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Chemoradiotherapy With or Without AE-941 in Stage III Non–Small Cell Lung Cancer: A Randomized Phase III Trial

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Background   AE-941 is a standardized aqueous shark cartilage extract with antiangiogenic properties that has previously been evaluated in phase I and II clinical trials. Our objective was to determine the effect of adding AE-941 to chemoradiotherapy on overall survival of patients with unresectable stage III non–small cell lung cancer (NSCLC).

Methods   A randomized, double-blinded, placebo-controlled, phase III clinical trial was designed to test the efficacy of AE-941 in unresectable stage III NSCLC patients who were treated with chemoradiotherapy. Between June 5, 2000, and February 6, 2006, 379 eligible patients were enrolled in community and academic oncology centers across the United States and Canada. In February 2006, the trial was closed to new patient entry before meeting the target sample size because of insufficient accrual. All subjects received induction chemotherapy followed by concurrent chemotherapy with chest radiotherapy. Each participating center administered one of the two chemotherapy regimens, either carboplatin and paclitaxel, or cisplatin and vinorelbine. The primary endpoint was overall survival, and secondary endpoints were time to progression, progression-free survival, tumor response rate, and toxic effects. Event–time distributions were estimated by the Kaplan–Meier method. All statistical tests were two-sided.

Results   There was no statistically significant difference in overall survival between the chemoradiotherapy plus AE-941 group (n = 188; median survival = 14.4 months, 95% confidence interval = 12.6 to 17.9 months) and the chemoradiotherapy plus placebo group (n = 191; median survival = 15.6 months, 95% confidence interval = 13.8 to 18.1 months) (*P* = .73). Time to progression, progression-free survival, and tumor response rates were not statistically significantly different between the AE-941 and the placebo groups. No differences between the two groups were observed in common grade 3 or higher toxic effects attributable to chemoradiotherapy.

Conclusions   The addition of AE-941 to chemoradiotherapy did not improve overall survival in patients with unresectable stage III NSCLC. This study does not support the use of shark cartilage–derived products as therapy for lung cancer.

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Lung cancer continues to be the leading cause of cancer-related death in Canada and the United States, estimated to account for 166 280 deaths in 2008 in the United States (1). Based on histology, more than 80% of lung cancers are non–small cell lung cancers (NSCLCs) (2). One-third of the NSCLC patients present with stage III disease, which is often characterized by unresectable, locally advanced tumor. The current standard treatment for stage III NSCLC includes both platinum-based chemotherapy and thoracic radiotherapy (3). Randomized studies have shown that the median survival time in stage III NSCLC patients treated with chemoradiotherapy ranges from 11 to 18 months; therefore, new treatment strategies are needed in such patients to improve overall survival.

Angiogenesis is a recognized hallmark of tumor growth (4), and antiangiogenic therapy can improve survival in NSCLC patients (5). AE-941 (also known as Neovastat) is a standardized, water-soluble, shark cartilage extract with evidence of antiangiogenic and antimetastatic activity (6). Preclinical data on chick embryo, human umbilical vein endothelial cells, and other studies showed evidence of antiangiogenic activity of AE-941, including inhibition of endothelial cell proliferation via induction of apoptosis (7,8). In vitro studies showed that molecules in AE-941 specifically interfere with the binding of vascular endothelial growth factor to its receptor and inhibit several matrix metalloproteinases (MMPs), including MMP-2, -9, and -12 (9,10). Mouse studies using a Lewis lung carcinoma metastasis model demonstrated a dose-dependent

CONTEXT AND CAVEATS

Prior knowledge
New treatment strategies are necessary to improve the overall survival of advanced-stage non–small cell lung cancer patients. AE-941 is a pharmaceutical agent derived from shark cartilage extract and exhibits antiangiogenic and antimetastatic properties.

Study design
A randomized, double-blinded, placebo-controlled trial was designed to evaluate the efficacy of AE-941 in stage III non–small cell lung cancer patients undergoing chemoradiotherapy. The primary endpoint was overall survival. Secondary endpoints were time to progression, progression-free survival, tumor response rate, and toxic effects.

Contribution
No statistically significant difference was observed between the placebo and the AE-941 groups in the primary and secondary endpoints.

Implications
This study does not support the addition of AE-941 to chemoradiotherapy regimen for the effective treatment of advanced-stage non–small cell lung cancer patients.

Limitations
The active molecules in AE-941 are not identified, and there is no knowledge of the pharmacological properties of these molecules.

From the Editors

antitumor and antimetastatic activity of AE-941 when administered orally (7). The antitumor activity was similar to that seen with the chemotherapy drug cisplatin. Moreover, mice receiving AE-941 demonstrated less toxicity.

Previously, an open-label phase I–II trial tested a range of AE-941 doses (30, 60, 120, and 240 mL/d) on 48 patients with locally advanced or metastatic NSCLC (11). Results showed a statistically significant improvement in survival in patients who received higher doses (approximately 180 mL/d in a 70-kg patient) of AE-941, with a median survival of 6.1 vs 4.6 months (P = .026). Approximately, 54% and 40% of the subjects had stages IV and IIIB cancer, respectively, and the majority had received prior chemotherapy and radiotherapy. No dose limiting toxicity was observed at the highest dose of 240 mL/d (11).

Based on the encouraging results of the above-mentioned phase I–II trial, we conducted a phase III trial to investigate whether adding AE-941 to standard chemoradiotherapy improved overall survival in patients with unresectable stage III NSCLC.

Patients and Methods

Patient Selection
Patients aged 18 years or older with histologically verified, untreated, unresectable stage IIIA or IIIB NSCLC were eligible for the study. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 (12), bidimensional or unidimensional measurable disease greater than or equal to 10 mm, serum alanine aminotransferase and/or aspartate aminotransferase

levels less than 1.5 times the upper limit of normal, serum total bilirubin within normal limits, adequate renal function (serum creatinine <1.5 mg/dL or calculated creatinine clearance >60 mL/min), and adequate hematologic function (absolute neutrophil count >1500/μL, platelet count ≥100 000/μL, and hematocrit >30%). Exclusion criteria included pleural effusions (unless cytologically negative for malignant cells); greater than 10% weight loss within the past 3 months; use of cartilage-derived products within 30 days; peripheral neuropathy greater than grade 1; pregnancy; breastfeeding; and history of another malignant disease (except in situ carcinoma of the cervix or nonmelanoma skin cancer), unless curatively treated and without evidence of recurrent disease for greater than 3 years.

Study Design
This study was a multicenter, randomized, double-blind, placebo-controlled trial for stage III NSCLC patients who were candidates for chemoradiotherapy. Before enrolling patients, each participating institution selected one of the two standard combination chemotherapy treatment regimens, either cisplatin and vinorelbine, or carboplatin and paclitaxel. Patients were randomly assigned in a 1:1 ratio to either AE-941 or placebo groups using a central permuted block randomization procedure with stratification for stage (IIIA vs IIIB), chemotherapy regimen (cisplatin and vinorelbine vs carboplatin and paclitaxel), and sex. The coordinating center was the Community Clinical Oncology Program Research Base at the University of Texas M. D. Anderson Cancer Center, Houston, Texas. The study was endorsed by the Radiation Therapy Oncology Group (RTOG). Participating centers included academic and community oncology programs in the United States and Canada, including RTOG member institutions. The protocol was approved by the institutional review boards of all participating institutions and was carried out in accordance with local ethical and legal requirements. All patients provided written informed consent. The study was registered at http://www.clinicaltrials.gov, identifier number NCT00005838.

Randomization and Treatment Allocation
Between June 5, 2000, and February 6, 2006, a total of 379 patients were randomly assigned to receive 120 mL of AE-941 (n = 188) or an equal dose of placebo (n = 191) administered orally twice daily. The dose was based on the results of a previous phase I–II trial (11). Patients began their study drug at the start of chemoradiotherapy and continued until disease progression or the development of unacceptable toxic effects. The study drug was stored frozen and defrosted immediately before ingestion. Subjects received 60 Gy of thoracic radiotherapy in 30 fractions, prescribed at isocenter point without inhomogeneity correction. Radiotherapy was initiated on day 50 after the completion of induction chemotherapy. The use of conformal radiotherapy was optional. Each participating center selected one of the two intravenous chemotherapy regimens. One chemotherapy regimen was carboplatin (area under the concentration–time curve 6) and paclitaxel (200 mg/m²) every 21 days for two cycles followed by thoracic radiotherapy with concurrent weekly carboplatin (area under the concentration–time curve 2) and paclitaxel (45 mg/m²) for six doses. The other chemotherapy regimen was cisplatin (75 mg/m²,

day 1) and vinorelbine (30 mg/m², days 1 and 8) every 21 days for two cycles followed by thoracic radiotherapy with concurrent cisplatin (75 mg/m², day 1) and vinorelbine (15 mg/m², days 1 and 8) every 21 days for two cycles.

Tumor status was assessed at baseline, before thoracic radiotherapy, and at 6 weeks after the completion of radiotherapy with chest computed tomography. Subsequent imaging included chest radiographs every 3 months and chest tomography every 6 months for 3 years, with the latter reduced to every 12 months after 3 years. Toxic effects were assessed according to the common toxicity criteria grading system (version 2.0) of the National Cancer Institute (NCI) (13). Patients who discontinued AE-941 or placebo were contacted every 3 months to determine their survival status.

Endpoints and Statistical Methods

The primary endpoint of the trial was overall survival, defined as the time from randomization to the date of death. The secondary endpoints were time to progression (TTP), progression-free survival, tumor response rate, and toxic effects. TTP was defined as the time from randomization to the date of disease progression documented by imaging studies. Progression-free survival was defined as the time from randomization to the date of disease progression or death from any cause. Tumor response was determined in accordance with standard World Health Organization criteria (14).

The original projected sample size was 756 patients based on the following assumptions: a 13-month median survival period for the control group, a two-sided type I error (α = .05), a 36-month accrual period, an additional 24-month follow-up period, and an estimated 636 observed deaths. This sample size provided 80% power to detect a 25% difference in median survival between the two groups. The study design specified conducting an interim toxicity analysis after 40 patients were randomly assigned and an interim survival analysis after 320 deaths occurred. After 68 months of accrual (June 5, 2000, to February 6, 2006), 51% of the target sample size (384 patients) had been entered onto the trial. The trial design is shown in Figure 1. Five patients were rendered ineligible for the trial and excluded from the primary analysis: three patients because of incorrect disease stage, one patient withdrew consent, and one patient for unspecified reasons. The remaining 379 eligible patients were included in the primary analysis, with 188 patients randomly assigned to treatment with AE-941 and 191 patients randomly assigned to receive placebo. A change in the per-case financial reimbursement to the participating sites in April 1, 2004 led to a dramatic reduction in the rate of accrual. Based on the study's low accrual, the primary sponsor, NCI, recommended closure of the trial to the Institutional Data Monitoring Committee (DMC). At the time, the study had not yet reached the scheduled interim analysis with 320 observed deaths. The DMC subsequently performed an unplanned interim analysis of the trial, which included futility analyses. The DMC found no statistically significant difference in overall survival between the two treatment groups. Although continuing the trial until completion of accrual was not a viable option, futility analyses were performed based on calculating the predictive probability of the chance of having a positive study at the end of the trial should the study be carried out to reach its planned sample size and the current trend continued. The predictive probability calculation assumes
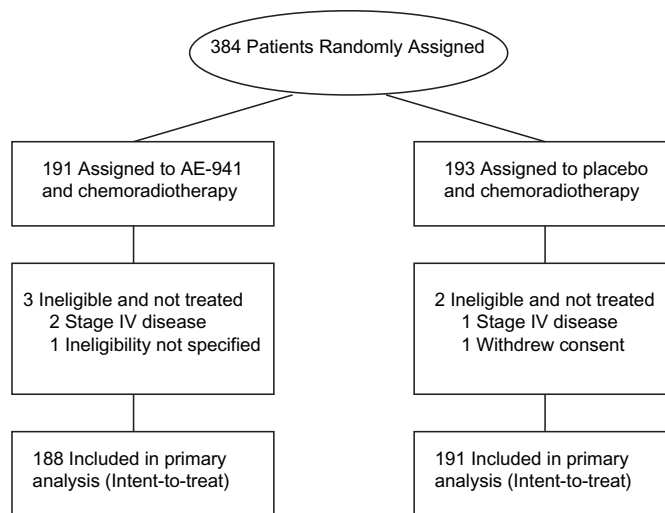

Figure 1. A CONSORT diagram of study design and participants. Ineligible patients who were not treated were excluded from the study analysis. All remaining patients were included in the primary intent-to-treat analysis.

that the overall survival for each arm follows an exponential distribution and the parameter of the exponential distribution follows a gamma distribution. Using the Bayesian predictive probability calculation, at the end of the study, if $\Pr(l_A > l_C \mid \text{data})$ is greater than 0.975, AE-941 is declared efficacious (Pr = probability; l_A and l_C correspond to the parameters of the AE-941 and control group, respectively). The calculation showed that if the trial were conducted to its completion by enrolling the targeted 756 patients, the probability that the AE-941 group would have a lower hazard ratio of death was 0.026.

Based on these data, the DMC concurred with the NCI recommendations to close the trial to further accrual. Enrollment was halted at 384 patients on February 6, 2006.

Event–time distributions were estimated by the Kaplan–Meier method. Both the log-rank test and the stratified log-rank test based on the three-tiered stratification method were used to compare event-free survival between groups. When appropriate, 95% confidence intervals (CIs) were provided. A multivariable Cox proportional hazards model was used for independent predictors of survival analysis. Proportional hazards assumption was verified using the test proposed by Grambsch and Therneau (15). The χ^2 test was used to compare categorical variables between groups. All tests were two-sided, and P values less than .05 were considered statistically significant. All analyses were performed using statistical software SAS v.9.1 (SAS Institute Inc., Cary, NC) and S-plus v.8.0 (TIBCO Software Inc., Palo Alto, CA).

Results

Patients

The baseline characteristics of the eligible patients by treatment group (AE-941 vs placebo) are shown in Table 1. The two groups were equally balanced with regard to sex, age, stage, chemotherapy regimen, race, performance status, and NSCLC histology. The results reported here include follow-up through November 30, 2006, with a median follow-up of 3.7 years and 283 observed deaths.

Table 1. Baseline characteristics of patients*

Characteristic	AE-941 (n = 188)	Placebo (n = 191)	P†
Age, median (range), y	62.7 (37.6–83.4)	62.9 (36.9–84.4)	.46
Sex, No. (%)			.66
Male	111 (59.0)	117 (61.3)	
Female	77 (41.0)	74 (38.7)	
Stage, No. (%)			.63
IIIA	81 (43.1)	87 (45.5)	
IIIB	107 (56.9)	104 (54.5)	
Chemotherapy regimen, No. (%)			.94
Carboplatin/paclitaxel	109 (58.0)	110 (57.6)	
Cisplatin/vinorelbine	79 (42.0)	81 (42.4)	
Race, No. (%)			.94
White	172 (91.5)	175 (91.6)	
Black	8 (4.3)	9 (4.7)	
Other	8 (4.2)	7 (3.7)	
ECOG performance status, No. (%)			.95
0	88 (46.8)	90 (47.1)	
1	100 (53.2)	101 (52.9)	
Histology, No. (%)			.09
Adenocarcinoma	76 (40.4)	65 (34.0)	
Squamous cell carcinoma	63 (33.5)	64 (33.5)	
Large cell carcinoma	13 (6.9)	7 (3.7)	
Other or NOS	36 (19.2)	55 (28.8)	

* Results include follow-up through November 30, 2006, with a median follow-up of 3.7 years. ECOG = Eastern Cooperative Oncology Group; NOS = not otherwise specified.

† P values (two-sided) were calculated using the Student t test for continuous variables and the χ^2 test for categorical variables.

Efficacy of AE-941

There was no statistically significant difference in the primary endpoint of overall survival between the AE-941 and the placebo groups. The median survival period was 14.4 months (95% CI = 12.6 to 17.9 months) in patients who received AE-941 with chemoradiotherapy vs 15.6 months (95% CI = 13.8 to 18.1 months) in patients who received placebo with chemoradiotherapy (P = .73, log-rank test; P = .60, stratified log-rank test) (Figure 2, A). At years 1, 3, and 5, overall survival rates in the AE-941 group were 59%, 25%, and 14%, respectively, and overall survival rates in the placebo group were 61%, 21%, and 14%, respectively.

There was no statistically significant difference between the AE-941 and the placebo groups in the secondary endpoints of the trial. The median TTP in the AE-941 group was 11.3 months (95% CI = 9.0 to 16.8 months) vs a median TTP of 10.7 months (95% CI = 9.5 to 21.6 months) in the placebo group (P = .65, log-rank test; P = .82, stratified log-rank test) (Figure 2, B). Similar results were obtained for the analyses with progression-free survival (data not shown).

A comparable number of deaths occurred in the AE-941 and placebo groups before documented disease progression. Most of these deaths, 37 of the 49 in the AE-941 group and 41 of the 55 in the placebo group, were judged to be cancer related.

Analyses using multivariable Cox proportional hazards models incorporating treatment group and the three stratification factors (stage of lung cancer, sex, and chemotherapy regimen) did not demonstrate any statistically significant associations between

these four variables and overall survival or TTP (Table 2). The hazard ratio indicated improved overall survival with the cisplatin and vinorelbine chemotherapy regimen vs the carboplatin and paclitaxel chemotherapy regimen; however, the difference was not statistically significant (P = .14). Tumor response rates to therapy were 39% and 48% in the AE-941 and placebo groups, respectively (P = .12).

Toxic Effects

Both AE-941 and placebo were well tolerated by the patients, and the adverse events observed during the trial were primarily attributable to chemotherapy, to radiotherapy, or to the cancer itself. A prespecified interim toxicity analysis of the first 40 patients by the DMC demonstrated no difference in toxic effects between the two groups that would warrant early closure of the trial. The most frequent grade 3 or higher toxic effects, regardless of attribution, are listed in Table 3. No statistically significant differences were observed in the rates of these toxicities between the two groups. Less common grade 3 or higher hematologic toxic effects included thrombocytopenia and anemia. Thrombocytopenia occurred in 5% and 3% of subjects in the AE-941 and placebo groups, respectively (P = .42), and anemia occurred in 3% of subjects in both groups. Among the grade 3 or higher adverse events, 5% and 6% were judged to be possibly or probably attributable to AE-941 and placebo, respectively (P = .26). Overall, fewer subjects in the AE-941 group experienced any grade 3 or higher adverse events (66% vs 77%, P = .018). During the study period, there were 20 and 29 deaths in the AE-941 and placebo groups, respectively. None of these deaths were attributed to either AE-941 or placebo.

Discussion

In this trial, the addition of AE-941 to standard chemoradiotherapy did not improve overall survival, progression-free survival, or response rates in patients with locally advanced NSCLC. To better understand the ramifications of these results, it is worthwhile to briefly review the genesis of this clinical trial. The study drug, AE-941, was selected independently by the NCI Cancer Therapy Evaluation Program as a shark cartilage–derived product that merited advanced clinical testing based on preclinical and clinical data supporting antiangiogenic activity and improved outcome in patients with advanced NSCLC (7,8,11). It is noteworthy that AE-941 was developed as a pharmaceutical agent through the standard process of clinical trial testing, and AE-941 has never been available as an over-the-counter dietary supplement.

Dating back to 1976, more than 40 publications in the medical literature, including high-impact journals beyond the scope of cancer, were related to shark cartilage and its possible use for cancer treatment. The willingness of the NCI to fund this trial was influenced by the widespread use of poorly regulated complementary and alternative medicine products by patients likely to be vulnerable to unsubstantiated marketing claims. Products such as shark cartilage–derived agents are widely used among patients with various types of advanced cancer (16,17). Rigorous clinical testing of a standardized shark cartilage–derived compound was deemed to be a priority because results of such a study could have a broad public health impact.
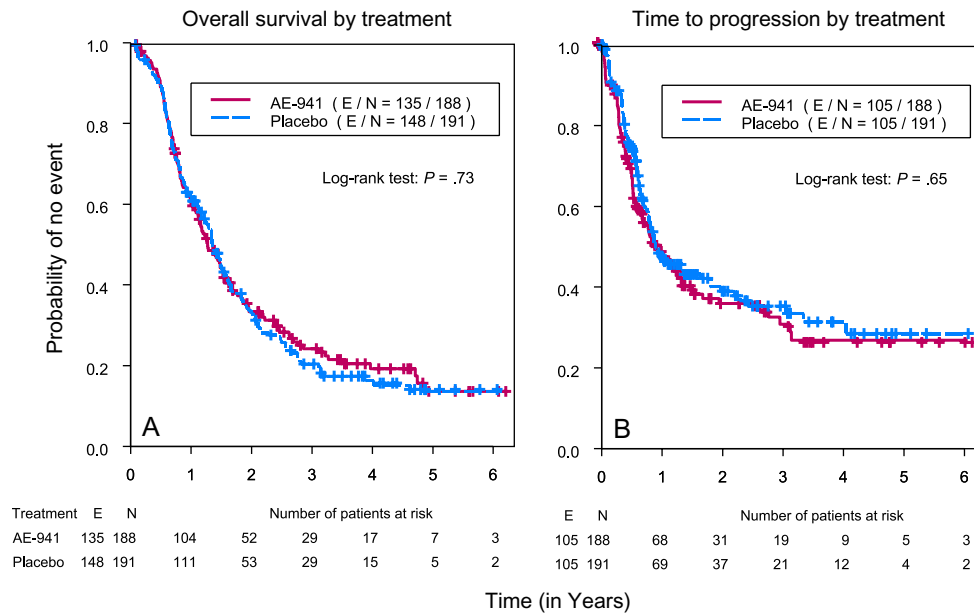
Figure 2. Survival rates from time of randomization estimated using Kaplan–Meier analyses. **A**) Overall survival. **B**) Time to progression. In each treatment group, E = number of events; N = total number of patients. Log-rank test *P* values (two-sided) are provided.

To our knowledge, this report represents the first published phase III trial of a shark cartilage–derived pharmaceutical agent. Although this trial was ongoing, AE-941 was evaluated in another phase III trial in metastatic renal cell carcinoma patients refractory to immunotherapy, but the results were presented only in abstract form and as a press release from the manufacturer (Aeterna Zentaris, Inc, Quebec City, Quebec, Canada) (18,19). Unfortunately, this latter trial also failed to reach its primary endpoint of improving overall survival, and AE-941 is no longer in clinical development.

One limitation of this trial is the lack of available pharmacokinetic and pharmacodynamic correlative studies. AE-941 is a standardized extract of a natural product, and currently, the active molecules in this extract remain poorly understood. Therefore,

there have been no human pharmacokinetic studies or validated pharmacodynamic or predictive biomarkers of activity. The absence of validated pharmacokinetic and pharmacodynamic assays clearly limits our ability to investigate potential explanations for AE-941's lack of activity observed in our study. The absence of predictive biomarkers also resulted in a study population of unselected NSCLC patients, and this type of trial design may further compromise the ability to demonstrate efficacy of targeted agents.

Several shark cartilage crude extracts, sold over the counter as dietary supplements, have also been tested in clinical trials (20,21). Unlike drugs, dietary supplements do not require FDA approval before marketing. A phase III trial of Benefin Shark Cartilage (LaneLabs, Allendale, NJ) in advanced cancer patients was conducted, although it was closed early because of lack of accrual. With a total of 83 evaluable patients, the study failed to demonstrate an improvement in its primary endpoint of overall survival (20). Another shark cartilage dietary supplement was tested in a phase I–II trial in 60 patients with previously treated advanced

Table 2. Multivariable analyses of treatment group and stratification factors and their associations with overall survival and time to progression*

	Overall survival		Time to progression	
Factor	**HR (95% CI)**	**P†**	**HR (95% CI)**	**P†**
Treatment group				
AE-941 vs placebo	0.95 (0.75 to 1.20)	.65	1.06 (0.81 to 1.38)	.70
Stage				
IIIB vs IIIA	1.13 (0.89 to 1.43)	.31	1.05 (0.80 to 1.39)	.72
Chemotherapy regimen				
Carboplatin vs cisplatin	1.20 (0.94 to 1.52)	.14	1.17 (0.89 to 1.55)	.27
Sex				
Male vs female	1.04 (0.82 to 1.32)	.76	1.31 (0.98 to 1.74)	.07

* Multivariable Cox proportional hazards model adjusted for treatment group, stage, chemotherapy regimen, and sex. CI = confidence interval; HR = hazard ratio.

† *P* values (two-sided) were calculated using the Wald test under the Cox proportional hazards model.

Table 3. Most frequent grades 3 to 5 toxic effects in stage III non–small cell lung cancer patients treated with either chemoradiotherapy and AE-941 or chemoradiotherapy and placebo

	% of patients		
Toxic effect	**AE-941**	**Placebo**	**P***
Dyspnea	26	31	.57
Neutropenia	20	26	.43
Esophagitis	20	15	.38
Fatigue	14	17	.71
Pneumonitis†	8	12	.49
Febrile neutropenia‡	6	8	.79

* *P* values (two-sided) were calculated using the χ² test.

† Includes one death in the AE-941 group and two deaths in the placebo group.

‡ Includes one death in the AE-941 group and two deaths in the placebo group.

cancers. No responses were observed, and the investigators concluded that there was no indication of anticancer activity (21).

Although our study did not reach its original accrual goal, it is nevertheless the largest phase III study ever conducted, to our knowledge, of a shark cartilage–derived agent, and the study outcome is unambiguous. Unlike the aforementioned shark cartilage dietary supplements, AE-941 was manufactured and developed as an anticancer drug. Therefore, these results represent the highest level of clinical data available for the role of a shark cartilage–derived agent as a cancer therapy. Another strength of our study is the recruitment of subjects from both academic and community oncology centers, which enhances the generalizability of these findings. We hope that this trial will provide physicians with relevant evidence-based information that can be conveyed to cancer patients who inquire about the activity of shark cartilage in their disease.

Although the results of our study were negative, other antiangiogenic drugs have demonstrated clinical activity in NSCLC. A phase III trial of bevacizumab, a monoclonal antibody against vascular endothelial growth factor, in selected patients with non-squamous NSCLC demonstrated a statistically significant survival benefit when combined with paclitaxel and carboplatin (5), leading to approval for first-line treatment in the United States. Several oral small molecules, such as vandetanib, sorafenib, and sunitinib, which target vascular endothelial growth factor receptors and other receptor tyrosine kinases, are in advanced phase III testing in NSCLC after phase II studies yielded encouraging results (22–25). Other antiangiogenic compounds in different stages of clinical development include thalidomide analogues, integrin inhibitors, and small-molecule vascular disrupting agents (26).

This study reports a rigorous attempt to address a valid scientific question related to the use of a shark cartilage product in a specific and common treatment setting. The addition of AE-941 to chemoradiotherapy did not improve overall survival in patients with unresectable stage III NSCLC, and therefore, these results do not support the use of shark cartilage–derived products as a therapy for lung cancer.

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Notes

The principal investigator (C. Lu) and the study biostatistician (J. J. Lee) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the

manuscript draft and approved the final version for submission. No authors reported financial disclosures. National Cancer Institute was involved in the design and conduct of the study, as well as review and approval of the manuscript. Aeterna Zentaris, Inc, was not involved in the design and conduct of the study. Aeterna Zentaris, Inc, was allowed to review the manuscript before submission.

The participating centers were Bloomington Hospital, Springfield, IL; CHUM-Saint Luc Hospital, Greenfield Park, QC, Canada; CHUS-Hopital Fleurimont, Fleurimont, QC, Canada; CancerCare Manitoba, Winnipeg, MB, Canada; Cape Breton Cancer Centre, Sydney, NS, Canada; Carle Clinic Association, Urbana, IL; Central Illinois CCOP, Decatur, IL; Centre De Sante Et De Services Sociaux De Chicoutimi, Chicoutimi, QC, Canada; Centre Regional de Sante et de Services Sociaux Rimouski, Rimouski, QC, Canada; Christus St Frances Cabrini Hospital, Alexandria, LA; Greenville CCOP, Greenville, SC; Hartford Hospital, Hartford, CT; Ingalls Memorial Hospital, Harvey, IL; Kalamazoo CCOP, Kalamazoo, MI; Kansas City CCOP, Kansas City, MO; Kingston General Hospital, Kingston, ON, Canada; LDS Hospital, Salt Lake City, UT; Lakeridge Health Oshawa, Oshawa, ON, Canada; M. D. Anderson Cancer Center-Orlando, Orlando, FL; Marshfield Clinic, Marshfield, WI; McGill University Department of Oncology, Montreal, QC, Canada; Methodist Cancer Center, Omaha, NE; Metro-Minnesota CCOP, St Louis Park, MN; Michigan Cancer Research Consortium Community Clinical Oncology Program, Ann Arbor, MI; Nevada Cancer Research Foundation CCOP, Las Vegas, NV; Norwalk Hospital, Norwalk, CT; Ottawa Regional Cancer Center, Ottawa, ON, Canada; Ozark Health Ventures, LLC, Springfield, MO; Saint Clare's Hospital, East Syracuse, NY; Saint John's Hospital, Springfield, MO; San Juan Minority Based CCOP, San Juan, PR; Santa Rosa Memorial Hospital, Santa Rosa, CA; Scott and White Memorial Hospital, Temple, TX; Southern Illinois University, Springfield, IL; Summa Health System, Akron, OH; Tallahassee Memorial Hospital, Tallahassee, FL; Thunder Bay Regional Health Sciences Centre, Thunder Bay, ON, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Trinity Cancer Care Center, Minot, ND; University of Connecticut, Farmington, CT; University of Florida Shands Cancer Center, Gainesville, FL; University of Missouri—Ellis Fischel, Columbia, MO; University of Texas M. D. Anderson Cancer Center, Houston, TX; Upstate Carolina CCOP, Spartanburg, SC; Veteran's Administration Medical Center, Wichita, KS; Virginia Mason CCOP, Seattle, WA; Wichita CCOP, Wichita, KS; Florida Radiation Oncology Group, Jacksonville, FL; Jewish General Hospital, Montreal, QC, Canada; Gonzalez Martinez Hospital, San Juan, PR.

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