienced disease progression within 1 month of their last taxane dose. The response rate was 12% (95% CI, 4.7% to 26.5%). All responses (n = 6) were partial. Each of the responders had extensive tumor metastases at baseline and had experienced progressive disease after multiple prior therapies. Five of these patients entered the study having experienced disease progression within 1 month of their last dose on their most recent taxane-containing regimen, while only one had responded to the most recent taxane therapy. In responders, the median response duration was 10.4 months. In 20 patients (41%), stable disease was the best outcome. Median time to progression was 2.2 months (95% CI, 1.4 to 3.2 months); median survival was 7.9 months. For treated patients across all cohorts (intent-to-treat population), the response rate was also 12% (eight of 66). Treatment-related adverse events in the study were manageable and primarily grade 1/2. The most frequent treatment-related grade 3 adverse events were fatigue (27%), sensory neuropathy (12%), myalgia (10%), nausea (6%), and vomiting (6%). Treatment-related neuropathy was mostly sensory, mild to moderate in severity (grade 1 or 2), cumulative, and reversible, not unlike the experience with the taxanes. Treatment-limiting or severe neuropathy generally resolved or lessened in intensity within 1–2 months after therapy discontinuation, again not unlike the taxanes. In terms of hematological toxicities, only six patients (12%) required growth factor support for neutropenia during their treatment. Treatment-related febrile neutropenia was reported in three patients (6%) (two patients reported febrile neutropenia; one patient reported infection with neutropenia). The results of this study provided further support for the pre-clinical observations demonstrating ixabepilone could be active against taxane-resistant tumors of cross-resistance especially since in the latter study, the taxane had to have been the most recent therapy administered and there had to be evidence of disease progression while on therapy or within 4 months of the last dose. Thus, the patient population consisted of those with tumors highly resistant to a taxane and as such provided a very demanding test of the hypothesis.

On October 16, 2007, the U.S. Food and Drug Administration (FDA) approved ixabepilone for injection (Ixempra™, made by Bristol-Myers Squibb) for the following two indications:

- Ixabepilone is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.
- Ixabepilone is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

Approval was based on:

- A randomized, multinational, open-label trial of 752 patients with locally advanced or metastatic breast cancer that evaluated the efficacy and safety of ixabepilone administered at a dose of 40 mg/m<sup>2</sup> IV once every three weeks plus capecitabine compared to therapy with capecitabine alone [56].
- A single arm trial of ixabepilone monotherapy in 126 patients with metastatic or locally advanced breast cancer previously treated with an anthracycline, a taxane and capecitabine, and who had disease progression or, in the case of the anthracycline, received a minimum required cumulative dose [57].

In the randomized, multinational, open-label trial that evaluated the efficacy and safety of ixabepilone plus capecitabine compared to therapy with capecitabine alone, patients had to have previously received an anthracycline and a taxane, had evidence of disease progression or resistance, or, in the case of the anthracycline, received a minimum required cumulative dose. Treatment arms were balanced with regards to prior therapies, disease sites, hormone receptor status and HER2 expression. Patients receiving combination therapy had a statistically significant improvement in progression-free survival (PFS), defined as radiologic progression or death from any cause (hazard ratio 0.69,  $p < 0.0001$ ). The median PFS was 5.7 months in the combination arm and 4.1 months in the capecitabine alone arm. Patients in the combination arm also had an increased objective tumor response rate. Survival data for this trial are to be reported in late 2008. In this trial treatment with ixabepilone caused new or worsening peripheral neuropathy in ~65% of patients treated. Grade 3/4 peripheral neuropathy occurred in 23% of patients treated with ixabepilone and capecitabine. Grade 3/4 peripheral neuropathy was not reported in the capecitabine alone arm. By comparison, in the ixabepilone monotherapy trial, 14% of patients experienced grade 3/4 peripheral neuropathy. With cessation of therapy neuropathy was reversible to grade 1 or better in the majority of patients. Ixabepilone in combination with capecitabine resulted in a 68% incidence of grade 3/4 neutropenia compared to 11% with the capecitabine alone regimen. That ixabepilone was the principal offending agent was supported by a 54% incidence of grade 3/4 neutropenia when ixabepilone was used as monotherapy. Twelve patients receiving ixabepilone with capecitabine died from complications arising from neutropenia. The incidence of neutropenia-associated deaths was higher in patients with moderate or severe hepatic impairment baseline when treated with both ixabepilone and capecitabine. These observations led the FDA to recommend that the combination of capecitabine plus ixabepilone should not be used in patients with moderate or severe hepatic impairment. Other commonly observed toxicities (> 20%) included anemia, leukopenia, thrombocytopenia, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis.

In the single arm trial of ixabepilone monotherapy patients with measurable disease who had tumor progression while receiving prior anthracycline, taxane, and capecitabine were enrolled. Ixabepilone 40 mg/m<sup>2</sup> monotherapy was administered as a 3-hour intravenous infusion on day 1 of a 21-day cycle. The primary end point was objective response rate (ORR), assessed by an independent radiology facility (IRF). A total of 126 patients were treated and 113 were assessable for response. Patients were heavily pretreated with 88% having received at least two lines of prior chemotherapy in

the metastatic setting. IRF-assessed ORR was 11.5% (95% CI, 6.3% to 18.9%) for response-assessable patients. Investigator-assessed ORR for all treated patients was 18.3% (95% CI, 11.9% to 26.1%). Fifty percent of patients achieved stable disease (SD); 14.3% achieved SD  $\geq$  6 months. Median duration of response and progression-free survival were 5.7 and 3.1 months, respectively. Median overall survival was 8.6 months. Patients received a median of 4.0 treatment cycles (range, one to 16 cycles), and 25% of patients received  $\geq$  eight cycles. Grade 3/4 treatment-related events included peripheral sensory neuropathy (14%), fatigue/asthenia (13%), myalgia (8%), and stomatitis/mucositis (6%). Resolution of grade 3/4 peripheral sensory neuropathy occurred after a median period of 5.4 weeks. The authors concluded that ixabepilone demonstrated clear activity and a manageable safety profile in patients with MBC resistant to anthracycline, taxane, and capecitabine. Responses were durable and notable in patients who had not previously responded to multiple prior therapies.

Ixabepilone has also been evaluated in the neoadjuvant setting [58]. That study was designed to determine the pathological response obtained with ixabepilone as neoadjuvant therapy for breast cancer and to obtain tumor samples for analysis of gene expression and identification of potential predictors of response to ixabepilone. Based on the genomic study, patients with hormone receptor–negative disease were more likely to respond to ixabepilone [58].

Finally, based on the presence of Cremophor® EL in the formulation of ixabepilone, the potential for hypersensitivity reactions exists with intravenous administration of this compound. Although the quantity of Cremophor® EL in ixabepilone is equivalent to three times that in the same dose of Taxol®, its greater potency has resulted in a Cremophor® EL to total volume that is less than that achieved when Taxol®, which includes Cremophor® EL in its formulation, has been administered (15). In clinical trials, anaphylaxis and severe hypersensitivity reactions (dyspnea, hypotension requiring treatment, angioedema, and generalized urticaria) have occurred in 2% of patients receiving Taxol®. It is not known whether the hypersensitivity reaction is due to paclitaxel, Cremophor® EL, or both. The reported incidence of anaphylaxis with other Cremophor® EL-containing compounds is much lower than with Taxol® (16). For example, cyclosporine for injection has rarely been associated with anaphylactic reactions (approximately 1 in 1,000). Although the low incidence of anaphylactic reactions with Cremophor® EL containing compounds other than Taxol®, suggest this may not be a significant problem, some cases of hypersensitivity have been reported with ixabepilone but the incidence of this has been very low and very rare in the NCI experience with a daily administration on 5 consecutive days. Prophylaxis for hypersensitivity reactions has been similar to the “standard” Taxol® pre-medication regimen but has not included steroids; instead consisting of the following: (1) diphenhydramine 50 mg IV, 30 to 60 minutes before the administration of ixabepilone; and (2) cimetidine 300 mg or ranitidine 50 mg IV, 30 to 60 minutes before the administration of ixabepilone.

#### 1.2.5 Translational Studies

Every attempt will be made to recruit patients with disease that can be sampled by biopsy. In these patients, every attempt will be made to obtain tissue before the start of treatment and after the completion of the fourth or fifth dose of ixabepilone. Both

biopsies will be processed in one of three ways: (1) for immunohistochemical staining; (2) for RNA; and (3) for protein isolation, if a sufficient quantity is available. We would note here that we have extensive experience examining the effect of microtubule targeting agents on tumors both in renal cell carcinoma and in breast cancer using both immunoblot analysis and immunohistochemistry [59]. In renal cell carcinomas, we pursued a strategy validated in our laboratories that exploited the fact that alpha-tubulin can undergo several posttranslational modifications after assembly into stabilized microtubules, including acetylation and detyrosination. We had previously observed these modifications in cell culture after exposure to agents that stabilize microtubules. Our objective was to develop a straightforward and dependable assay to show tubulin target engagement in tumor tissue after treatment of patients with ixabepilone. To that end we assessed the levels of post-translationally modified alpha-tubulin in lysates of cultured malignant cell lines, as well as in both tumor tissue and peripheral blood mononuclear cells derived from patients before and after treatment with ixabepilone. Modification-specific antibodies permitted quantitative Western blot analysis. In cultured cell lines, the levels of detyrosinated (glu-terminated) and acetylated alpha-tubulin increased after microtubule stabilization induced by ixabepilone. ixabepilone treatment also induced a 2-fold to 25-fold increase in detyrosinated alpha-tubulin levels in 11 of 13 serial biopsies and a 2-fold to 100-fold increase in acetylated alpha-tubulin in 11 of 12 serial biopsies obtained from patients receiving ixabepilone. Overall, little or no difference in tubulin modifications were observed between the before and after ixabepilone treatment in lysates from their peripheral blood mononuclear cells at the time point examined. We concluded based on this experience that assessing the levels of detyrosinated and/or acetylated alpha-tubulin provides a simple and reliable assay to show target engagement by the microtubule-stabilizing agent, ixabepilone. Furthermore, this type of analyses can provide further understanding of therapeutic success or failure of microtubule-stabilizing agents in cancer therapy, since one can discern whether failure to benefit a patient by shrinking their tumor is a consequence of failure of the drug to engage its target or a consequence of a distal block to cell death – the possibility we wish to further elucidate in the current study. In breast cancer biopsies were collected at baseline and during cycle 2 from five patients (one patient had a partial response, two patients had stable disease, and two patients had progressive disease) and were confirmed by pathology to contain tumor. Four of these paired patient biopsies were analyzed by Western blot. For one patient, the baseline sample was not adequate. Increased acetylation of alpha-tubulin was seen by Western blot for all four patients, as was increased detyrosination (glu terminated alpha-tubulin). Because the protein lysates run on Western blot contain both tumor and stromal components of the biopsy, we next chose to quantify tumor changes alone by immunohistochemistry. Four of the five paired patient biopsies had tissue available for sectioning for immunohistochemistry. For one patient who had a partial response to ixabepilone, levels of acetylated alpha-tubulin were detected in both tumor and stromal cells in the baseline sample and increased in both cellular compartments with treatment. In contrast, in a patient who had progressive disease, levels of acetylated alpha-tubulin were detected only in stromal cells at baseline and increased in the stroma but were still absent in the tumor cells with treatment. Baseline levels of acetylated alpha-tubulin were present before treatment and increased after treatment in the patients with response and stable



disease, and levels of glu-terminated alpha-tubulin increased in all patients with treatment. Thus from the available paired tumor biopsies, we observed increased levels of both glu-terminated and acetylated alpha-tubulin after treatment, indicating that ixabepilone stabilized microtubules in the target tissue. Measures of stabilized microtubules may not only demonstrate a drug effect, but may also help to predict response when examined in a pretreatment specimen. Interestingly, we found that acetylated alpha-tubulin levels were higher at baseline in the tumor cells of patients whose tumors responded or in patients with stable disease than in the patient whose tumor did not respond. In the patient with progressive disease, baseline levels of acetylated alpha-tubulin within the tumor were not detectable by immunohistochemistry. Thus, our results suggest that a tumor with inherent microtubule stability might be more likely to respond to a stabilizing agent with additional microtubule stabilization and decreased proliferation. Although the small numbers of patients biopsied in this group limits our ability to make more definitive statements, these interesting observations are hypothesis generating and should be considered for additional study. This again is an observation we seek to pursue in this trial.

The following translational studies will be performed:

- 1) Immunohistochemical staining will be performed using antibodies that as described above can assess the extent of tubulin stabilization (antibodies that detect acetylated alpha-tubulin and detyrosinated (glu-terminated) alpha-tubulin. Specifically we will be looking to see if in the malignant cells, tubulin polymerization occurs following treatment with ixabepilone as evidenced by enhanced staining with the acetylated alpha-tubulin and detyrosinated (glu-terminated) alpha-tubulin antibodies. If there are normal cells in the biopsy (a likely possibility) we will be able to compare the observations in malignant cells with that in normal cells. This will allow us to determine if ixabepilone has reached its target and resulted in tubulin polymerization, by comparing the results in the post-treatment sample with those in the pre-treatment sample. This information will be valuable in analyzing the reasons for treatment failure by discriminating between an absence of an effect on the target (tubulin) versus a lack of subsequent events that leads to cell death. Because both the pre-treatment and post-treatment samples will be in blocks we will be able to easily perform additional studies, including additional immunohistochemical stains. One such stain will utilize an antibody that detects the 85kDa fragment generated when PARP cleavage occurs. We are aware of the use of this antibody in other settings, and in one center, it has been used to examine some tumor samples obtained after the administration of ixabepilone. In one patient with breast adenocarcinoma metastatic to the skin, investigators were able to demonstrate immunostaining with the antibody against 85kDa fragment 24 hours after the administration of ixabepilone. Immunostaining for p53 will also be performed [42].
- 2) RNA, and will be extracted and this will be banked. Its fate will depend on the response rates observed in this trial. If ixabepilone is found to be active in over 20% of patients, then all samples obtained will be analyzed by cDNA microarray to determine if differences exist which can discriminate responding from non-responding tumors. However, if no significant activity is observed with ixabepilone in cervical cancer, it is unlikely that cDNA microarray, which entails a

substantial amount of work, will be carried out. Also, if ixabepilone is found to be active in over 20% of patients, the expression of beta-tubulin isotypes will be determined to discern in a preliminary analysis if there is any correlation between b-tubulin isotype expression pattern and response to therapy. In NSCLC a correlation between the expression of  $\beta$ -tubulin isotypes and response to therapy has been demonstrated with reduced response to therapy found in patients with higher level of class III beta-tubulin [61, 62].

- 3) If the sample is sufficiently large, we will isolate protein and determine the extent to which tubulin polymerization has occurred using the antibodies used in the immunohistochemical analyses described above. This would be performed in a manner similar to that described for the peripheral mononuclear cells.

#### 1.2.6 Rationale for current trial

The conduct of this trial is supported by the knowledge that tubulin is an excellent target for chemotherapeutic agents, combined with the clinical success of the taxanes, and the putative advantages of the epothilones. The possibility that an agent with activity as broad as that observed with the taxanes might be active in cervical carcinoma is an exciting possibility. The recent approval of ixabepilone for the treatment of breast cancer confirms the activity of this microtubule-stabilizing agent, and its superiority over the taxanes. In addition the trial seeks to use the tissue obtained from the patients enrolled on study who undergo biopsies to further our understanding of the mechanisms of drug sensitivity clinically. As detailed, assessment of microtubule stabilization and the activation of cell death pathways will be queried to assist in understanding drug sensitivity clinically.

The treatment of metastatic and recurrent cervical carcinoma and cervical adenocarcinoma remains a difficult and challenging problem. We have treated two patients with adenocarcinoma of the cervix (described below) in which an objective tumor response was observed following treatment with ixabepilone. These patients were part of our phase I study of patients with solid tumors who had progressed after standard chemotherapy. Despite the devastating clinical outcome of the first case, in both cases presented, we were impressed with the remarkable reduction in tumor volume seen after extensive prior chemotherapy. We feel that ixabepilone will replace the taxanes in the therapy of breast cancer, and if activity is demonstrated in cervical cancer, and this activity, as that observed in breast cancer is superior to that of the taxanes, then this agent could be beneficial to women suffering from this disease, that when it presents with metastases is incurable.

The infrequent occurrence of cervical adenocarcinoma has made it difficult to evaluate the efficacy of chemotherapy in a rigorous manner. Although it is difficult to draw firm conclusions, the available data suggests that combination therapy may be better, and that as a single agent, paclitaxel may be the most beneficial chemotherapeutic agent. Given existing data demonstrating paclitaxel's efficacy in adenocarcinoma of the cervix, it is not surprising that the epothilones would be shown to have activity. However, both patients whom we treated and in whom we observed a response to therapy had received prior paclitaxel, without a response, and the demonstration of a response to ixabepilone, especially after additional chemotherapy had been administered, is

encouraging, albeit preliminary. The ultimate role of ixabepilone and multiagent chemotherapy in the treatment of adenocarcinoma of the cervix remains to be determined.

While these patients had cervical adenocarcinoma, the trial will recruit all patients with a diagnosis of cervical cancer, and will stratify patients into squamous carcinoma or non-squamous carcinoma. The latter will include patients with adenocarcinoma as well as patients with adenosquamous histology.

Furthermore while we have extensive experience examining tubulin polymerization in patients with kidney cancer, we will seek to extend those observations in these patients, while also trying to probe further the effect of ixabepilone. To that end we will also examine whether there is evidence of activation of pathways of cell death, initially by examining the activation of PARP.

### **CASE REPORTS**

MF was a 54 year old Hispanic female who was diagnosed in 1/99 with stage 4 adenocarcinoma of the cervix with metastases to the small bowel, omentum, both fallopian tubes, ovaries, paracolic fat and surface of the small intestine. She underwent a modified radical hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Postoperatively she received six cycles of carboplatin and paclitaxel (2/99 -7/99). In 12/99 a needle biopsy of a vaginal mass was positive for adenocarcinoma, and she was subsequently treated with five doses of weekly gemcitabine (3/00), three cycles of doxil (5/00), seven doses of weekly vinorelbine (7/00), five cycles of topotecan (ending 12/00), and one cycle of carboplatin (1/01). Because of a rising CA-125 she was referred to the NCI for a clinical trial on 3/21/01. Her initial evaluation revealed a left lower quadrant abdominal mass most prominent at the level of the umbilicus, 1.0 cm right axillary and 1.5 cm left inguinal nodes, and multinodular extension of tumor from the vaginal apex and anterior wall of the vagina to within 5 cm of the introitus. The CT scan showed scattered nodules in both lungs (largest 1 cm in diameter), a mediastinal mass (1.8 cm x 1.0 cm), an ill-defined mass in the pelvis (approximately 3.4 cm x 3.0 cm), a soft tissue mass anterior to the left psoas muscle (4 cm x 2.9 cm), and bilateral axillary adenopathy. Her CA-125 was 5,391. She started treatment with ixabepilone at a dose of 6 mg/m<sup>2</sup>/d X 5d every three weeks on 3/22/01. She tolerated the first cycle well but during cycle 2, she was admitted for dizziness and fever and found to have oral thrush, mucocutaneous herpes simplex, and neutropenia. Other side effects of chemotherapy included grade 2 fatigue, grade 1 nausea, nail changes, alopecia, and grade 1 neuropathy. Repeat CT scan after the second cycle of ixabepilone demonstrated a marked improvement, with a reduction in the size of the mediastinal adenopathy (1.6 cm x 0.4 cm), and the pelvic mass (2.1 cm x 2.0 cm) complete disappearance of the soft tissue mass anterior to the psoas, and nearly complete disappearance of axillary adenopathy. Pelvic examination revealed dramatic resolution of the previously noted tumor. Her CA-125 had fallen to 21. Her next two cycles were uneventful, and a CT scan performed prior to the start of the fifth cycle demonstrated continued shrinkage or disappearance of tumor at sites of previous disease. Mediastinal adenopathy had been replaced by a thin tissue remnant measuring 1.4 cm x 0.3 cm, while the mass in the pelvis measured at most 1.4 cm x 0.7 cm. On 7/29/01 midway through her fifth cycle she was admitted to the hospital with complaints of constipation,

abdominal pain and light-headedness. Because of persistent hypotension unresponsive to intravenous hydration she was transferred to the intensive care unit but her condition continued to deteriorate and she expired during intubation. Postmortem examination of the chest and abdomen revealed no gross evidence of disease. There was cardiac tamponade with microscopic evidence of adenocarcinoma in the intrapericardial fibrin clot. Pericardial involvement with tumor had not been appreciated prior to the autopsy and was felt to be etiologic in the patient's demise. It was felt that this was not a drug-related toxicity. The only other microscopic tumor found was in intraparenchymal lymph nodes in the lung and a single small cluster of adenocarcinoma in the left upper lobe of the lung. No tumor was found in the pelvis.

LY a 43 -year old white female underwent a radical hysterectomy for a grade 2 deeply infiltrative mucin secreting adenocarcinoma of the cervix on 4/22/96. Ten left and seven right pelvic nodes were negative for metastatic disease. Postoperatively, she received 5.4 gy of total pelvic irradiation. Follow-up examination in 8/96 revealed residual disease and on 11/96 she underwent a total pelvic exenteration with an ileal conduit, transverse colostomy, an omental pelvic graft, and a gracilis myocutaneous flap for neovaginal reconstruction. The final pathology reported only residual adenocarcinoma-in-situ at the vaginal apex. The patient was in remission until 5/99 when a single right lung nodule was detected on chest x-ray. A CT scan several months later showed bilateral multiple pulmonary nodules. Biopsy of one of the lung nodules revealed recurrent moderately differentiated adenocarcinoma. The patient was then treated with three cycles of cisplatin and paclitaxel between 1/00 and 3/00. Follow-up CT scans revealed stable disease and chemotherapy was discontinued because of two hospitalizations for pyelonephritis. Tamoxifen was started on 3/00 and discontinued on 9/00 because of progressive disease. She was then treated with thalidomide from 9/00 to 1/01, and this was discontinued because of progressive disease. The patient was first evaluated at the NCI on 2/2/01 at which time a CT scan revealed multiple pulmonary nodules and a pelvic mass. She was treated with two cycles of vinorelbine in combination with the P-glycoprotein antagonist tariquidar (XR-9576). She was taken off study in 04/01 because of progressive disease. On 8/9/01 she began a phase I trial of ixabepilone at a dose of 8 mg/m<sup>2</sup>/d X 5d every 21 days. After the first cycle, she reported a decrease in pelvic pressure. The dose was escalated to 10 mg/m<sup>2</sup>/d X 5d, and she subsequently developed fatigue, thrush, a urinary tract infection, and neutropenia requiring hospitalization. Repeat CT scans obtained after completion of the first two cycles of ixabepilone demonstrated a decrease in the size of her tumor. Two pelvic masses shrank from 3.6 X 1.7 cm and 3.3 X 3.1 cm to 2.5 X 1.1 cm and 2.5 X 2.1 cm). The size of the largest lung nodule was reduced from 2.9 X 1.7 cm to 2.0 X 0.6 cm with marked resolution of an area of lung consolidation. In addition, her CA-125 fell from a pre-treatment value of 50 to 24 by 10/24/01. The third and fourth cycles were given at a dose of 8 mg/m<sup>2</sup>/d X 5 and were well tolerated. A restaging CT scan after cycle four revealed a further reduction in the size of all lesions, with nearly complete disappearance of her pelvic masses. This was the first chemotherapeutic agent to which the patient's tumor had demonstrated an objective response. Non-hematologic toxicities included grade 2 fatigue, stomatitis, vomiting, and neuro-sensory changes, with grade 1 diarrhea. She received two additional cycles of ixabepilone and upon restaging was noted to have had a small increase in the size of the largest pulmonary

metastasis and was removed from the study. No further therapy was planned and the patient was referred home. She subsequently developed pneumonia, but despite aggressive pulmonary care died of respiratory failure on 2/10/02.

## 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

### 2.1 ELIGIBILITY CRITERIA

#### 2.1.1 Inclusion criteria:

Patients must fulfill all of the following criteria to be eligible for study admission:

1. Age  $\geq$  18 years.
2. Histologic or cytologic confirmation of cervical carcinoma, squamous or non-squamous. Within the non-squamous cohort is adenocarcinoma and adenosquamous as well as non-squamous (not otherwise specified).
3. Subjects with unresectable recurrent cervical cancer are eligible.
4. Measurable disease that can be assessed using RECIST criteria.
5. Performance Status ECOG 0-2.
6. Life expectancy of 3 months or greater.
7. Suitable candidate for receiving planned therapy as evidenced by screening laboratory assessments of hematologic, renal, hepatic, and metabolic functions: platelet count  $\geq$  75,000/mm<sup>3</sup>, absolute granulocyte count (AGC)  $\geq$  1,000/mm<sup>3</sup>, serum creatinine  $\leq$  1.6 or a measured creatinine clearance  $\geq$  40 ml/min, SGPT and SGOT  $\leq$  2.5 x NL, and total bilirubin  $\leq$  1.5 x NL (in patients with clinical evidence of Gilbert's disease,  $\leq$  3 x NL).
8. Note: A diagnosis of Gilbert's disease will be made in the presence of (1) unconjugated hyperbilirubinemia noted on several occasions; (2) normal results from CBC count, reticulocyte count, and blood smear; (3) normal liver function test results; and (4) an absence of other disease processes that can explain the unconjugated hyperbilirubinemia.
9.  $\geq$  4 weeks from prior radiation, intravenous chemotherapy or immunotherapy;  $\geq$  6 weeks from prior nitrosourea;  $\geq$  2 weeks from a prior "phase 0 study".
10. No serious intercurrent medical illness.
11. The ability to understand and willingness to sign a written informed consent form, and to comply with the protocol.
12. Prior therapy with cisplatin or carboplatin is required.

#### 2.1.2 Exclusion criteria:

Patients with any of the following will be excluded from study entry:

1. Pregnant or nursing women are not eligible; neither are women of childbearing potential unless using effective contraception as determined by the patient's physician.
2. Patients with a history of CNS metastases, because symptoms/signs of progressive disease may be confused with drug-related toxicities, unless control has been achieved with either radiation or surgical resection at least three months prior to enrollment on study.
3. Patients who are poor medical risk because of other non malignant systemic disease or active, uncontrolled infection.

4. HIV positive patients will be considered for eligibility; as long as they are not receiving antiretroviral drugs with strong CYP3A4 inhibitory activity (see 3.6 and Appendix C).
5. Prior craniospinal radiation, or total body irradiation (TBI).
6. Patients receiving other investigational drugs, or strong CYP3A3 inhibitors (see Section 3.6 for details) that cannot be discontinued or substituted.
7. CTCAE Grade 2 or greater motor or sensory neuropathy.
8. Known prior severe hypersensitivity reactions to agents containing Cremophor® EL.
9. Women with localized disease who are potentially curable through surgical resection.

## 2.2 RESEARCH ELIGIBILITY EVALUATION

1. Pathological confirmation of diagnosis by the Laboratory of Pathology, CCR, NCI.

### Within 4 weeks of study entry:

2. Imaging studies: PA and lateral chest X-ray; CT or MRI scans as medically indicated.
3. Metastatic bone series, bone scan, or nuclear scans as medically indicated.
4. HIV screen.
5. Urinalysis.

### Within 7 days of study entry\*:

6. Complete history and physical examination with documentation of measurable disease and performance status.
7. Laboratory tests: CBC with differential and platelet count, and CHEM 20 Panel.
8. Urine or serum pregnancy test in women of childbearing potential.

\*Any abnormal laboratory tests of clinical significance (CHEM 20 Panel) should be repeated within 48 hours of study initiation. The principal investigator should be contacted to determine if the test(s) need to be repeated.

## 2.3 PATIENT REGISTRATION AND TREATMENT RANDOMIZATION

1. On-study: Ms Maureen Edgerly, RN (301-435-5604, pager 102-10728) or her designee must be notified before entering any patients on study. Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (<http://intranet.cancer.gov/ccr/welcome.htm>) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. A recorder is available during non-working hours. *Please note, it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information.*
2. Off-study: Authorized staff must notify Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the web site (<http://intranet.cancer.gov/ccr/welcome.htm>) main page must be completed and faxed to 301-480-0757.

3. This trial does not involve randomization. Patients will be stratified according to histology: (1) squamous cell cohort and (2) non-squamous cell cohort consisting of adenocarcinoma, adenosquamous and non-squamous (not otherwise specified).

### 3 STUDY IMPLEMENTATION

#### 3.1 STUDY DESIGN

This is a phase II trial designed to determine the activity of ixabepilone administered daily x 5, every three weeks, in women with cervical carcinoma. The dose will be 6 mg/m<sup>2</sup>/day, daily x 5, for a total dose per cycle dose of 30 mg/m<sup>2</sup>. There will be no dose escalations. If indicated the dose may be reduced to 4.5 mg/m<sup>2</sup>/day level. Every attempt to administer cycles at intervals of 3 weeks will be made. Following cycle 6, at the discretion of the PI, cycles may be extended to 4 or 5 weeks in duration to accommodate neurosensory changes and or fatigue. This will be determined on a case-by-case basis.

Research biopsies will be done prior to Day 1 and post Day 4 or 5 dosing to assess tubulin polymerization and the extent of PARP activation. On Day 4 or 5, the patient will receive ixabepilone in the morning hours and have the biopsy within 4 hours of completing the infusion.

The primary and secondary endpoints for the study are tumor response per RECIST and the degree of tubulin polymerization as it relates to cellular death pathways. Patients will be evaluated for tumor response after every 2 cycles. Biopsies will be obtained during cycle one only, before and after chemotherapy to obtain tubulin polymerization data and to examine other molecular markers.

#### 3.2 DRUG ADMINISTRATION

##### 3.2.1 General guidelines

Chemotherapy may be administered as an inpatient or as an outpatient. Inpatient administration may be chosen if this is in the patient's best interest. Administration may be through either a peripheral IV site or a central venous access catheter. Both options are acceptable. Care should be taken to avoid extravasation, since this drug is likely to be a vesicant. If a catheter is used a single lumen central venous access catheter is sufficient and should be in place before initiating therapy. Placement may be arranged before the start of therapy, or a catheter may be placed immediately before a cycle.

##### 3.2.2 Ixabepilone administration and dosage

Ixabepilone will be given on days 1, 2, 3, 4, and 5 of each three week cycle as a one hour intravenous infusion. The dose will be 6 mg/m<sup>2</sup>/day on five successive days. For ixabepilone preparation instructions, see Section 8, Pharmaceutical Information.

##### 3.2.3 Potential for hypersensitivity reactions related to Cremophor®EL

**Premedication:** All patients must be pre-medicated before each administration of ixabepilone to prevent a hypersensitivity reaction.

- **Regimen 1** described below is the pre-medication regimen recommended for routine use.

- If a patient experiences a hypersensitivity reaction with oral H<sub>1</sub> and H<sub>2</sub> blockers (Regimen 1) then the patient, if re-treated, should be pre-medicated according to **Regimen 2** below. See the section **3.2.4** below for immediate management of reactions.
- If a subject continues to experience a HSR with Regimen 2 then the subject, if retreated, the patient should be pre-medicated according to the recommended **Regimen 3**.
- **Regimen 4** is suggested as the approach for re-treatment with ixabepilone after a Grade 2 or greater HSR despite premedication with Regimen 1, 2 or 3.

**Regimen 1:** Premedicate approximately one hour prior to the infusion of ixabepilone with:

- a) Oral H<sub>1</sub> antagonist (may consist of diphenhydramine 50 mg or equivalent H1 antagonist) and
- b) Oral H<sub>2</sub> antagonist (may consist of ranitidine 150 - 300 mg or cimetidine 300 - 800 mg or nizatidine 150 - 300 mg or famotidine 20 - 40 mg or another H2 antagonist)

Note: In the event a given patient does not tolerate the specified antihistamines, alternatives may be substituted at the Investigator's discretion. In addition, if the specified antihistamine is not available, alternatives may be substituted including IV formulations

**Regimen 2:** Premedicate approximately 30 - 45 minutes prior to each infusion of ixabepilone with:

- a) Dexamethasone 20 mg IV (or equivalent)
- b) Diphenhydramine 50 mg IV (or equivalent), and
- c) Ranitidine 50 mg IV (or equivalent).

**Regimen 3:** Premedicate with:

- a) Dexamethasone 20 mg po administered, approximately 12 and 6 hours prior to the infusion of ixabepilone,
- b) Diphenhydramine 50 mg IV, approximately 30 - 45 minutes prior to each infusion of ixabepilone,
- c) Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent), approximately 30 - 45 minutes prior to each infusion of ixabepilone.

**Regimen 4:** A suggested approach for re-treatment with ixabepilone after a Grade 2 or greater HSR despite premedication with Regimen 1, 2 or 3 is as follows:

- a) Dexamethasone 20 mg IV or p.o. (or equivalent) every 6 hours for 4 doses with the last dose administered 30 minutes before rechallenge with ixabepilone; With the last dexamethasone dose begin:
  - Diphenhydramine 50 mg IV (or equivalent) 30 minutes before ixabepilone,
  - Cimetidine 300 mg or ranitidine 50 mg IV (or equivalent) 30 minutes before ixabepilone.
- b) Begin ixabepilone at 25% of the previous rate for 1 hour;
- c) Increase rate gradually to complete the total infusion within 6 hours from the time the drug was initially diluted.

### 3.2.4 Immediate management of Allergic/Hypersensitivity Reaction



Allergic/Hypersensitivity Reaction (transient rash, drug fever < 38°C): Supervise without further treatment. If progression of symptom(s) is(are) noted, follow the guidelines described below.

Allergic/Hypersensitivity Reaction (urticaria, drug fever greater than or equal to 38°C and/or asymptomatic bronchospasm): Interrupt the infusion. Administer additional doses of H1 and/or H2 blockers intravenously as needed. Typically 25 mg diphenhydramine IV is sufficient to relieve symptoms. If symptoms abate, attempt re-infusion at a slower rate, as detailed. Restart the remaining infusion at one quarter the hourly rate x 15 minute, then increase the rate to one half the hourly rate x 15 minutes, then increase the rate to complete the remaining infusion within one hour of the restart time. If the symptoms recur, discontinue infusion and follow guidelines below.

Subsequent Infusions following Allergic/Hypersensitivity Reactions:

When a patient experiences an allergic/hypersensitivity reaction and is able to resume the infusion without recurrence of the reaction, the following day's infusion will be given according to the following rate schedule: First start the infusion at one quarter the hourly rate x 15 minutes, then increase the rate to one half the hourly rate x 15 minutes, then increase the rate to complete the remaining infusion within one hour of the start time. If the patient does not have another reaction, the subsequent infusions may be given at the full hourly rate from the start of the infusion. No additional H1 or H2 blockers are indicated for these doses, beyond the standard premedications administered 30 to 60 minutes before the administration of ixabepilone. Consultation with study team is indicated to determine if steroids are indicated per Regimen 2.

Recurrent CTCAE Grade 2 or CTCAE Grade 3 or 4 Allergic/Hypersensitivity Reactions: Stop the infusion. Administer additional doses of H1 and H2 blockers intravenously. Administer IV steroids (see discussion below) and consider epinephrine and bronchodilators as clinically indicated. Further treatment should be delayed 24 hours. Prior to re-challenge and with all subsequent cycles, give both an H1 and H2 blocker intravenously plus dexamethasone 20 mg x 2 doses (orally or intravenously) 12 and 6 hours pre ixabepilone. Dexamethasone could be used at the investigator's discretion in subsequent cycles for recurrent (i.e. occurring despite slowing infusion as discussed above) grade 2 reactions but is not mandated.

Grade 4 (anaphylaxis): Discontinue therapy. Do not attempt re-challenge.

Note: The administration of dexamethasone immediately prior to ixabepilone is unlikely to be effective.

Note: If dexamethasone is administered, it will initially be administered prior to all doses. However, since dexamethasone has a long half-life, and since daily administration would mean patients would receive 100 mg or more of dexamethasone every three weeks, a dose reduction to 5 mg dexamethasone administered intravenously prior to each dose of ixabepilone may be attempted at the discretion of the Principal Investigator. Please note that the above regimens 1 – 4 are standard for ixabepilone that is given as a one day infusion every 3 weeks, not a daily x 5 schedule. The decision to administer this regimen will be guided by: (1) the severity of the initial reaction that prompted the use of dexamethasone; (2) the patient's reaction to

ixabepilone after the institution of dexamethasone premedication; and (3) the number of additional cycles the patient is anticipated to receive. Regarding the latter, if a patient appears to be responding to the treatment and it is anticipated that he/she will receive several more cycles, then in such a patient attempts to reduce the steroid dose would be beneficial.

Note: Dexamethasone premedication may be used, if in the opinion of the Principal Investigator such precaution should be taken. For example, in a patient with a prior history of sensitivity to paclitaxel or cyclosporin.

### 3.3 TREATMENT MODIFICATIONS

#### 3.3.1 General guidelines for treatment modifications at the time of re-treatment

##### Adverse Events:

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

Dose adjustments will be made according to the guidelines below, with dose levels defined as follows:

Level -1:	4.5 mg/m <sup>2</sup> /day x 5 days
Level 1:	6 mg/m <sup>2</sup> /day x 5 days

There is only one dose reduction allowed. Patients who have continued toxicities on the reduced dose level (4.5 mg/m<sup>2</sup>/day x 5 days) will be removed from study.

#### 3.3.2 Treatment modifications for hematologic toxicities and delay in start of cycle

Doses will be modified if the start of a cycle is delayed more than two weeks (in all cycles after the first cycle, the day 1 dose will be administered only when the ANC is greater than 1000/mm<sup>3</sup> and the platelet count is above than 75,000/mm<sup>3</sup>). There will be no dose modification for a delay of two weeks or less.

Doses will also be modified based upon the nadir from the previous cycle according to the following guidelines.

<u>Toxicity:</u>	<u>Dose Adjustment:</u>
ANC $\leq$ 500/mm <sup>3</sup> for $\geq$ 4 days	Reduce ixabepilone one dose level
Platelet count $\leq$ 50,000/mm <sup>3</sup>	Reduce ixabepilone one dose level
Delay in starting cycle > 2 weeks	Reduce ixabepilone one dose level

#### 3.3.3 Treatment modifications for non-hematologic toxicities

If non-hematologic grade 3 and 4 toxicities occur, treatment will be interrupted until the toxicity:

- Resolves to grade 2 or less if the toxicity is fatigue, anorexia, or fingernail changes, or

- Resolves to grade 1 or less if the non-hematologic toxicity is other than those enumerated in the previous bullet.

If toxicity does not resolve to  $\leq$  grade 2 within two weeks, that patient will be removed from study. Once a toxicity resolves to the required grade as enumerated above, treatment may be restarted and drug dosing modified according to the guidelines below. However, patients who experience grade 4 non-hematologic toxicities will be individually evaluated with regard to continuation of treatment. These patients should not be restarted on therapy once toxicity resolves unless there is some clear indication of patient benefit in the form of objective tumor response. In these cases, the reason(s) for restarting therapy will be clearly indicated in the case report form, and the medical record, and the risks and potential benefits will be discussed with the patient.

Dose modifications for non-hematologic toxicities will be based upon the toxicity from the previous cycle. All toxicities must resolve to grade 2 or less as indicated above prior to the initiation of a subsequent cycle. The following apply:

Maximum toxicity grade:	Ixabepilone dose
1	Unchanged
2	Unchanged
3 <sup>Note 1</sup>	Reduce ixabepilone one dose level
4 <sup>Note 2</sup>	Reduce ixabepilone one dose level

Note 1: If grade 3 fatigue occurs but resolves to grade 2 or less by the start of the next cycle, the dose of ixabepilone will remain unchanged.

Note 2: As noted above, patients who experience grade 4 non-hematologic toxicities will be individually evaluated with regard to continuation of treatment. Exceptions to the need for individual evaluation include patients with a grade 4 toxicity included in the list that follows, in which case adjustments will be made in accordance with the guidelines listed above.

Grade IV hypocalcemia with normal ionized calcium

Grade IV hypokalemia that responds to medical intervention

Grade IV hypomagnesemia that responds to medical intervention

Grade IV hypophosphatemia that responds to medical intervention

Grade IV sepsis with source identified and treatment successfully instituted

Grade IV stomatitis

### 3.4 CORRELATIVE STUDIES

#### 3.4.1 Biopsies for Research Purposes

As indicated in the introduction, every attempt will be made to recruit patients with disease that can be sampled by biopsy. In these patients, every attempt will be made to obtain tissue before the start of treatment and after the completion of the fourth or fifth

dose of ixabepilone. Both biopsies will be processed in one of three ways: (1) for immunohistochemical staining; (2) for RNA; and (3) for protein isolation, if a sufficient quantity is available. The laboratory correlates on the biopsies will attempt to examine tubulin polymerization, and also seek to probe further the effect of ixabepilone. To that end attempts will be made to examine whether there is evidence of activation of pathways of cell death, initially by examining the activation of PARP, a protein whose cleavage generates fragments that can be measured and are recognized as markers of cell death or apoptosis.

Biopsies will be obtained from all patients only if they can be performed under local anesthesia. General anesthesia will not be used to obtain biopsies that are to be used only for research purposes. In order to process the biopsy in the three ways described above a tru-cut type core biopsy needle must be used. Ideally three core biopsies would be obtained and if possible four. These biopsies may be obtained with the assistance of either a surgical consultant or a member of the interventional radiology staff. As an alternative, a needle aspiration may be obtained with the assistance of the cytology staff or a member of the interventional radiology staff. In the case of a needle aspiration, the sample will only be processed for immunohistochemical staining.

Note: It is recognized that a patient may agree to a first biopsy and then decide to not have a second biopsy. In such a case, the biopsy will nevertheless be processed as planned, although the value of the pre-treatment modification of alpha tubulin in predicting response has not been established.

Biopsies performed for research purposes will only be obtained after the procedure has been explained to the patient, and informed consent has been secured.

3.4.2 Pharmacokinetics  
(not applicable)

3.4.3 Pharmacodynamics

To evaluate the pharmacologic activity of ixabepilone in patients, peripheral blood mononuclear cells (PBMCs) will be evaluated to determine the extent to which ixabepilone induces a shift from unpolymerized tubulin to tubulin in a polymerized state. These samples will only be collected on those patients who undergo research biopsies.

Schedule for blood sample collection for tubulin polymerization assay using peripheral blood mononuclear cells (PBMCs): The ability of ixabepilone to induce tubulin polymer formation in peripheral blood mononuclear cells (PBMCs) will be determined for patients during cycle one, following the first intravenous dose of ixabepilone. A blood sample (8 mL) will be collected prior to the drug infusion, to determine each patient's baseline status of unpolymerized tubulin within lysed PBMC pellets versus tubulin that exists in the polymerized state. Following IV administration of ixabepilone, additional blood samples (8 mL each) will be collected at 1, 8 and 24 hours, relative to the start of the 1-hour infusion on Day One.

One additional sample will be drawn within one hour of the biopsy following Day 4 or Day 5 dosing. The purpose of this blood will be to determine if there exists any correlation between the extent of tubulin polymerization in the tumor sample and in the

blood sample. See Appendix A for further information regarding the handling, storage and tracking of these samples.

### 3.5 ON STUDY EVALUATION

#### 3.5.1 Cycle one

Obtained within one week prior to study entry, unless otherwise indicated.

1. History and physical examination.
2. Laboratory studies: CBC with differential, platelet count, and CHEM 20 Panel.
3. Imaging studies: CT or MRI (obtained within four weeks prior to study entry).

#### 3.5.2 Every restaging cycle

(Following the second, fourth and sixth cycles, and then every third cycle)

1. History and physical examination (for medical record only; not for Research record).
2. Laboratory studies: CBC with differential, platelet count, and CHEM 20 Panel.
3. Imaging studies: CT or MRI of known/suspected areas of disease (for medical record only; not for research record).

#### 3.5.3 Every cycle

1. History and physical examination (for medical record only; not for Research record).
2. Laboratory studies: CBC with differential, platelet count, and CHEM 20 Panel.

#### 3.5.4 Weekly treatment monitoring

1. CBC with differential and platelet count will be obtained twice weekly on Monday/Thursday, or Tuesday/Friday during the first two cycles; unless the ANC falls below 500 cells/mm<sup>3</sup> or the platelet count falls below 50,000 cells/mm<sup>3</sup>, in which case every attempt should be made to obtain counts every other day until the ANC is above 500 cells/mm<sup>3</sup> and the platelet count is above 50,000 cells/mm<sup>3</sup>. If the ANC and platelet count do not fall below the above-mentioned parameters in the first two cycles, CBCs may be obtained once weekly thereafter.

### 3.6 CONCURRENT THERAPIES

Potential Drug Interactions: Ixabepilone may have a minimal potential to alter the metabolic clearance of drugs that are highly metabolized by CYP3A4. When ixabepilone was incubated with human liver microsomes along with compounds specific for the inhibition of individual cytochrome P450s, significant inhibition was observed only with the CYP3A4 inhibitors (troleandomycin and ketoconazole) suggesting that ixabepilone may be a substrate for CYP3A4 in humans. Data also indicate that the main route of metabolism of ixabepilone is through CYP3A4.

The following strong CYP3A4 inhibitors are prohibited on this study: ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, and voriconazole). Other CYP3A4 inhibitors can be given with caution.

A more complete list of CYP3A4 inhibitors is found in Appendix C and should be consulted when making decisions regarding concurrent therapies.

In addition, patients should not drink grapefruit juice while on this study.

### 3.7 SURGICAL GUIDELINES

Elective surgical procedures (dental extractions, mediport placement) for patients enrolled on study will be scheduled during the last week of a cycle in order to avoid the nadir periods for leukocytes and platelets. All procedures should be done only when counts are sufficiently recovered to lessen any risk of infection and or bleeding. Radio-frequency ablation (RFA) will be allowed for symptomatic relief of pain.

### 3.8 RADIATION GUIDELINES

No concurrent radiation therapy will be allowed on study.

### 3.9 OFF TREATMENT CRITERIA

1. Progression of disease during treatment on study protocol. Decisions will be made at the time of restaging (restaging planned after the second, fourth and sixth cycles and then every third cycle). However, if clinically indicated, a decision may be made following the first cycle, after obtaining the appropriate staging studies.
2. Grade 3/4 toxicity lasting greater than 2 weeks or when therapy is judged detrimental to the patient's health.
3. Grade 4 hypersensitivity reaction to drug administration (anaphylaxis).
4. Patient non-compliance or voluntary withdrawal.
5. Discretion of the Principal Investigator.
6. Unacceptable toxicities that have not resolved at time of "off treatment" or "off study" must be followed until stabilization or resolution.

The reason for treatment removal and the date the patient was removed will be documented in the Case Report Form.

#### 3.9.1 Post-Treatment Evaluation (Upon Meeting Off Treatment Criteria)

1. History and physical examination (for medical record only)
2. Laboratory studies: CBC with differential and platelet count, and CHEM 20 Panel.
3. Chest X-ray.
4. Appropriate diagnostic imaging.
5. ECOG performance status assessment

### 3.10 OFF-STUDY CRITERIA

This study does not involve a preset period of monitoring or follow-up after a patient has reached off treatment status. In most cases the Off-treatment and Off-Study dates will be the same. If a patient has a treatment related toxicity, and in the opinion of the PI it is prudent and medically necessary to monitor the patient further, an individual patient may remain on-study, but off-treatment until such time the PI determines it safe to remove them from study.

### 3.10.1 Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the web site

<http://intranet.cancer.gov/ccr/welcome.htm> must be completed and faxed to 301-480-0757.

### 3.11 Follow-Up for Progression Free Survival and Duration of Response

An objective of this study is to determine progression free survival and duration of response in patients who achieve either a Complete Response (CR) or a Partial Response (PR). Patients who achieve either a CR or PR and stop receiving study drug will be monitored periodically to follow the course of their response. This follow-up period will vary per patient, but in general will consist of a CT scan every 6 weeks, extending to every 3 to 4 months, per PI discretion. This follow-up may be done here at the NIH Clinical Center, or via the patient's local physician, with scans sent in for inclusion in our trial results. Physical exams, including pelvic exams, will also be done at the same time points.

## 4 SUPPORTIVE CARE

1. Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics. Growth factors may be used in accordance with the ASCO guidelines. Growth factors should not be used to raise neutrophil counts in order to begin chemotherapy on time. Such cases will be evaluated individually to determine the toxicity grade.
2. Symptomatic anemia should be treated with appropriate red blood cell support and transfusion is recommended if the hemoglobin falls below 8 g/dl. Alternately recombinant erythropoietin may be used if desired by the patient's local physician.
3. Thrombocytopenia should be treated conservatively. In the absence of bleeding or a planned invasive procedure, platelet transfusions should only be given for a platelet count below 10,000. If invasive procedures are planned or the patient develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count  $\geq 50,000/\text{mm}^3$ .
4. Central venous access devices such as a temporary internal jugular line, PICC lines via the brachial vein, semi-permanent HICKMAN®, GROSHONG®, or medi-port implanted devices are acceptable for this study. All devices will have nursing supervision to include patient self care and cleaning/flushing of the devices.
5. Nutritional assessment and psychological support: Refractory neoplasms are commonly complicated by malnutrition. Patients with weight loss or evidence of wasting syndrome should have a nutritional consult. Patients who are having emotional difficulties dealing with their treatment, and disease, or those patients who request assistance, will be referred to a Social Worker for evaluation and support.
6. Care of the fingernails during ixabepilone trial participation is encouraged. A patient information form is included in APPENDIX D.

## 5 DATA COLLECTION and EVALUATION

### 5.1 DATA COLLECTION AND RECORD KEEPING

Data will be prospectively collected and entered into the database at least once every two weeks. The NCI C3D database will be used for this report. The responsible investigator is Dr. Tito Fojo. All radiographic images will be stored in the Department of Radiology, Clinical Center, NIH. All radiographic images will be reviewed by a staff radiologist for validity and reliability. The original signed consent goes to Medical Records; copy placed in research record

All patients must have signed an informed consent and an on study confirmation of confirmation of eligibility form must be filled out before enrollment.

Complete records must be maintained on each patient. These will consist of the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will serve as the primary source material that forms the basis for the research record. All relevant data will also be entered into the NCI C3D database from which formal analyses are done. The primary source documentation will assure the following: on study information, including patient eligibility data and patient history; and off-study summary sheets, including a final assessment by the treating physician.

Data will be submitted to the CTEP/CDUS every three months via the NCI C3D database.

### 5.2 RESPONSE CRITERIA (RECIST)

#### Eligibility:

Only patients with measurable disease at baseline can have objective tumor response evaluated as an endpoint.

Measurable disease: The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology, if possible.

Measurable lesions: Lesions that can be accurately measured in at least one dimension with longest diameter  $\geq 20$  mm using conventional techniques or  $\geq 10$  mm with spiral CT scan.

Non-measurable lesions: All other lesions, including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm with spiral CT scan), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.



- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement:

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. However, US is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Baseline documentation of "Target" and "Non-Target" lesions:

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria:

Evaluation of target lesions:

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded

since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of non-target lesions:

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/  
Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair)].

Evaluation of best overall response:

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesion	Non-Target Lesion	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete Response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation:

- The main goal of confirmation of objective response is to avoid overestimating responses. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome that the response(s) is(are) not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval, not less than 6 weeks.

Duration of overall response:

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease:

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Response review:

- Responses will be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images will be conducted.

Reporting of results:

- All patients initially considered evaluable will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria and are evaluable, will be included in the main analysis of responses. Patients in response categories 4-8 will be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of a response.
- All conclusions will be based on all eligible patients.
- Sub-analyses may be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for

drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported.

### 5.3 Toxicity Criteria: Adverse Event Reporting Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

### 5.4 STATISTICAL SECTION

#### STUDY OBJECTIVES:

Primary: To establish the activity of ixabepilone administered daily as a one-hour infusion on five successive days (daily x 5), every three weeks in patients with cervical carcinoma previously treated with chemotherapy, as determined by overall response (PR+CR). Activity will be measured using standard RECIST guidelines.

Secondary: Assess pharmacodynamic endpoints after ixabepilone administration to determine the extent of tubulin polymerization and whether or not there has been activation of cellular death pathways “distal” to the target, and to estimate the progression free survival and duration of response.

#### 5.4.1 Trial Design:

This trial of Ixabepilone in patients with cervical carcinoma will be conducted using a two-stage optimal design (Simon, R, Controlled Clinical Trials, 10:1-10, 1989). With  $\alpha = 0.10$  (the probability of incorrectly accepting a poor agent), and  $\beta = 0.10$  (the probability of incorrectly rejecting a good agent), we will try to rule out an undesirably low overall response (PR+CR) probability of 5% ( $p_0 = 0.05$ ) in favor of a level indicative of modest activity, 20% ( $p_1 = 0.20$ ).

Several histologic subtypes of cervical carcinoma are recognized including: (1) squamous cell (2) adenocarcinoma (3) adenosquamous carcinoma and (4) other. Among these, squamous is the most common histologic diagnosis, with adenocarcinoma second in frequency. While chemotherapy has not been shown to be very effective in cervical carcinoma, differences among the histologic subtypes in response to therapy may exist. In order to properly evaluate the activity of ixabepilone in cervical cancer, we will stratify patients into two cohorts according to histologic subtypes: (1) squamous cell (2) non-squamous including adenocarcinoma, adenosquamous carcinoma and non-squamous-not otherwise specified.

Initially, 12 evaluable patients will be enrolled in each of the two cohorts. If 0/12 demonstrate an objective response (PR +CR), then accrual to that cohort will stop and the agent will be considered inactive in this population. If one or more patients have a response, accrual will continue until a total of 37 evaluable patients have been enrolled in that cohort. If 1 - 3 of 37 patients demonstrates a response in a cohort, this will be

considered insufficient activity, and the agent will not be considered worthy of further development in that cohort. If 4 or more of 37 patients in the entire cohort have a response, then the agent will be considered active in that group (and at least potentially able to produce a response level consistent with 20%). Under the null hypothesis ( $p_0 = 0.05$ ), the probability of early termination of accrual to any one group is 0.54. With two cohorts of patients, the maximum number of evaluable patients in the two cohorts would be 74. However, in the event that an inevaluable patient is enrolled in each cohort, a total enrollment ceiling of 76 patients will be requested. Our goal is to enroll adenocarcinoma patients, but we do not want to refuse squamous cell carcinoma patients who have no other therapeutic options.

As secondary endpoints, progression free survival and duration of response will also be evaluated, using Kaplan-Meier curves. Progression free survival will be measured from the on-study date until the date of progression or last follow-up if the patient has not progressed. Response duration will be determined beginning at the date a PR or CR is first noted and will last until the patient is noted to have progressive disease relative to the response identified.

Women, 18 years of age or older, from all racial and ethnic backgrounds, will be eligible for the study.

#### 5.4.2 Duration of trial:

It is expected that 1 to 4 patients may be accrued onto this study per month. In order to accrue up to 76 patients (the maximum requested) it is anticipated that about 18 to 24 months will be needed. **Furthermore, the trial will be terminated for futility if less than 12 patients are enrolled in the first 9 months of the trial.**

### 5.5 MULTI-INSTITUTIONAL GUIDELINES

Not applicable

## 6 Human Subjects Protections

### 6.1 RATIONALE FOR SUBJECT SELECTION

#### 6.1.1 Selection based on gender, ethnic background, or race

Subjects from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in any one patient group. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of patients exposed to potentially toxic treatments on the one hand and the need to explore ethnic aspects of clinical aspects of clinical research on the other. If differences in the outcome which correlate with ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate these differences.

#### 6.1.2 Strategies/procedures for recruitment

Referrals from within the NCI and National Naval Medical Center (NNMC), and from the community will be welcomed. In addition, a letter describing the protocol will be mailed

to potential referring physicians. This protocol also will be available through the PDQ database.

#### 6.1.3 Justification for exclusions

1. Patients infected with the HIV virus will be excluded from this trial because the effect of the combination of Ixabepilone on HIV replication and/or the immune system is unknown and potentially harmful.
2. Patients that are pregnant or lactating will be excluded from this trial because the anti-proliferative activity of the experimental agent may be harmful to the developing fetus or the nursing infant. In addition, patients of child-bearing age will be instructed to use contraception while receiving Ixabepilone.

#### 6.2 PARTICIPATION OF CHILDREN

Only patients 18 years of age or older will be enrolled on this study, since the safety of this agent has not been previously defined in a pediatric population.

#### 6.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

##### 6.3.1 Potential benefits to subjects expected from the trial

As a result of participating in this trial, patients will receive evaluation and treatment of their tumor at the National Cancer Institute's Clinical Center. All the medications, tests, hospitalizations and physician services rendered at the NCI will be free of charge to them. This protocol may or may not be helpful to a specific patient, but the results may help the investigators learn about the administration of Ixabepilone and may aid in the treatment of other patients. This research treatment is not curative but may offer temporary control of the disease. Benefit cannot be promised nor can the chance of benefit be accurately predicted.

##### 6.3.2 Alternative approaches or treatments

Patients will be consented verbally and in writing regarding the risks and benefits of this trial, the treatment requirements, and alternative approaches to entering on this trial.

##### 6.3.3 Procedure for protecting against or minimizing any potential risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients that are currently unforeseeable. Patients enrolled in this trial will receive their treatment either in the inpatient ward or the outpatient day hospital on a day 1 - day 5 schedule and will be assessed each time. Monthly evaluations to monitor the treatment of patients will be performed and recorded in the patient chart. In addition to the Clinical Center health care providers, all patients will be asked to have a local physician to improve long term care and to monitor for complications. If patients suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

In addition all patient on-study are discussed at the weekly team meeting, usually on Wednesdays, prior to clinic. Any known issues or concerns from the patient or staff regarding the patient are discussed at that time.

#### 6.3.4 Provisions for monitoring data collection to ensure safety of subjects

As information is gathered from this trial, clinical results will be shared with patients although insuring total patient confidentiality. Laboratory and clinical data will be frequently gathered and any new significant findings(s) found during the course of the research, which may affect a patient's, willingness to participate further will be explained. Moreover, in all publications and presentations resulting from this trial, patients' anonymity will be protected to the maximum extent possible; although, authorized personnel from the National Cancer Institute (NCI) and Food and Drug Administration (FDA) may have access to research files in order to verify that patient rights have been safeguarded. Representatives from Bristol-Myers Squibb Co. will also have access to research files, at all times guarding a patient's anonymity. In addition patient names will be given to the Central Registration Office to register and verify patient eligibility.

#### 6.3.5 Evaluation of risk/benefit ratio for patients in this trial

Patients enrolled on this study will be those who have no further standard treatment options, and generally have a poor prognosis. Thus, patients may experience significant treatment related morbidity, and/or have progressive complications of their disease. Although ixabepilone is FDA-approved for the treatment of metastatic breast cancer, for the purpose of this study it is considered experimental. Experience with the use of this agent in humans has been gathered from completed and ongoing phase I, II & III studies, and that information has been and will continue to be used to ensure maximum patient safety. Because of the lack of experience with the use of this agent in cervical cancer, we cannot predict what activity, if any, this agent will have in patients with this type of cancer. However, it is hoped that some patients participating in this trial may have a positive benefit/risk ratio, and that this trial may provide some palliation to patients with few remaining therapeutic options.

The potential benefit that may result from this study balances the potential risks to the patients. Extensive evidence has been gathered which indicates that the microtubules are good targets for chemotherapeutic agents. Furthermore experience with the taxanes has shown that agents that stabilize microtubules have a broad spectrum of activity. Extensive preclinical data indicates that like the taxanes, the epothilones stabilize microtubules. Furthermore this data indicates that ixabepilone has activity in a broad range of animal models, including many which have been previously shown to be resistant to paclitaxel. While all preclinical data has limitations, the evidence is encouraging.

#### 6.4 CONSENT AND ASSENT PROCESSES AND DOCUMENTS

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks, discomforts, and potential benefits will be carefully explained to the patient or the patient's advocate. This process will include a general description of the disease process, as well as a description of the patient's expected

clinical course. Alternative therapies will be fully described, and outlined in the consent document. The patient will be asked to read the consent at his/her convenience and will be encouraged to ask questions. Enrollment on this study will only occur if the patient meets all eligibility criteria, is judged by the Principal Investigator to potentially benefit from the therapy, is able and willing to provide full consent, and has signed the consent document. Moreover, any experimental invasive procedure will require a separate consent form (standard procedure consent form).

Investigators are responsible for informing patients of the nature of the study, the risks and benefits of, and alternatives to participation necessary for the subjects to make a considered decision whether or not to participate. Investigators are responsible for assessing that subjects understand the information provided and that individuals give voluntary consent, free of coercion or undue influence. Written consent must be obtained by the Principal Investigator (PI) or by a PI-designated member of the research team who is knowledgeable about the protocol

## **7 SAFETY REPORTING REQUIREMENTS/DATA SAFETY MONITORING PLAN**

### **7.1 Definitions**

#### **7.1.1 Adverse Events**

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

#### **7.1.2 Suspected adverse reaction**



Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

#### 7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### 7.1.4 Serious

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### 7.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

#### 7.1.6 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

#### 7.1.7 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved study procedures in a research protocol that **does not** have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

### 7.1.8 Protocol Violation (NIH Definition)

Any change, divergence, or departure from the IRB-approved study procedures in a research protocol that **does** have a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.

### 7.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND
- Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 7.2 NCI –IRB Reporting

### 7.2.1 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

### 7.2.2 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

The protocol PI will report to the NCI-IRB:

1. All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
2. All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
3. All Grade 5 events regardless of attribution;
4. All Serious Events regardless of attribution.

**NOTE:** Grade 1 events are not required to be reported.

### 7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that require a sponsor recommended change to the protocol or the consent form or in the opinion of the PI increases risks to study participants will need to be reported to the NCI IRB.

### 7.3 CTEP ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via AdEERS) reporting **in addition** to routine reporting.

#### 7.3.1 Comprehensive Adverse Events and Potential Risks List (CAEPR) Ixabepilone (BMS 247550, NSC 710428)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. *Frequency is provided based on 1572 patients.* Below is the CAEPR for ixabepilone (BMS 247550).

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, December 5, 2011<sup>1</sup>

Adverse Events with Possible Relationship to Ixabepilone (BMS 247550) (CTCAE 4.0 Term) [n= 1572]			Specific Protocol Exceptions to Expedited Reporting (SPEER)  (formerly known as ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>			
Anemia			<b><i>Anemia (Gr 3)</i></b>
	Febrile neutropenia		<b><i>Febrile neutropenia (Gr 3)</i></b>
<b>CARDIAC DISORDERS</b>			
	Atrial fibrillation		<b><i>Atrial fibrillation (Gr 2)</i></b>
	Atrial flutter		<b><i>Atrial flutter (Gr 2)</i></b>
	Paroxymal atrial tachycardia		<b><i>Paroxymal atrial tachycardia (Gr 2)</i></b>
	Sinus bradycardia		<b><i>Sinus bradycardia (Gr 2)</i></b>
	Sinus tachycardia		<b><i>Sinus tachycardia (Gr 2)</i></b>
	Supraventricular tachycardia		<b><i>Supraventricular tachycardia (Gr 2)</i></b>
<b>EYE DISORDERS</b>			
	Watering eyes		<b><i>Watering eyes (Gr 2)</i></b>
<b>GASTROINTESTINAL DISORDERS</b>			

	Abdominal pain		
	Anal mucositis		<b>Anal mucositis (Gr 2)</b>
	Constipation		<b>Constipation (Gr 3)</b>
Diarrhea			<b>Diarrhea (Gr 3)</b>
		Ileus	
	Mucositis oral		<b>Mucositis oral (Gr 3)</b>
Nausea			<b>Nausea (Gr 3)</b>
	Rectal mucositis		<b>Rectal mucositis (Gr 2)</b>
	Small intestinal mucositis		<b>Small intestinal mucositis (Gr 2)</b>
Vomiting			<b>Vomiting (Gr 3)</b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
Fatigue			<b>Fatigue (Gr 3)</b>
	Fever		<b>Fever (Gr 2)</b>
	Pain		
<b>IMMUNE SYSTEM DISORDERS</b>			
	Allergic reaction		<b>Allergic reaction (Gr 2)</b>
<b>INFECTIONS AND INFESTATIONS</b>			
	Infection <sup>2</sup>		<b>Infection<sup>2</sup> (Gr 3)</b>
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>			
	Radiation recall reaction (dermatologic)		<b>Radiation recall reaction (dermatologic) (Gr 3)</b>
<b>INVESTIGATIONS</b>			
	Alanine aminotransferase increased		<b>Alanine aminotransferase increased (Gr 2)</b>
Alkaline phosphatase increased			<b>Alkaline phosphatase increased (Gr 2)</b>
	Aspartate aminotransferase increased		<b>Aspartate aminotransferase increased (Gr 2)</b>
	Blood bilirubin increased		
	Creatinine increased		
	INR increased		<b>INR increased (Gr 3)</b>
Neutrophil count decreased			<b>Neutrophil count decreased (Gr 4)</b>
Platelet count decreased			<b>Platelet count decreased (Gr 4)</b>
White blood cell decreased			<b>White blood cell decreased (Gr 4)</b>
<b>METABOLISM AND NUTRITION DISORDERS</b>			
	Anorexia		<b>Anorexia (Gr 3)</b>
	Dehydration		<b>Dehydration (Gr 3)</b>
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
	Arthralgia		<b>Arthralgia (Gr 2)</b>
	Generalized muscle weakness		<b>Generalized muscle weakness (Gr 2)</b>
Myalgia			<b>Myalgia (Gr 2)</b>
	Pain in extremity		<b>Pain in extremity (Gr 2)</b>
<b>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</b>			
	Tumor pain		<b>Tumor pain (Gr 2)</b>
<b>NERVOUS SYSTEM DISORDERS</b>			
	Dizziness		<b>Dizziness (Gr 2)</b>
	Dysgeusia		<b>Dysgeusia (Gr 2)</b>
	Dysphasia		<b>Dysphasia (Gr 2)</b>
	Headache		
	Neuralgia		<b>Neuralgia (Gr 2)</b>

	Peripheral motor neuropathy		<i>Peripheral motor neuropathy (Gr 3)</i>
Peripheral sensory neuropathy			<i>Peripheral sensory neuropathy (Gr 3)</i>
	Syncope		<i>Syncope (Gr 2)</i>
<b>PSYCHIATRIC DISORDERS</b>			
	Insomnia		<i>Insomnia (Gr 2)</i>
<b>RENAL AND URINARY DISORDERS</b>			
	Urinary retention		<i>Urinary retention (Gr 2)</i>
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
	Cough		<i>Cough (Gr 2)</i>
	Dyspnea		<i>Dyspnea (Gr 3)</i>
	Hiccups		<i>Hiccups (Gr 2)</i>
	Hypoxia		<i>Hypoxia (Gr 3)</i>
	Laryngeal mucositis		<i>Laryngeal mucositis (Gr 2)</i>
	Pharyngeal mucositis		<i>Pharyngeal mucositis (Gr 2)</i>
		Pleural effusion	
	Pneumonitis		<i>Pneumonitis (Gr 3)</i>
	Tracheal mucositis		<i>Tracheal mucositis (Gr 2)</i>
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>			
Alopecia			<i>Alopecia (Gr 2)</i>
		Erythema multiforme	
	Nail loss		<i>Nail loss (Gr 2)</i>
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		<i>Pruritus (Gr 2)</i>
	Rash maculo-papular		<i>Rash maculo-papular (Gr 2)</i>
<b>VASCULAR DISORDERS</b>			
		Capillary leak syndrome	<i>Capillary leak syndrome (Gr 2)</i>
	Flushing		<i>Flushing (Gr 2)</i>
	Hypotension		<i>Hypotension (Gr 2)</i>

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

<sup>3</sup>Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

**Also reported on ixabepilone (BMS 247550) trials but with the relationship to ixabepilone (BMS 247550) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Disseminated intravascular coagulation

**CARDIAC DISORDERS** - Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericardial effusion

**EYE DISORDERS** - Blurred vision; Conjunctivitis

**GASTROINTESTINAL DISORDERS** - Colitis; Dry mouth; Dyspepsia; Dysphagia; Esophagitis; Gastrointestinal disorders - Other (impaired gastric emptying); Gastrointestinal perforation<sup>3</sup>; Rectal hemorrhage; Upper gastrointestinal hemorrhage

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema face; Edema limbs; Edema trunk; Injection site reaction; Non-cardiac chest pain

**HEPATOBIILIARY DISORDERS** - Hepatic failure

**INFECTIONS AND INFESTATIONS** - Infections and infestations – Other (Opportunistic infection associated with  $\geq$ Grade 2 Lymphopenia)

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Cardiac troponin T increased; Lymphocyte count decreased; Weight gain; Weight loss

**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyponatremia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Back pain; Bone pain

**NERVOUS SYSTEM DISORDERS** - Ataxia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Seizure; Vasovagal reaction

**PSYCHIATRIC DISORDERS** - Agitation; Anxiety; Confusion; Depression

**RENAL AND URINARY DISORDERS** - Acute kidney injury; Hematuria; Renal hemorrhage; Urinary incontinence

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Hematosalpinx; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Allergic rhinitis; Bronchopulmonary hemorrhage; Epistaxis; Respiratory failure

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Dry skin; Skin and subcutaneous tissue disorders - Other (pigmentation changes); Urticaria

**VASCULAR DISORDERS** - Hot flashes; Hypertension; Phlebitis; Thromboembolic event

**Note:** Ixabepilone (BMS 247550) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

### 7.3.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy

of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

- **“Expectedness”**: AEs can be ‘Unexpected’ or ‘Expected’ (see Section 7.1 above) for expedited reporting purposes only. ‘Expected’ AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1.1).
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

### 7.3.3 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (<http://ctep.cancer.gov>). The reporting procedures to be followed are presented in the “CTEP, NCI Guidelines: Adverse Event Reporting Requirements” which can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). These requirements are briefly outlined in the table below (Section 7.3.4).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

### 7.3.4 Expedited Reporting Guidelines

**AdEERS Reporting Requirements for Adverse Events that occur within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials**

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected Hospitalization		Expected		Unexpected	Expected
				With	Without	With	Without		
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

<sup>1</sup>Adverse events with attribution of possible, probable, or definite that occur **greater than 30 days after the last dose of treatment with an agent under a CTEP IND** require reporting as follows:

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

<sup>2</sup>Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

#### 7.3.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through AdEERS must also be reported in routine study data submissions.** Routine data will be reported to CTEP via the web-based Clinical Data Update System on a quarterly basis.

#### 7.3.6 Secondary Malignancy

*A secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via AdEERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.



#### 7.4 DATA AND SAFETY MONITORING PLAN:

Monitoring of this protocol will consist of continuous, close monitoring by the Principal Investigator, with prompt reporting of serious adverse events to the IRB and the Cancer Treatment and Evaluation Program (CTEP). The Principal Investigator will monitor the trial with the assistance of the Associate Investigators including the Research Nurse(s). In the event that any severe or unexpected side effects are noted, these will be reported to the IRB and CTEP in accordance with the guidelines in Section 7.1 and 7.2. This approach will ensure that adverse event reporting requirements are met. In addition, data will be examined weekly at a Protocol Review Meeting, usually conducted on the day of clinic. These meetings will assess the progress of the protocol and discuss any side effects observed, including both expected and unexpected side effects. At this time the accuracy of the accrued data is verified.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (<http://ctep.cancer.gov>). **Note:** All adverse events that have occurred on the study, including those reported through AdEERS, must be reported via CDUS.

#### 7.5 Clinical Trials Agreement

The agent used in this protocol, ixabepilone, (hereinafter referred to as the Agent) is provided to the NCI under a Clinical Trials Agreement (CTA) between Bristol Myers Squibb (hereinafter referred to as the Collaborator) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational agent used in combination with (an)other investigational agent(s), each the subject of different CTAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data):
  - a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

- b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
  - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI  
Executive Plaza North, Suite 7111  
Bethesda, Maryland 20892  
FAX 301-402-1584  
Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

## 8 PHARMACEUTICAL INFORMATION

### 8.1 BMS-247550 (710428)

#### 8.1.1 Chemical Name

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

#### 8.1.2 Other Names

Epothilone B analog, Ixabepilone, Ixemptra®

#### 8.1.3 Molecular Formula

C<sub>27</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub>S M.W.: 506.7 grams/mole

#### 8.1.4 Mode of Action

BMS-247550 is a semi-synthetic analog of the natural product epothilone B. The epothilones are a novel class of non-taxane microtubule-stablizing agents obtained from the fermentation of cellulose degrading myxobacteria, *Sorangium cellulosum*.

#### 8.1.5 Description

Epothilone B analog

#### 8.1.6 How Supplied

BMS-247550 appears as a lyophilized, white to off-white color, whole or fragmented cake in a vial. The drug product is available in 15 mg and 45 mg vials.

BMS-247550 vial size	Diluent provided	Volume of diluent needed for reconstitution of drug vial	Final concentration	Actual Amount of Drug in Vial**
15 mg	8 mL vial	8 mL	2 mg/mL	16 mg
45 mg	23.5 mL vial	23.5 mL	2 mg/mL	47 mg

\*\*To account for vial/needle/syringe loss, the actual amount of drug in the vial differs from the amount of drug on the product label.

The Vehicle for Constitution of BMS-247550 for injection (diluent) appears clear to slightly hazy and is colorless to pale in color. The diluent is an ethanol plus polyoxyethylated castor oil (Cremophor® EL) mixture (1:1 by volume).

Reconstitute the drug vial with the provided diluent only. Diluents are not interchangeable and should only be utilized to reconstitute a particular strength.

#### 8.1.7 Preparation

Prior to constitution of the lyophile, bring the lyophile and diluent vial to room temperature for approximately 30 minutes. (If the diluent is stored in the refrigerator, a

white precipitate may appear when it is first removed. The precipitate will disappear once the vehicle reaches room temperature.)

Slowly inject 8 mL or 23.5 mL of the diluent into the 15 mg vial or 45 mg vial, respectively. Gently swirl the vial until the lyophile is dissolved completely. This results in a 2mg/mL solution.

Further dilute with Lactated Ringer's Injection (LRI) to a final BMS-247550 concentration of 0.2 mg/mL to 0.6 mg/mL in a non-PVC container before administration to the patient. (Please note: BMS-247550 concentrations below 0.2 mg/mL are no longer recommended.)

#### 8.1.8 Storage

Store BMS-247550 for Injection in the refrigerator (2° to 8°C) prior to use and protect from light.

**Store the Vehicle for Constitution in the refrigerator or at room temperature (2°C to 25°C).**

#### 8.1.9 Stability

Shelf life surveillance is ongoing. After initial constitution with the accompanying diluent, the product may be stored for a maximum of one (1) hour at room temperature and room light. **After final dilution in Lactated Ringers for Injection (LRI) to concentrations between 0.2 and 0.6 mg/mL, the drug product is stable at room temperature and light for a maximum of 6 hours.**

#### 8.1.10 Route of Administration

Administer the BMS-247550 infusion intravenously through an appropriate in-line filter with a microporous membrane of 0.22 to 5 microns. Flush the IV line or extension set with LRI at the end of the infusion, if flushing is required.

#### 8.1.11 Incompatibilities

Avoid contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl)phthalate (DEHP) to prevent DEHP leaching into the infusion medium. Store diluted BMS-247550 solutions in bottles (glass, polypropylene) or plastic bags (polyethylene, polypropylene, polyolefin, ethylene-vinyl-acetate) and administer through polyethylene-lined administration sets or PVC sets plasticized with TOTM (trioctyl trimellitate). IV sets and components typically used for the administration of paclitaxel are compatible with BMS-247550 infusions.

#### 8.1.12 Potential Drug Interactions

The following strong inhibitors of CYP3A4 are prohibited: ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, nelfinavir, delavirdine, and voriconazole.

If there are no other treatment options other than the above named drugs, consultation with the PI is mandatory and each patient's situation will be reviewed on a case by case basis with final decision made by the PI.

Use caution when considering the use of other CYP3A4 inhibitors with BMS-247550. Co-administration of BMS-247550 with CYP3A4 inducers may decrease its plasma concentrations and therapeutic effects.

*In vitro*, BMS-247550's weak inhibition of human CYP3A4 suggests that it may have a minimal potential to alter the metabolic clearance of drugs metabolized by CYP3A4.

A more complete list of CYP3A4 inhibitors is found in Appendix C and should be consulted when making decisions regarding concurrent therapies.

#### 8.1.13 Drug ordering and accountability

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions, unless prior approval from PMB is obtained. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD, through an annual submission of FDA form 1572 and a CV. If there are several participating investigators at one institution, CTEP supplied investigational agents should be ordered under the name of one lead investigator at that institution. Drug may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Pharmaceutical Management Branch, DCTD, NCI, EPN Room 7149, Bethesda, MD 20892 or faxing it to (301) 480-4612. For questions call (301) 496-5725.

#### 8.1.14 Precautions/overdose

BMS-247550 is an investigational agent and is contraindicated for all conditions other than those mentioned in the protocol and the Investigator Brochure. In the case of extravasation of drug into the subcutaneous tissues, the infusion should be stopped immediately and appropriate local measures instituted, as per the Nursing Department Policy: Hazardous Drugs (HD): Extravasation Guideline:

<http://intranet.cc.nih.gov/nursing/practicedocs/procedures.html>.

It should be noted that a specific antidote for administration is not available and the recommendations for paclitaxel will be followed.

Also, please refer to the Nursing Department Standard of Practice: Care of the patient receiving cytotoxic or biologic agents:

[http://intranet.cc.nih.gov/nursing/practicedocs/sop\\_pdf/SOP\\_Cytotoxic\\_orBiologic\\_Agents.pdf](http://intranet.cc.nih.gov/nursing/practicedocs/sop_pdf/SOP_Cytotoxic_orBiologic_Agents.pdf)

#### 8.1.15 Disposition of study medications

Any remaining solution should be discarded according to institutional procedures for cytotoxics. At the end of the study all unused stock will be returned to CTEP who will arrange for its disposition.

## 8.2 DIPHENHYDRAMINE HYDROCHLORIDE (HCI) INJECTION

### 8.2.1 General issues

Diphenhydramine hydrochloride (Benadryl) is an antihistamine drug having the chemical name 2-(Diphenylmethoxy)-N, N-dimethylethylamine hydrochloride. It occurs as a white, crystalline powder, is freely soluble in water and alcohol and has a molecular weight of 291.82. The molecular formula is  $C_{17}H_{21}NO \cdot HCl$ .

8.2.2 Other pharmaceutical issues:

8.2.2.1 Supply: Commercially available.

8.2.2.2 Product description: Diphenhydramine HCl injection is available in an injectable solution at a 50 mg/ml concentration in single dose ampoules, syringes and vials as well as multi-dose vials from multiple manufacturers.

8.2.2.3 Solution Preparation: Diphenhydramine HCl may be given by direct intravenous injection without additional dilution. Alternatively the prescribed dose may be diluted in a small volume (e.g. 25 - 50 ml) of 5% dextrose in water (D5W) or 0.9% sodium chloride (NS) and infused over 10 - 15 minutes.

8.2.2.4 Storage: Store commercially available injectable product at controlled room temperature.

8.2.2.5 Route of Administration: Diphenhydramine HCl injection may be administered by direct IV injection (IV push) at a rate generally not exceeding 25 mg/min. Alternatively, diphenhydramine HCl injection may be diluted and given over 10 - 15 minutes (see solution preparation).

8.2.2.6 Toxicities: Sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, thickening of bronchial secretions. Diphenhydramine can produce additive effects with alcohol or other CNS depressants. Diphenhydramine can cause anticholinergic side effects (e.g. dry mouth, fixed or dilated pupils, flushing, urinary retention). Diphenhydramine should be used with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension.

PLEASE REFER TO THE PACKAGE INSERT FOR FURTHER INFORMATION.

### 8.3 RANITIDINE HYDROCHLORIDE (HCl) INJECTION

#### 8.3.1 General issues

Ranitidine hydrochloride (HCl) (the active ingredient in Zantac Injection and Zantac Injection Premixed) is a histamine  $H_2$ -receptor antagonist. Chemically it is N[2-[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride. The empirical formula is  $C_{13}H_{22}N_4O_3S \cdot HCl$ , representing a molecular weight of 350.87.

#### 8.3.2 Other pharmaceutical issues:

8.3.2.1 Supply: Commercially available.

8.3.2.2 Product Description: Ranitidine HCl injection is available in an injectable solution at a 25mg/ml concentration in 2, 10 and 40 ml vials and in a 2 ml syringe. It is also available in a single dose pre-mixed 50 mg parenteral bag in

50 ml of 0.45% sodium chloride (1/2NS). Ranitidine HCl is manufactured by Glaxo Wellcome Inc. under the trade name Zantac.

- 8.3.2.3 Solution preparation: For direct intravenous injection, dilute prescribed dose with a compatible diluent [e.g. 5% dextrose in water (D5W), 0.9% sodium chloride (NS) or lactated ringers (LR)] to a total volume of 20 ml prior to injection. For intermittent intravenous infusion, dilute prescribed dose in 25 – 100ml of a compatible diluent (e.g. D5W, NS or LR). Once diluted in a compatible diluent, ranitidine is stable for 48 hours at room temperature and 4 days refrigerated.
- 8.3.2.4 Storage: Ranitidine HCl injection should be stored between 4°C and 25°C and protected from light and excessive heat. The premixed infusion solution should be stored between 2°C and 25°C.
- 8.3.2.5 Route of administration: Ranitidine HCl may be administered by direct intravenous injection or infusion. For direct intravenous injection, dilute prescribed dose to a volume of 20 ml with a compatible diluent and inject over a period of not less than 5 minutes. For intermittent intravenous infusion, infuse prescribed dose over 15 - 20 minutes.
- 8.3.2.6 Toxicities: Headache, reversible confusional states (e.g. mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), increased transaminase levels, increased serum creatinine, rash, allergic reactions, and hematologic toxicity (e.g. leucopenia, thrombocytopenia, pancytopenia).

PLEASE REFER TO THE PACKAGE INSERT FOR FURTHER INFORMATION.

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## 10 Appendices

### APPENDIX A: Data/Specimen Collection, Storage and Disposition Procedures

#### Intended use of samples - translational studies on tumor samples:

*Tubulin immunostaining:* Immunohistochemistry (IHC) will be performed on formalin fixed, paraffin embedded sections using microwave antigen retrieval. An automated immunohistochemical staining procedure will be used according to manufacturer's recommendations (TechMate 1000™, Ventana, Tucson, AZ). Primary antibodies will be DO-7 for p53 (Dako, Santa Barbara, CA), and DM1A, a monoclonal anti- $\alpha$ -tubulin (Sigma, St Louis, MO).

*PARP activation:* Fresh patient core biopsies will be Dounce homogenized at 22°C in hypotonic lysis buffer [1 mM MgCl<sub>2</sub>, 2 mM EGTA, 0.5% Nonidet P-40, 20 mM Tris-HCl, pH 6.8, containing protease inhibitors] and vortexed vigorously. The samples will be pulse sonicated to clarity prior to centrifugation for 1 min at 1000 rpm to remove unlysed debris. Total protein concentrations in the lysates will be determined using the Biorad assay and equal amounts of protein will be separated on 4-15% gradient SDS-PAGE gels for each pair of pre- and post-treatment samples. To assess apoptosis, PARP cleavage will be assayed by probing the Western blot with a rabbit polyclonal anti-PARP antibody that detects both the full length and the 85 kDa cleavage product (SC-7150 [H-250] Santa Cruz, CA). Anti Fractin antibody may also be used. Immunoblots probed with either of these antibodies will also be simultaneously or sequentially probed with an antibody to either actin or GAPDH, as loading controls for each pair.

*cDNA Micro-array:* Biopsy material that will be used for micro-array analyses will be flash-frozen as soon as practically possible after obtaining the sample (< 20 minutes). The biopsy will be flash-frozen using either liquid nitrogen or a dry ice ethanol bath and then stored at -70 °C to -80 °C. Total RNA will be prepared from frozen biopsy tissue using RNeasy® Kits (Qiagen, Valencia, CA) following the manufactures instructions. Micro-arrays will be used to measure the steady state expression level of nearly all known human genes in the fresh-frozen biopsies. Approximately 3 - 10 mg of total RNA will be used to generate fluorescent-labeled cDNA for hybridization to the Human Genome U95 gene set (Affymetrix, Inc. Santa Clara CA). The complete Human U95 gene set contains 60,000 expression elements that represent approximately 12,000 full length genes and 50,000 ESTs.

Collection, handling, and storing of blood specimens for tubulin polymerization assay using PBMCs: (1) Collection: Blood samples are to be collected from an indwelling catheter or by direct venipuncture. Each blood sample should be collected into a pre-labeled 8 mL Becton-Dickinson CPT Vacutainer® tube. (2) Handling: Following blood collection, the tubes should be inverted several times to ensure mixing with the anticoagulant. Tubes should remain at room temperature and be centrifuged for 30 minutes at approximately 1700 x g at 20°C within 15 minutes of collection. The PBMCs should be transferred to a separate polypropylene tube and washed twice with 10 mL of ice-cold phosphate buffered saline (PBS). Following each washing, cells should be separated by centrifugation at 1700 x g for 10 minutes. Following the second washing, remove as much liquid as possible. The tube may be inverted on a paper towel for a few minutes to remove residual liquid, provided the cell pellet does not become dislodged from the tube bottom. (3) Storing: The PBMC cellular pellet should be stored at -70 to -80°C until

assayed. Samples should be labelled. Each label will have the study number, sample matrix, and nominal sample time. Once affixed on tubes, the labels should be wrapped completely by applying protective transparent tape for protection during handling, and storage. The actual time, as well as the date, for each sample should be recorded.

### Tracking and Storage of Samples

#### Disposition of samples:

When initially collected, all specimens should be labeled with the patient's name, hospital number, date and time of collection. Once the samples reach the laboratory they will be appropriately labeled and coded without names. The information on the subjects' names and ID numbers will be kept in a log book in a locked cabinet.

At this time (11/2008) the samples are recorded in a laboratory notebook in room 12N220. The information includes the patient's name, ID number, date of biopsy and whether the sample is pre- or post-ixabepilone administration. We intend to upgrade the tracking process to an electronic spreadsheet that contains the patient ID, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Samples remaining after the study completes will be stored in the same freezer in Dr. Fojo's lab and eventually transferred to Dr. Figg's core facility for possible future study as outlined below. The study consent contains a section asking patients for permission to keep the tissue for use in research to learn about, prevent, or treat cancer or other health problems.

Material remaining after completion of correlative studies (with the exception of biopsy samples) will be transferred to the laboratory of Dr. William Figg to be entered into the Clinical Pharmacology Program's "Patient Sample Database Management System" (PSDMS) - Labrador. This is a secure program that can only be accessed by authorized users in Dr. Figg's lab. PSDMS creates a unique barcode ID for every sample and sample box that cannot be traced back to patients without PSDMS access. These samples will be managed in accordance with the laboratory's policies and procedures.

The data recorded for each sample includes the patient ID, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. There are patient demographics that can be obtained to correlate with the samples through the PSDMS system. For each samples, there are notes describing the processing method (delay in sample processing, storage conditions on the ward, etc.). Bar-coded samples are stored in bar-coded boxes in a locked freezer at either -20 or -85°C according to stability requirements. These freezers are located onsite in Dr. Figg's lab and offsite at NCI Frederick Central Repository Services (Fisher Bioservices) in Frederick, MD.

Samples will be stored until requested by the researcher assigned to the protocol (however, those requests must come from a member of Dr. Figg's laboratory with PSDMS access/clearance). All requests are monitored and tracked in the PSDMS system. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol – that protocol is stored in the PSDMS system) and that any unused samples must be returned to Dr. Figg's laboratory.

#### Guidelines for reporting loss or destruction to IRB:

The PI will report any loss or destruction of samples to the IRB. Any new use of the samples, specimens, or data outside of this protocol will require prospective IRB review and approval.

APPENDIX B: Study Calendar

EVALUATIONS REQUIRED PRE, DURING, AND POST THERAPY:

	A	B	C	D	E	F
Complete medical history		X				
Interim medical history				X		X
Physical examination		X		X		X
Weight and height		X		X		
Vital signs		X		X		X
ECOG performance status	X	X		X		X
Urine pregnancy test		X				
HIV Screen/Hepatitis B and C Screen	X					
Staging laboratory evaluation		X			X	X
Routine laboratory evaluation		X		X		X
CBC with differential and platelet count		X	X	X		X
Staging imaging studies	X				X	X
<u>Biopsy &amp; Research bloods (if indicated)*</u>				✗		✗

A: Within 4 weeks prior to initiating therapy

B: Within 1 week prior to initiating therapy

C: Weekly or twice weekly during period of anticipated neutropenia

D: Every cycle

E: Every 2 cycles (Imaging studies and chest radiograph every third cycle after cycle 6)

F: Study termination.

\*Biopsies will be obtained after consent but before Day 1 dosing, and again on either Day 4 or Day 5. Biopsies are optional.

Research Labs for tubulin polymerization will be obtained prior to the Cycle 1 Day 1 drug infusion, and 1, 8 and 24 hours after Day 1 infusion start, and on either Day 4 or 5, within 1 hour of the biopsy. The research labs will only be done in those patients who have biopsies performed.

APPENDIX C: List of drugs that may have potential CYP3A4 interactions

(source: ctep.cancer.gov) [Updated on May 1, 2007]

When drugs classified as 'substrates' are co-administered with BMS-247550 there is the potential for higher concentrations of the 'substrate'. When BMS-247550 is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of BMS-247550 is the potential outcome. The co-administration of 'inducers' would potentially lower plasma BMS-247550 concentrations. Only major substrates and effective inducers are listed.

**List of drugs that may have potential CYP3A4 interactions**

**CYP3A4 Substrates**

Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylates	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylethylgonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspiron	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil
Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Dasatinib (1)	Isosorbide	Primaquine	Zonisamide
Delavirdine	Isosorbide dinitrate	Progesterone	Zopiclone
Diazepam	Isosorbide mononitrate	Quetiapine	



### CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice (2)	Norfloracin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

### CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

When drugs classified as 'substrates' are co-administered with (*Study Agent*), there is the potential for higher concentrations of the 'substrate'. When (*Study Agent*) is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of (*Study Agent*) is the potential outcome. The co-administration of 'inducers' would potentially lower plasma (*Study Agent*) concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15<sup>TH</sup> ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed.

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at <http://medicine.iupui.edu/flockhart/>.

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## APPENDIX D: Care of fingernails during treatment with Ixabepilone

During the course of chemotherapy some patients have experienced pain in their fingertips, especially in their fingernails. This is especially true when they are trying to open a can or apply any pressure to their nails. Some patients have developed infections in their nail beds. Others have had their nails “lift off” over a period of time, as a new nail grows in. Sometimes the nails have streaks of color in them. This doesn’t happen all at once, rather it happens gradually over the course of several months. We have developed some guidelines to help you care for your fingernails during chemotherapy. These techniques might help prevent or minimize the problems.

### Prevention

1. Minimize hand and nail trauma.
2. Avoid repeated hand washing or soaking, for example, wear waterproof gloves when washing dishes.
3. Avoid nail polish and solvents.
4. Avoid using instruments to dig under nails.
5. Avoid exposing nails to direct sunlight (this has been a problem with a different chemotherapy. In that case, avoiding the sunlight helped).
6. Wear gloves in the winter and sunscreen (containing titanium or iron oxide) on nails in the summer.
7. Dry hand/nails thoroughly whenever they become wet. Some patients find a blow dryer is very helpful to dry the nails.
8. Wear gloves when gardening or in situations that your nails might be exposed to dirt or solvents.

### Treatment

1. Signs of infections include nail discoloration, pus forming under the nail, or pus draining from the nail. If possible, the pus should be sent for “culture” to determine if any bacteria are present. This can be done by your local doctor or by the staff at the NIH.
2. If you have an infection you can clean your nails with either hydrogen peroxide or dilute vinegar. You can put the solution in a small bowl and soak your fingertips for a few minutes, twice a day. Dry thoroughly when done.
3. Some patients have found that trimming their nails very short has helped the infections clear more quickly.
4. You may need antibiotics to treat the infection.