P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

# HerbClip™



**File: ■ Turmeric (*Curcuma longa*)**
**■ Curcumin**
**■ Metastatic Breast Cancer**

**HC 011051-394**

**Date: February 15, 2010**

**RE: Safety/Tolerability of Curcumin plus Docetaxel in Breast Cancer Treatment**

Bayet-Robert M, Kwiatkowski F, Leheurteur M, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biol Ther*. January 2010;9(1):1-7.

Breast cancer is often treated with the chemotherapeutic agent docetaxel, a semisynthetic taxane, its precursor deriving from *Taxus baccata*. However, not all patients respond to docetaxel treatment. Combining agents is common to improve outcomes, but the combination should not significantly increase toxicity. Curcumin is extracted from turmeric (*Curcuma longa*) root. It has activity against human breast cancer cells in vitro. Clinical studies have shown that high doses of curcumin are tolerable in cancer patients. The purpose of this study was to evaluate the maximal tolerated dose of curcumin when combined with docetaxel chemotherapy.

Men or postmenopausal women (≥ 18years) (n = 14; 13 female,1 male) with histologically confirmed (Her2/neu not overexpressed) metastatic or locoregionally recurrent advanced breast cancer who had previously received an anthracycline-based adjuvant chemotherapy, except for primarily metastatic or inoperable patients, participated in this open-label, Phase I clinical trial. The study was conducted at a single center in France. Included patients had a life expectancy of ≥ 3 months. Participants were treated with docetaxel 100 mg/m$^2$ as a 1 hour intravenous infusion on day 1 of each 3-week cycle for 6 cycles. Patients were premedicated with oral methylprednisolone 50 mg 2 times daily, 2 days before and after chemotherapy. Curcumin was formulated as 500 mg capsules containing 450 mg of curcumin (Sabinsa Corporation; Piscataway, New Jersey). Patients consumed 500, 1000, 2000, 4000, 6000, or 8000 mg/day curcumin for 7 consecutive days at each cycle. Dose limiting toxicity was defined as the occurrence of any of the following: (1) grade IV neutropenia (low white blood cell count) lasting for ≥ 7 days, (2) grade III-IV febrile neutropenia (fever with low white blood cell count), (3) grade III lasting for ≥ 7 days or grade IV thrombocytopenia (low platelets), (4) grade III-IV non-hematological toxicity, excluding alopecia (hair loss), nausea, and vomiting, and (5) patient's refusal to continue treatment due to adverse events or relative matter.

Initially, 1 patient was enrolled to each dose of curcumin. If dose limiting toxicity was not observed after 2 cycles of treatment, the subsequent patient was enrolled at the next higher dose. If dose limiting toxicity occurred in 1 patient, 2 additional patients were enrolled at the same dose. If no further dose limiting toxicities were observed in these 2 additional patients, 1 patient was enrolled at the next higher dose. If dose limiting toxicity occurred (2 or 3 toxicities/3 patients) in a dose group, 3 additional patients (for a total of 5 patients, depending on the initial number enrolled) were enrolled in the same dose group. The dose that ≥ 3 of 5 patients experienced dose limiting toxicity would be considered the maximal tolerated dose. The previous dose would be the recommended Phase II dose of curcumin to be combined with docetaxel therapy in advanced and metastatic breast cancer patients. The primary endpoint of this study was to determine the maximal tolerated dose of the combination of curcumin and standard dose of docetaxel.

The docetaxel dose was reduced to 75 mg/m$^2$ in 4 patients to avoid toxicity in the older patients. Ten patients completed the treatment (5 or 6 cycles), and 13 were evaluable for toxicity assessment. Three patients experienced dose limiting adverse event toxicities: 1 patient treated with 6000 mg/day curcumin had grade III diarrhea, 1 patient treated with 8000 mg/day curcumin had grade IV neutropenia, and 1 patient treated with 8000 mg/day curcumin had grade III diarrhea. Also, 2 patients treated with 8000 mg/day curcumin stopped treatment because they considered 16 capsules/day unacceptable (considered a dose limiting toxicity). Hence, the maximal tolerated dose was 8000 mg/day since 4 of 5 patients had dose limiting toxicities. The recommended dose for Phase II trials was 6000 mg/day of curcumin, the next highest acceptable dose. In general, the safety profile of the combination treatment was consistent with the safety profile of docetaxel.

In 7 patients, biological response was documented as a decrease of tumor markers. Tumor markers decreased up to 50% in 4 patients. No progressive disease was observed in any patient. The decreases in vascular endothelial growth factor levels demonstrate the antiangiogenic (reduction in the growth of new blood vessels that supply the tumor) effect of the combination treatment.

This was the first clinical trial to evaluate the combination of curcumin and docetaxel in patients with advanced and metastatic breast cancer. It should be noted that this study was not designed as an efficacy study, but rather as a safety and tolerability study (Phase 1). The results from this study were used to guide a Phase II efficacy study. The authors state that such a Phase II trial is underway to compare curcumin 6000 mg/day plus docetaxel versus docetaxel alone in patients with advanced and metastatic breast cancer.

*—Heather S. Oliff, PhD*

Enclosure: Referenced article reprinted with permission from Landes Bioscience.