Current Clinical Trials of Epothilone B Analog (BMS-247550)

Review Article [1] | September 01, 2001
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BMS-247550 is a methyl, semi-synthetic analog of the natural product epothilone B. Provided to the National Cancer Institute (NCI) by Bristol-Myers Squibb, BMS-247550 was chosen for clinical development because it demonstrated antitumor activity in paclitaxel (Taxol)-sensitive, paclitaxel-insensitive, and paclitaxel-resistant human tumor models. The first NCI-sponsored clinical trial of BMS-247550 was initiated in February 2000.

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community.

It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician's Data Query (PDQ).*

We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study.

This month’s installment of Clinical Trials Referral Resource is devoted to clinical trials of epothilone B analog (BMS-247550). For patient entry information, see the individual trials.

Taxanes represent one of the most effective classes of anticancer therapeutics; however, many human cancers either do not respond to or become resistant to taxane-based therapy. Therefore, screening programs have sought microtubule-stabilizing compounds with a broader range of activity and/or activity against taxane-refractory cancers. Fermentation products in the culture broth of the cellulose-degrading myxobacteria Sorangium cellulosum were found to have antifungal and cytotoxic activity. German investigators isolated epothilones A and B from this culture broth and elucidated their structures.[1,2]

Bollag and colleagues found that the epothilones A and B induce polymerization of tubulin and enhance microtubule stability.[3] The epothilones compete with the taxanes for binding to tubulin, suggesting a single pharmacophore for these two classes of agents. The epothilones’ microtubule stabilization causes mitotic arrest and therefore, precipitates cell-cycle arrest at the G2/M transition, with resultant apoptosis.[4] The epothilones, unlike the taxanes, retain their activity against P-glycoprotein-expressing, multiple drug-resistant tumors and cell lines as well as tumors resistant to the taxanes based on tubulin mutations.[3]

Epothilone B, unlike paclitaxel, does not elicit endotoxin-signaling pathways in murine macrophages, yet the effects of microtubule stabilization are preserved. Therefore, the production of proinflammatory cytokines and nitric oxide seen with paclitaxel has not been observed with epothilone B.[5] These preclinical data raise the possibility that the antitumor effects of paclitaxel may be preserved in epothilone B, whereas some adverse reactions such as arthralgias and myalgias associated with a proinflammatory state, may not. Investigators at Bristol-Myers Squibb conducted an extensive screening program of more than 300
semisynthetic analogs of epothilones A and B. BMS-247550, a lactam analog of epothilone B, emerged as the leading candidate for further development, having outperformed paclitaxel in a series of preclinical tumor models.[6]

Preclinical Studies

BMS-247550 has demonstrated a broad spectrum of activity against a panel of tumor lines in vitro, including human ovarian, breast, prostate, colon, lung, and epithelial cancer lines and leukemia cell lines. Median inhibitory concentration (IC50) values were between 1.4 and 34.5 nM, based on a 72-hour exposure. BMS-247550 retained its activity against paclitaxel-resistant lines, compared to paclitaxel-sensitive lines. Tubulin polymerization assays demonstrated a 2.5-fold greater potency for BMS-247550 over paclitaxel. BMS-247550 causes virtually complete cell-cycle arrest in G2/M at 7.5 nM, which is approximately the mean IC50 in vitro.[6]

Mouse tumor models, including models of mouse fibrosarcoma and human pancreatic, ovarian, colon, and breast cancers have shown that log cell kill of BMS-247550 is equal or superior to that of paclitaxel in both paclitaxel-sensitive and -resistant tumors in virtually all cases, when the drugs are administered according to their respective optimal doses and schedules. Preclinical data suggest that the efficacy of BMS-247550 may be schedule-dependent. A study of A2780 (ovarian) tumors in mice demonstrated a less frequent dosing schedule, allowing for higher doses to be administered, with a maximum tolerated dose of 16 mg/kg per injection on an every-4-days × 3 schedule vs 6.3 mg/kg per injection on an every-2-days × 5 schedule. Similar results were demonstrated in an HCT116 (colon) model: A maximum tolerated dose of 24 mg/kg per injection on an every-8-days × 2 schedule vs 6.3 mg/kg per injection on an every-2-days × 5 schedule. In both of these models, the antitumor effects were markedly superior in the mice treated on the intermittent schedules as well.[6] In two other studies in the Pat-7 (pancreas) and HCT116/VM46 (paclitaxel-resistant colon) tumors, the efficacy of two IV treatment schedules (every 2 days × 5 and every 4 days × 3) were compared, and in both cases, the two regimens yielded essentially equivalent antitumor activities.

BMS-247550 is bioavailable orally. Experiments with the HC116 (colon) mouse tumor model have demonstrated that the antitumor activity of oral BMS-247550 is identical to that of the intravenous regimen.

Clinical Studies

Phase I studies of BMS-247550 evaluating three schedules are ongoing and have been reported in abstract form. Adverse reactions attributed to BMS-247550 have included neutropenia, arthralgia/myalgia, fatigue, weakness, constipation, diarrhea, nausea, vomiting, rash, alopecia, and peripheral neuropathy. Dose-limiting toxicities on the every-21-day schedule are neutropenia, neuropathy, and arthralgia/myalgia, and the maximum tolerated dose on this schedule is 50 mg/m² per cycle. The maximum tolerated doses of the every-7-day and 5 × daily every-21-day schedules have not yet been defined, but the patterns of toxicity are similar thus far, with the possible exception of diminished neuropathy on the daily × 5 days schedule. BMS-247550 is administered in Cremaphor EL solution, and hypersensitivity reactions have been observed in patients who were not premedicated. There have been no reports of clinically relevant hypersensitivity in patients receiving H1 and H2 blockers as premedication.[7-11]

Preliminary pharmacokinetic and pharmacodynamic studies in humans demonstrate a wide volume of distribution for BMS-247550 (399-1157 L/m²) and a terminal half-life of approximately 1 to 2 days, with a clearance of 230 to 423 mL/min/m².[12] Enhanced tubulin polymerization in peripheral blood mononuclear cells has been seen at several dose levels. Plasma area under the concentration-time curve (AUC) values appear to be proportional to dose.

Preliminary evidence of antitumor activity has been reported on all schedules under investigation and has included the following tumor types: ovarian, colon, breast, melanoma, non-small-cell lung, anal, and head and neck cancers.[7,9-11] The Cancer Therapy Evaluation Program (CTEP) at the NCI is sponsoring a broad range of phase I and II clinical trials of BMS-247550, both as a single agent and in combination with other agents on various schedules. Bristol-Myers Squibb is sponsoring trials in patients with breast, colorectal, gastric, melanoma, and non-small-cell lung cancer. The following list includes approved and/or active clinical trials examining treatments with the epothilone B analog BMS-247550, which are being sponsored by CTEP. Information about these studies can be obtained from the principal investigator.
Current Clinical Trials of Epothilone B Analog (BMS-247550)
Published on Physicians Practice (http://www.physicianspractice.com)

or the contacts listed for each trial, or from A. Dimitrios Colevas, MD, at CTEP (colevasd@ctep.nci.nih.gov), 301-435-9128.

Gastrointestinal Cancer Phase II

**Title:** Phase II Study of BMS-247550 in Patients With Hepatobiliary Cancer  
**Protocol Number:** UCCRC-NCI-3656  
**Participating Institutions:** University of Chicago, Lutheran General Hospital, Evanston Hospital, University of Illinois, Weiss Memorial Hospital, Decatur Memorial Hospital, Oncology-Hematology Associates, Montefiore Medical Center, Fort Wayne Medical Oncology/Hematology Inc, Michigan Hematology Oncology, PC, Central Illinois Hematology Oncology Center  
**Protocol Status:** Approved; not yet active  
**Contact:** Hedy L. Kindler, MD, (773) 702-0360, hkindler@bsd.uchicago.edu  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of BMS-247550 in Patients With Advanced Pancreatic Adenocarcinoma  
**Protocol Number:** SWOG-S0107  
**Participating Institution:** Southwest Oncology Group  
**Protocol Status:** Active  
**Contact:** Robert P. Whitehead, Chair, (409) 772-1164; for a complete listing of study contacts, click here  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

Genitourinary Cancer Phase II

**Title:** A Phase II Clinical Trial of BMS-247550 (NSC # 710428) in Patients With Renal Cell Carcinoma  
**Protocol Number:** 3654  
**Participating Institution:** National Cancer Institute Medicine Branch  
**Protocol Status:** In review  
**Contact:** Antonio T. Fojo, MD, (301) 402-1357, tfojo@helix.nih.gov  
**Title:** Phase II Study of BMS-247550 in Patients With Advanced Carcinoma of the Urothelium  
**Protocol Number:** E-E3800  
**Participating Institution:** Eastern Cooperative Oncology Group  
**Protocol Status:** Active  
**Contact:** Robert Dreicer, Chair, (216) 445-4623; for a complete listing of study contacts, click here  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of BMS-247550 in Patients With Hormone-Refractory Prostate Cancer  
**Protocol Number:** SWOG-S0111, CTSU  
**Participating Institution:** Southwest Oncology Group  
**Protocol status:** Open/active  
**Contact:** Maha Hadi A. Hussain, Chair, (313) 745-2357; for a complete listing of study contacts, click here  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

Phase I/II

**Title:** Phase I/II Randomized Study of BMS-247550 With or Without Estramustine in Patients With Progressive Androgen-Independent Adenocarcinoma of the Prostate  
**Protocol Number:** MSKCC-01064A, NCI-3634  
**Participating Institutions:** Memorial Sloan-Kettering Cancer Center  
**Protocol Status:** Open/active  
**Contact:** William K. Kelly, MD, (212) 639-7992, kellyw@mskcc.org  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

Gynecologic Cancer Phase II

**Title:** Phase I/II Study of BMS-247550 in Patients With Advanced Solid Tumors or Advanced or Recurrent Ovarian Epithelial or Breast Cancer  
**Protocol Number:** AECM-9911378, NCI-98  
**Participating Institution:** Albert Einstein Comprehensive Cancer Center  
**Protocol Status:** Active/new
Contact: Franco M. Muggia, MD, (212) 263-6485

**Title:** Phase II Study of Epothilone B in Relapsed and/or Refractory Stage III or IV Ovarian Cancer, Following Front-Line Treatment With Platinum Plus Taxane-Based Chemotherapy

**Protocol Number:** 3632

**Participating Institution:** Moffitt Cancer Center

**Protocol Status:** In review

**Contact:** Kapil N. Bhalla, MD, (813) 903-6861, bhallak@moffit.usf.edu

**Title:** Phase II Study of BMS-247550 in Patients With Recurrent or Persistent Platinum and Paclitaxel-Refractory Ovarian Epithelial or Primary Peritoneal Cancer

**Protocol Number:** GOG-0126M

**Participating Institution:** Gynecologic Oncology Group

**Protocol Status:** Approved; not yet active

**Contact:** Robert C. Park, Chair, (215) 854-0770

**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Lymphoma Phase II**

**Title:** A Phase II Study of BMS-247550 Epothilone B in Patients With Aggressive Non-Hodgkin’s Lymphoma

**Protocol Number:** 4250

**Participating Institution:** Southern Europe New Drug Organization

**Protocol Status:** In review

**Contact:** Dr. Michele Ghie mini, 011-39-2-559-5349, mghielmini@ticino.com

**Title:** A Phase II Study of BMS-247550 in Low-Grade Lymphoproliferative Disorders

**Protocol Number:** 5342

**Participating Institution:** Memorial Sloan-Kettering Cancer Center

**Protocol Status:** In review

**Contact:** Owen A. O’Connor, MD, (212) 639-8889, oconnoro@mskcc.org

**Melanoma Phase II**

**Title:** A Phase II Study of Epothilone B Analogue, BMS-247550, in Stage IV Malignant Melanoma

**Protocol Number:** 4470

**Participating Institutions:** New York University Medical Center, Montefiore Medical Center, Ludwig Institute for Cancer Research, Albert Einstein College of Medicine, Fox Chase Cancer Center

**Protocol Status:** In review

**Contact:** Anna C. Pavlick, MD, (212) 263-6485, anna.pavlick@med.nyu.edu

**Sarcoma Phase II**

**Title:** Phase II Study of BMS-247550 in Patients With Advanced Soft Tissue Sarcoma

**Protocol Number:** MAYO-MC007C, NCI-3852

**Participating Institutions:** Mayo Clinic Cancer Center, Howard University College of Medicine, Johns Hopkins Oncology Center, Barbara Ann Karmanos Cancer Institute, Washington University School of Medicine, University of Wisconsin Comprehensive Cancer Center

**Protocol Status:** Active

**Contact:** Scott H. Okuno, MD, Chair, (507) 284-2511, okuno.scott@mayo.edu; for a complete listing of study contacts, click [here](http://cancernet.nci.nih.gov/)

**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Solid Tumors Phase I**

**Title:** Phase I Study of BMS-247550 (NSC # 710428D) Given Every 3 Weeks in Patients With Advanced Malignancies

**Protocol Number:** 87

**Participating Institution:** Wayne State University

**Protocol Status:** In review

**Contact:** Patricia M. Lorusso, MD, (313) 745-8860, lorusso@karmanos.org

**Title:** Phase I Study of BMS-247550 in Patients With Advanced Malignancies
Current Clinical Trials of Epothilone B Analog (BMS-247550)  
Published on Physicians Practice (http://www.physicianspractice.com)

**Protocol Number:** UTHSC-IDD-99-32, NCI-150, SACI-IDD-99-32  
**Participating Institutions:** University of Texas Health Science Center, Audie L. Murphy Veterans Affairs Hospital, Saint Luke’s Lutheran Hospital, Cancer Therapy and Research Center  
**Protocol Status:** Active  
**Contact:** Eric K. Rowinsky, MD, Chair, (210) 616-5945, erowinsk@saci.org  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)  
**Title:** Phase I Study of BMS-247550 in Patients With Refractory Neoplasms

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**Protocol Number:** NCI-00-C-0224, NCI-550  
**Participating Institutions:** Center for Cancer Research, Medicine Branch  
**Protocol Status:** Active  
**Contact:** Manish Agrawal, Chair, (301) 435-8724  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)  
**Title:** A Phase I Study of Epothilone B Analogue (BMS-247550) in Combination With Carboplatin in Recurrent and/or Refractory Solid Tumors

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**Protocol Number:** 5306  
**Participating Institution:** Moffitt Cancer Center and Research Institute  
**Protocol Status:** In review  
**Contact:** Daniel M. Sullivan, MD (813) 979-3878, sullivad@moffitt.usf.edu  
**Title:** Phase I Trial and Pharmacokinetic Study of BMS-247550 (NSC # 710428), an Epothilone B Analogue, in Pediatric Patients With Refractory Solid Tumors

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**Protocol Number:** 5425  
**Participating Institution:** National Cancer Institute Pediatric Oncology Branch  
**Protocol Status:** In review  
**Contact:** Brigitte C. Widemann, MD, (301) 496-7387, bw42y@nih.gov  
**Title:** Phase I Trial and Pharmacokinetic Study of BMS-247550 (NSC # 710428), an Epothilone B Analogue, in Pediatric Patients With Refractory Solid Tumors

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**References:**


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Links: