In this issue of the Journal, Lu et al. (1) report a clinical trial of chemoradiotherapy with or without the shark cartilage–derived product AE-941 to treat patients with unresectable stage III non–small cell lung cancer. Although the trial did not generate promising results, it has an important story to tell about the modern study of complex natural products. Complex natural products, for example, extracts of parts of plants or animals, infrequently rise through the tiers of preclinical and clinical research to the level of a large-scale, multicenter, randomized controlled clinical trial. This is particularly true of products studied in North America for their anticancer activity. A search of MEDLINE via PubMed revealed only two such trials reported in the past 20 years. One is a study of another shark cartilage product that was performed by the North Central Cancer Treatment Group (NCCTG) (2), and the other a multicenter, randomized, phase II trial of a herbal product, PC-SPES (3).

Both the current trial and the NCCTG shark cartilage trial were solicited by the National Cancer Institute in 1998 as the result of a collaborative venture between the National Cancer Institute and the Office of Alternative Medicine of the National Institutes of Health. The Office of Alternative Medicine, which was the predecessor to the National Center for Complementary and Alternative Medicine, was established in part to support research of unconventional therapies commonly used in the United States. In the years just before the initiation of this trial in 2000, there were several indicators that shark cartilage was prominent among unconventional cancer therapies. In 1993, the television news program, “60 Minutes,” aired a story about shark cartilage as a cancer therapy. By 1997, prominent complementary and alternative medicine practitioners were recommending its use to cancer patients (4). Over the past decade, several surveys in the United States and in other countries have reported that 6%-25% of cancer patients use shark cartilage (5–7).

Some complex natural products have been accepted as drugs in countries with medical practice and regulatory cultures as different as those in Germany and China. Even in the United States, some standardized complex natural products such as heparin and bleomycin are Food and Drug Administration–approved drugs. Few companies in the United States that are currently working with complex natural products have chosen to develop their products as a drug, as opposed to a dietary supplement. However, an encouraging sign is the recent approval by the United States Food and Drug Administration of a standardized fractionated extract of green tea as a topical drug for the treatment of external genital and perianal warts (8).

Many theoretical advantages have been proposed for complex natural products, including that they may be less expensive, less toxic, or both, compared with drugs consisting of purified single active compounds. Other rationales for using complex mixtures as therapeutics have been the opportunity for synergistic effects and the prevention of loss of activity with fractionation of the whole extract. Often, little or no data are offered to rationalize the use of a specific mixture, as is the case with the product used in the current study.

AE-941 is one of those rare products that underwent an extensive research-based development as a drug. In vitro studies indicated that it had little direct cytotoxic effect but rather showed direct inhibition of angiogenesis (9). Very few shark cartilage products have been studied in animal models of cancer; of the two previously published articles cited in MEDLINE (10,11), only one demonstrated anticancer activity in murine squamous cell carcinoma (11). Animal studies of AE-941 showed tumor growth inhibition in more than one model, and the combination of AE-941 with chemotherapy drug cisplatin showed an additive antimetastatic effect in Lewis lung carcinoma (9). Antiangiogenic effects were demonstrated in human subjects taking the oral compound (12). Finally, early-phase trials of AE-941 showed rare signs of tumor shrinkage with more patients experiencing stable disease and evidence of a dose–response effect with regard to survival (13). Consequently, AE-941 represented the most promising cartilage–derived anticancer agent within sight at the time the current trial was initiated.

This study (1) was well designed and conducted and has generated important and useful findings with regard to one specific product, AE-941. No statistically significant differences were noted in overall survival, time to progression, or response rate between the two study arms (placebo vs AE-941). However, questions will arise about the generalization of these findings to other, or all, shark cartilage products, and perhaps, to some or all complex natural products. Generalizations are common in discussions on complementary and alternative medicine practice and research, though the products and interventions are so diverse that often none of the findings from the study of one is relevant to another. Some researchers may have the urge to say a larger question has been answered, thus completely disproving the efficacy of shark cartilage; however, as tempting as this may be, there are reasons to be more reserved in drawing such a conclusion.

First, the current study is missing some important information. The process of standardization, which is critical in
research with complex natural products, was not described for AE-941. How many product lots were used? Was each lot standardized based on content parameters, or an activity assay? How much variability in composition or activity was considered acceptable? Was the best dose used? In the phase I trials of AE-941, no dose-limiting toxicity was identified. Doses higher than 240 mL/d were not studied because this dose “was judged as the maximum acceptable for chronic administration in cancer patients” (13). The authors remark on their inability to do pharmacokinetic studies and the absence of a validated biomarker of antiangiogenic effect, which is a limiting factor for further progress with antiangiogenesis agents in general. Compliance with treatment was also not discussed in the current study.

Given this study’s results (1) and those of smaller trials using powdered shark cartilage dietary supplements (2,14), the question of the potential value of any shark cartilage extract as an effective anticancer agent has become a much less important one to pursue. Others have and are exploring purified components of shark cartilage with activities seen in the unfractionated product, and one or more of these may hold some therapeutic promise (15,16). Also, the slight, but statistically significant, decrease in grade 3 toxicities noted in the AE-941-treated group in the current study may be a sign of activity that is worthy of further investigation. If this is a reproducible effect, the responsible component(s) may not be the same as those with antiangiogenic or antimetastatic activities.

A small group of companies in the United States are pursing the development of cancer therapeutic drugs using complex natural products. The ability of these products to compete with other drug candidates for the attention of the clinical cancer researchers will most likely improve with demonstration of activity in preclinical studies, early-phase clinical trials, or identification of an interesting mechanism of action. Sufficient analysis to allow standardization of a candidate product will be critical to the acceptance of such a drug. The demonstration of active components and biomarkers that permit pharmacokinetic and pharmacodynamic studies in vivo will also be helpful. Implementation of different approaches to phase II trials, such as the randomized discontinuation design for compounds like AE-941 showing predominantly cytostatic activity in preclinical studies or uncontrolled early-phase clinical studies, may also be a useful step before initiating large-scale phase III trials.

The results of the current trial (1) provide valuable information to health-care practitioners and patients for discussions about the use of shark cartilage in cancer management. More research is needed to assess how results from trials such as this one affect complementary and alternative medicine practice patterns and patient use of related agents. The potential value of complex natural products in the anticancer armamentarium remains an open question for many and one that can only be answered one step at a time with high-quality research.

References