VOLUME 26 · NUMBER 11 · APRIL 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial Comparing Carboplatin, Paclitaxel, and Bexarotene With Carboplatin and Paclitaxel in Chemotherapy-Naïve Patients With Advanced or Metastatic Non–Small-Cell Lung Cancer: SPIRIT II

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Submitted June 8, 2007; accepted November 5, 2007.

Presented in part at the 41st Annual Meeting of the American Society of Clinical Oncology, May 13-17, 2005, Orlando, FL; and the 11th World Conference on Lung Cancer, July 3-6, 2005, Barcelona, Spain.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2611-1879/$20.00

DOI: 10.1200/JCO.2007.12.2689

ABSTRACT

Purpose
The purpose of this study was to determine whether addition of the synthetic rexinoid bexarotene (Targretin; Eisai Inc, Woodcliff Lake, NJ) to standard first-line carboplatin and paclitaxel therapy provides additional survival benefit in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Patients with stage IIIB disease with pleural effusion, or stage IV NSCLC and Eastern Cooperative Oncology Group performance status 0 to 1, were randomly assigned to bexarotene 400 mg/m^2/d combined with carboplatin and paclitaxel, or assigned to carboplatin and paclitaxel alone. Bexarotene patients also received lipid-lowering agents on or before day 1. The primary efficacy end point was overall survival; secondary efficacy and supportive analyses were also conducted.

Results
A total of 612 patients (306 per arm) were enrolled onto the study. In the intent-to-treat population, no significant difference in survival occurred between the two arms. However, a subpopulation (approximately 40%) of bexarotene-treated patients who experienced National Cancer Institute grade 3/4 hypertriglyceridemia had significantly longer median survival than control patients (12.4 *v* 9.2 months; log-rank, $P = .014$). Bexarotene-treated patients with grade 3/4 hypertriglyceridemia who received the most benefit included those who were male, were smokers, experienced 6-month prior weight loss $\geq 5\%$, and had stage IV disease. The incidence and severity of most adverse events were similar between arms, although hyperlipidemia, neutropenia, fatigue, leukopenia, arthralgia, and diarrhea were more frequent in the bexarotene arm.

Conclusion
Although the addition of bexarotene to chemotherapy did not improve survival in the overall study population, occurrence of high-grade hypertriglyceridemia in bexarotene-treated patients strongly correlated with increased survival, suggesting that bexarotene may benefit a segment of first-line NSCLC patients.

J Clin Oncol 26:1879-1885. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Retinoid receptors, which play a critical role in cellular growth modulation, division, induction of differentiation, and activation of apoptosis, have been investigated as potential targets for novel cancer therapies for several years. The expression of many retinoid receptors, including retinoid-X receptor (RXR) β (RXRβ), is reduced in some non–small-cell lung cancer (NSCLC) biopsy specimens, and increased RXRβ expression has been associated with an increased survival in NSCLC patients.[1] Bexarotene (Targretin; Eisai Inc, Woodcliff Lake, NJ) is a synthetic retinoid modulator of RXR used for the treatment of cutaneous T-cell lymphoma.[2] It selectively binds and activates various RXR subtypes known to form heterodimers that transcriptionally regulate several gene networks.[3]

Bexarotene enhances the activity of several chemotherapeutic agents used in NSCLC, and has been shown to prevent or overcome paclitaxel resistance in NSCLC cell lines.[4] In early trials, bexarotene demonstrated both satisfactory safety and promising efficacy.[5,6] Impressive survival of 11.1 months was observed in phase I monotherapy trials in chemotherapy-refractory patients (Table 1). Additionally, in a first-line metastatic NSCLC phase I/II study, bexarotene combined with cisplatin and vinorelbine

Table 1. Outcomes of Bexarotene Phase I/II Studies in Stage IIIB/IV NSCLC

Study	Study Phase	No. of Patients	Outcome
Monotherapy MTD in multiple-treatment failures[5,12]	I	20	MTD = 400 mg/m^2; median survival = 11.1 months
Monotherapy MTD in NSCLC patients with multiple-treatment failures[6]	I	16	MTD = 500 mg/m^2
First-line bexarotene + cisplatin and vinorelbine[7]	I/II	43	Median survival = 13.7 months
Bexarotene monotherapy 300 *v* 600 mg/m^2 *v* placebo as maintenance after first-line treatment[8]	II/III	52	TTP = 18.3 weeks *v* 8 weeks for placebo
First-line bexarotene + carboplatin and paclitaxel[9]	I/II	43	33% OR + 52% SD; MTD = 500 mg/m^2/d
First-line bexarotene + carboplatin and gemcitabine[10]	II	48	Median survival = 12.7 months; median EFS = 7.5 months
Bexarotene monotherapy in NSCLC patients with multiple-treatment failures[11]	II	146	Median survival (all patients) = 5 months; median survival (patients with bexarotene-induced hypertriglyceridemia and skin rash) = 12 months

Abbreviations: NSCLC, non–small-cell lung cancer; MTD, maximum-tolerated dose; TTP, time to tumor progression; OR, objective response; SD, stable disease; EFS, event-free survival.

resulted in a median survival of 13.7 months (Table 1).[7] Based on the promising survival results from multiple phase I/II studies, two phase III trials were initiated to compare the efficacy and safety of bexarotene combined with carboplatin and paclitaxel (Studies Providing Investigational Research in Targretin [SPIRIT] II study, described in this article), or cisplatin/vinorelbine (SPIRIT I study)[7a] in advanced NSCLC. The primary end point of the SPIRIT II study was to determine overall survival, with a secondary end point of 2-year survival. Descriptive analyses included progression-free survival (PFS), number of cycles, doses of chemotherapy administered, and tumor response (discussed in Assessments); subgroup evaluation of population pharmacokinetics, and biochemical and genetic biomarkers are presented elsewhere. Dose- and time-dependent hyperlipidemia—primarily hypertriglyceridemia—was observed in early bexarotene studies and was expected because of known effects of retinoids on lipid metabolism.[13] This led to the administration of antilipid agents from baseline.

PATIENTS AND METHODS

Eligibility Criteria

The main eligibility criteria for this study included histologically or cytologically confirmed NSCLC (stage IIIB disease with pleural effusion, or stage IV disease), no prior platinum-based chemotherapy for any indication, and at least one measurable or assessable NSCLC lesion that had not been previously irradiated unless radiation therapy occurred more than 3 weeks before study entry and the lesion had progressed after the radiation therapy. Additional criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, anticipation of completion of at least four cycles of carboplatin/paclitaxel chemotherapy in approximately 3 months, no known brain metastasis, and acceptable organ function. Patients were required to have normal or normalized triglyceride levels before the study initiation. Informed consent was obtained from eligible patients before prestudy assessments. The study protocol was approved by the institutional review board or the ethics committee of each participating center in agreement with local regulatory requirements (Fig 1).

Trial Design

This was a multicenter, multinational, randomized, open-label, comparative phase III study. Before the patients were randomly assigned, they were stratified according to sex and disease stage (TNM stage IIIB disease with pleural effusion *v* stage IV disease). Eligible patients were randomly enrolled in one of two treatment arms (Fig 2). All patients received paclitaxel 200 mg/m^2 infused intravenously over 3 hours, followed by carboplatin-administered intravenously, dose-adjusted to achieve area under the time-concentration curve (AUC) 6 according to the Calvert formula once every 3 weeks. All patients were scheduled to have at least four cycles of chemotherapy, consisting of one cycle every 3 weeks. Bexarotene (75-mg capsules) 400 mg/m^2/d was administered orally once a day, and the total once-daily dose was rounded to the nearest 37.5 mg. If the initial dosage was not well tolerated, it was reduced by increments of 100 mg/m^2/d, or suspended if required. Patients enrolled in this arm also received an antilipid agent beginning on or before day 1. The suggested antilipid agents were atorvastatin and fenofibrate, with dose adjustments performed as necessary.

Statistical Analysis

The statistical design of this study aimed to detect a $\geq$ 30% survival benefit in the bexarotene arm, with 80% power at a two-sided, 5% α level using the log-rank test. A 600-patient accrual (300 in each arm) was planned to achieve the target of 456 death events; 612 patients (306 patients in the bexarotene arm, and 306 patients in the control arm) were actually enrolled onto the study and considered to be the intent-to-treat (ITT) population. The median follow-up period was 21.8 months (range, 18.3 to 32.5 months). The primary efficacy analysis was a log-rank test for overall survival between the two arms in ITT patients, stratifying for TNM stage and sex; the secondary efficacy end point was a 2-year survival rate. Other end points included median survival, 1-year survival, median PFS, and safety evaluations. The Cox regression method was used in additional survival analyses. Safety evaluation was based on all patients who were exposed to at least one dose of any study medication. The unplanned and retrospective analyses were conducted on a hypertriglyceridemia subgroup in the bexarotene arm to evaluate further the effects of bexarotene on this unique segment of NSCLC patients.

Assessments

During the treatment phase of the study, detailed data were collected on efficacy, safety, and all concomitant medications and therapies until the first follow-up visit, which was scheduled for 4 weeks after discontinuation of the last study drug. Tumor response was assessed using modified WHO criteria. In addition—subsequent to the discontinuation of the last study drug—information was collected on all medications and therapies relevant to the treatment of NSCLC on a periodic and frequent basis until the patient's death.

Levels of lipids, thyroid-stimulating hormone, and thyroid marker thyroxine were evaluated regularly in bexarotene-treated patients only. At the beginning of the study, patients enrolled in the bexarotene arm underwent more frequent CBC monitoring, which may have initially altered observed neutropenia incidence in the bexarotene arm. Subsequently, the protocol was amended to include CBC monitoring every 3 weeks in both treatment arms. Approximately 49% of the patients enrolled onto the study after this protocol amendment.

RESULTS

Patients

This multicenter study was primarily conducted in the United States (67%), but the study also enrolled patients from Canada (5%),

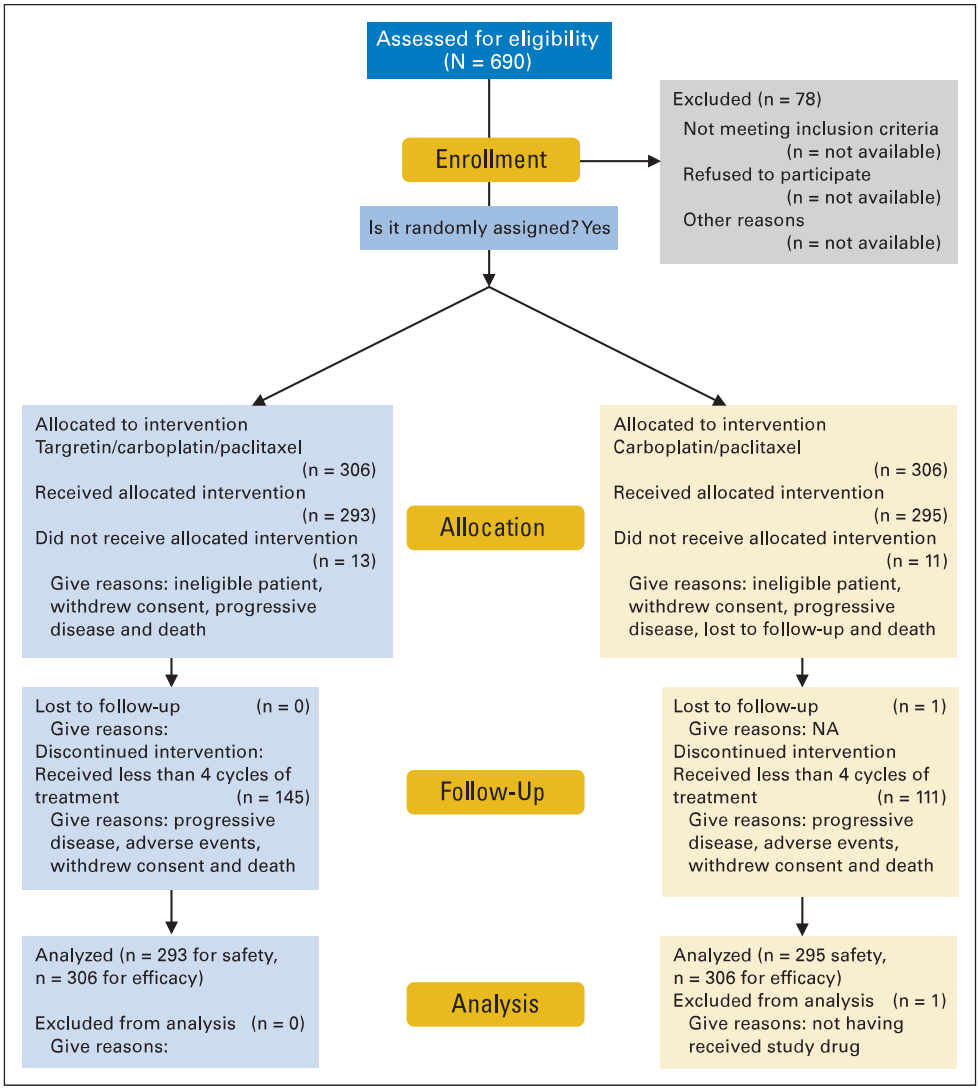

Fig 1. CONSORT diagram.

Germany (18%), France (7%), Spain (3%), and Austria (1%). Patient demographics are listed in Table 2. The patient populations in the two treatment arms were well balanced, with no significant differences between the two groups. In total, 612 patients were enrolled onto the study, with 588 patients (96%) receiving at least one dose of any of the study drugs. Of these, 293 patients (96%) were in the bexarotene arm and 295 patients (96%) were in the control arm. Patients in the bexarotene arm received a mean of 3.7 cycles of carboplatin/paclitaxel, whereas those in the control arm received a mean of 4.3 cycles ($P = .0002$). The average dose of carboplatin was 5.8 AUC (total dose, 21.1 AUC), and 5.9 AUC (total dose, 25.4 AUC) in the bexarotene and control arms, respectively; the average dose of paclitaxel was 194.2 mg/m^2 (total dose, 708.1 mg/m^2), and 195.5 mg/m^2 (total dose, 844.8 mg/m^2) in the bexarotene and control arms, respectively ($P < .0001$).

The overall bexarotene mean daily dose was 315 mg/m^2, with 60% of patients receiving doses above the mean and 40% of patients receiving doses below the mean. Patients in the bexarotene arm were given the following antilipid agents starting on or before day 1: atorvastatin (72%), other statins (14%), fenofibrate (18%), ciprofibrate (< 1%), or other antilipid agents (2%). Some patients received more than one of these antilipid agents.

The poststudy anticancer therapies received by the two treatment arms were similar (Appendix Table A1, online only).

Efficacy

No significant differences in the ITT population were observed between the two treatment arms with respect to the primary efficacy end point and overall survival. Median survival in the ITT analysis was 8.5 months in the bexarotene arm versus 9.2 months in the control arm, with a projected 2-year survival of 12.4% in the bexarotene arm and 16.3% in the control arm ($P = .2$; Appendix Fig A1A, online only). ITT PFS was 4.1 months in the bexarotene arm and 4.9 months in the control arm ($P = .061$; Appendix Fig A1B). Subset analysis of survival hazard ratios revealed no significant difference between the two treatment arms with respect to sex, cancer stage, histology, prior weight loss, smoking, or Eastern Cooperative Oncology Group performance status.

To rule out the possibility that the type of antilipid agent administered might have affected survival, survival in the bexarotene arm was also analyzed with respect to various antilipid agents. Median survival was 9.0 months among 232 patients treated with statins, and 7.7 months for 37 patients treated with fibrates (not significant).

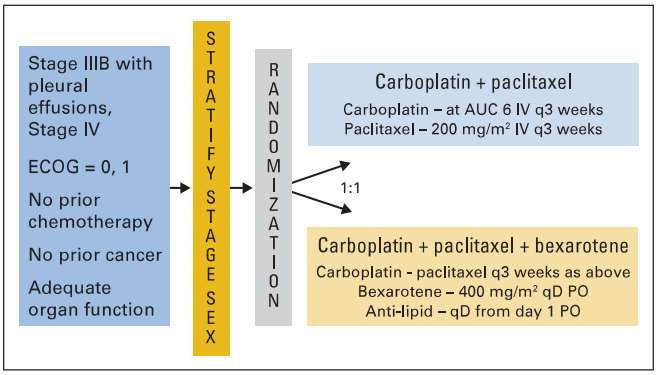

Fig 2. SPIRIT II study schema. ECOG, Eastern Cooperative Oncology Group; AUC, area under the time-concentration curve; IV, intravenously; PO, orally; qD, daily.

Tumor response did not differ significantly between the two treatment arms. Patients enrolled in the bexarotene arm had an overall tumor response rate of 19.3%, compared to an overall tumor response rate of 23.5% for patients enrolled in the control arm ($P = .24$). Disease stabilization was achieved in 40.2% and 37.6% of patients in the bexarotene and control arms, respectively.

Hypertriglyceridemia Subgroup Analysis

Lipid elevation is a well-documented adverse effect of retinoid therapy in general, and bexarotene specifically.[13] Significant correlations between bexarotene-induced hypertriglyceridemia and survival have been noted during retrospective analyses of both bexarotene monotherapy[11] and combination therapy (unpublished internal data) from previous phase I/II studies in NSCLC patients.

As expected, hypertriglyceridemia was noted in the majority of patients in the bexarotene arm. To determine whether bexarotene may have been under-administered in an effort to minimize hypertriglyceridemia, bexarotene-dose reduction was examined with respect to survival and to elevated triglycerides. Two distinct groups were identified: patients who were highly sensitive to bexarotene-induced triglyceride elevations and those who were not (Fig 3). Approximately 40% of patients in the bexarotene arm experienced rapid National Cancer Institute, grade 3/4, serum-triglyceride elevations (≥ 5 times the upper limit of normal), with the most rapid increases occurring during the first 3 to 4 weeks of therapy. These patients consequently underwent dose reductions of bexarotene, resulting in an average bexarotene dose of 260 mg/m^2/d in this patient subpopulation. The second group was comprised of patients who experienced grade 0 to 2 serum-triglyceride elevations, and who did not require similar bexarotene-dose reductions; the mean-bexarotene dose in these patients was 352 mg/m^2/d. Bexarotene-treated patients who experienced grade 3/4 hypertriglyceridemia had significantly longer median survival than patients in the control arm (12.4 *v* 9.2 months; $P = .014$), or patients with grade 0 to 2 hypertriglyceridemia (6.6 months; $P < .0001$).

Analyses of absolute triglyceride levels were conducted to validate these findings. When patients were divided into three subgroups correlating to the upper third (> 67%), middle third (> 33% to 67%), and lower third (≤ 33%) of absolute triglyceride levels following bexarotene administration, median survival was 12.4 months, 9.1 months, and 5.4 months, respectively; all subgroups were significantly different from each other ($P < .05$; Fig 4). Survival in the upper-third subgroup was similar to that of the bexarotene, grade 3/4, hypertriglyceridemia subgroup, and was better than that of the control group ($P = .0093$). The primary difference between the initial hypertriglyceridemia subgroup analysis and this analysis was that survival in the middle-third subgroup was similar to that of the control group ($P = .71$). Survival in the lower-third subgroup was similar to that of the bexarotene, grade 0 to 2, hypertriglyceridemia subgroup, and was shorter than that of the control group ($P < .0001$).

A survival hazard ratio analysis demonstrated that bexarotene-treated patients who experienced grade 3/4 hypertriglyceridemia had a better prognosis when evaluated along several parameters than patients in the control arm (Appendix Fig A2, online only). In particular, patients within this subgroup who were male, had stage IV disease, had demonstrated a prior 6-month weight loss ≥ 5%, or were smokers had significantly longer survival times than patients in the control arm, thereby demonstrating a survival benefit for NSCLC patients who typically have an unfavorable prognosis. A univariate Cox regression analysis in the ITT population demonstrated that survival differences by baseline prognostic factors were not significant among the treatment groups. A time-dependent multivariate analysis revealed that—regardless of subgroup criteria—bexarotene-treated patients who experienced high-grade triglyceride elevation experienced a survival advantage and a more favorable overall response to treatment.

Bexarotene-treated patients with grade 3/4 hypertriglyceridemia also had higher rates of skin rash and hypothyroidism compared with bexarotene-treated patients who did not experience high-grade hypertriglyceridemia. This suggests that other body systems, not just those involved in lipid metabolism, were sensitive to the effects of bexarotene.

Table 2. Patient Demographics

Characteristic	% of Patients	
	Carboplatin, Paclitaxel, and Bexarotene (n = 306)	Carboplatin and Paclitaxel (n = 306)
Sex		
Male	66	66
Median age, years	63	
Stage		
IIIB	13	13
IV	87	87
ECOG performance status		
0	34	34
1	65	65
Histopathology		
Adenocarcinoma	55	50
Squamous	20	21
Large cell	7	8
Other	18	21
Tobacco smoking		
Ever	90	91
Weight loss (preceding 6 months)	50	53
< 5%	18	20
5%-10%	40	38
Race/ethnicity		
White	88	89
Black	8	7
Hispanic	1	3
Other	3	1

NOTE. No significant differences were observed between the two study arms for any of the parameters listed in the table.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

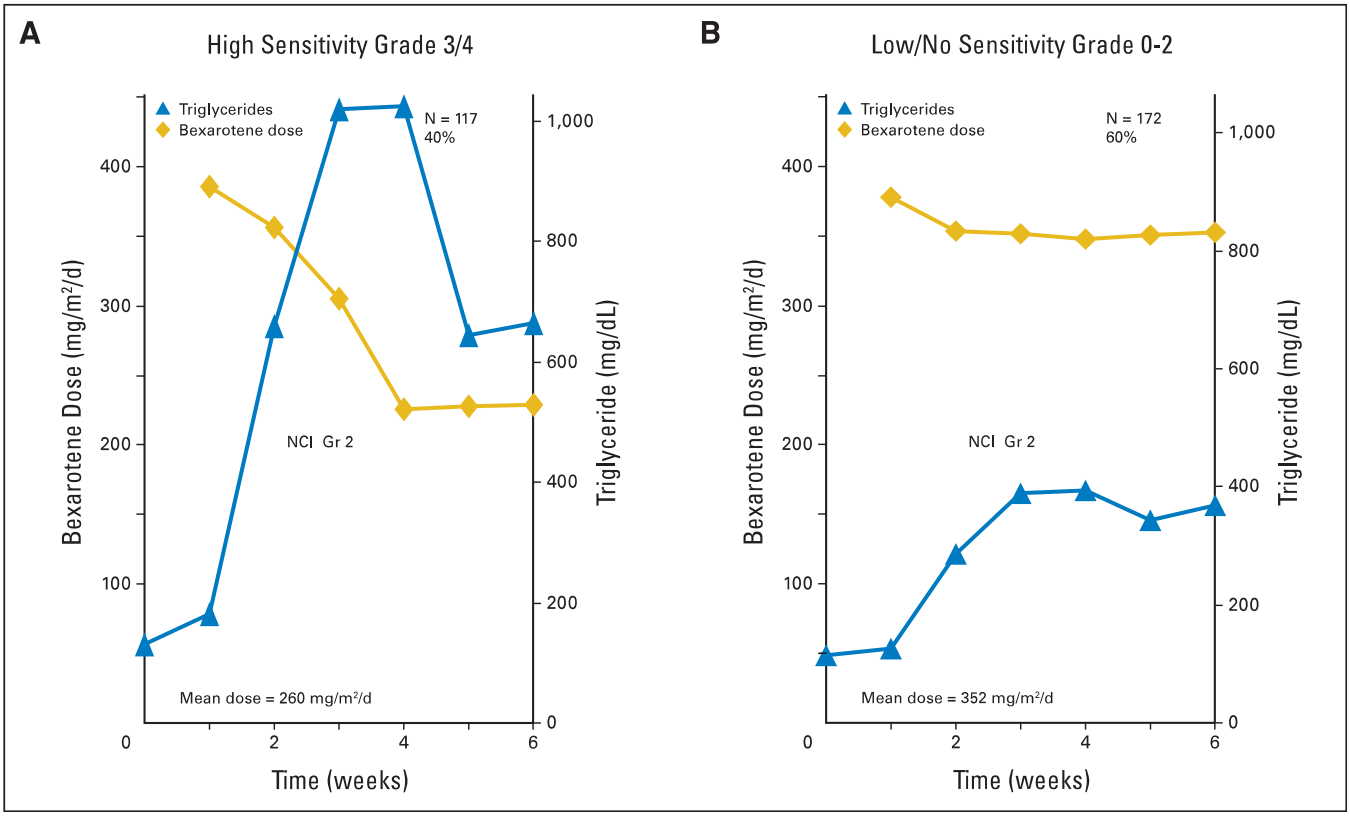

Fig 3. Use of triglyceride elevation as a biomarker differentiates two distinct populations within bexarotene-treated patients. The mean bexarotene dose given to (A) patients who experienced grade 3/4 triglyceride elevation was lower than that given to (B) patients who experienced grade 0 to 2 triglyceride elevation.

Safety and Tolerability

Overall, adverse events were similar both in incidence and severity in the two treatment arms; events that were significantly different between the two treatment arms are listed in Table 3. As expected, bexarotene-treated patients experienced a significant increase in triglycerides (65.9% *v* 2.0%; $P < .0001$). Low-grade hypothyroidism also occurred at a significantly higher rate in the bexarotene arm (24.9% *v* 0.7%; $P < .0001$), which was expected because of the known effects of RXRs on thyroid metabolism. The only significant differences in incidence of serious adverse events between bexarotene-treated and control patients were dehydration (6.5% *v* 2.4%; $P < .05$) and neutropenia (3.8% *v* 0.7%; $P < .05$).

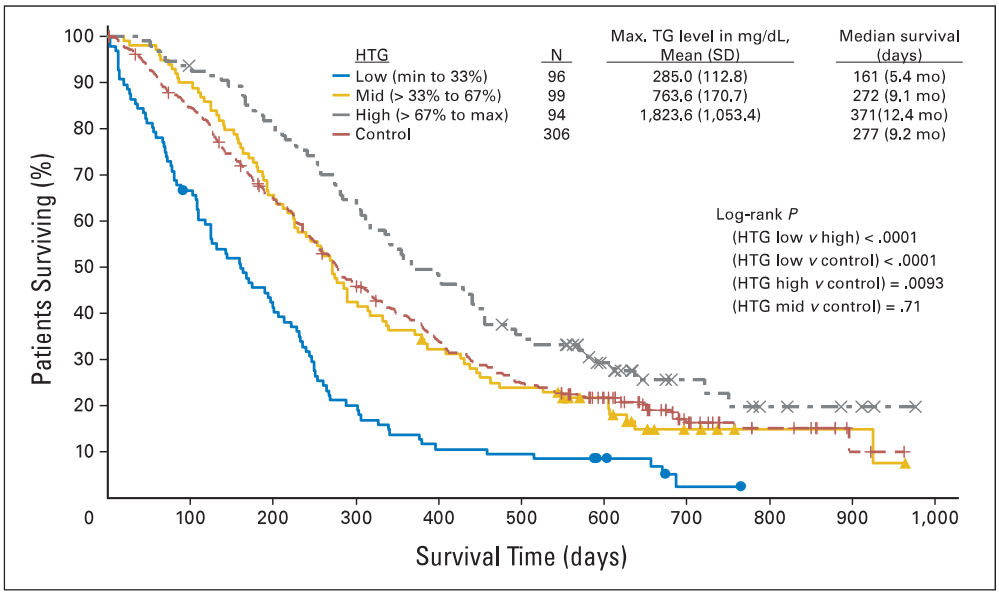

Fig 4. Kaplan-Meier survival estimates of bexarotene-hypertriglyceridemia subgroups (ranked in the low, medium, or high 33rd percentile) versus control patients. Bexarotene-hypertriglyceridemia subgroups were determined by the percentile of maximum triglyceride level of each bexarotene-treated patient during the study. HTG, hypertriglyceride; TG, triglyceride; mo, months; min, minimum; max, maximum; SD, standard deviation.

Table 3. Adverse Events That Occurred at a Greater Incidence ($P < .05$) in the Bexarotene Arm Compared With the Control Arm in the Safety Population

Events	% of Patients			
	Carboplatin/Paclitaxel/ Bexarotene (n = 293)		Carboplatin/Paclitaxel (n = 295)	
	All Grades*	Grade 3/4	All Grades	Grade 3/4
Hematologic				
Anemia	50.2	11.6	38.0	7.5
Neutropenia†	47.1	29.4	24.1	13.2
Leukopenia†	10.6	6.1	4.1	1.4
Nonhematologic				
Asthenia/fatigue†	65.5	16.4	55.3	8.8
Hypertriglyceridemia/blood triglyceride increase†	65.9	32.1	2.0	0
Diarrhea†	36.9	4.8	23.1	1.7
Arthralgia‡	26.6	6.1*	23.1	2.7
Dyspnea	25.3	9.9	17.6	5.8
Hypothyroidism	24.9	0	0.7	0
Anorexia	24.2	3.8	16.3	1.4
Pain in extremity	18.8	3.8	10.8	2.0
Rash	16.0	1.0	7.5	0
Dehydration†	13.7	5.5	7.5	1.4
Abdominal pain†	13.3	4.4	6.4	1.4
Hypercholesterolemia†	11.9	3.1	0.7	0
Dermatitis exfoliative	11.9	0	0.7	0

*Incidence of all grades (except grade 3/4) significantly greater in bexarotene-treated *v* control patients, except where noted.
†Incidence of all grades and grade 3/4 significantly greater in bexarotene-treated *v* control patients.
‡Incidence of grade 3/4 (but not all grades) significantly greater in bexarotene-treated *v* control patients.

More patients withdrew from the bexarotene arm than from the control arm with each subsequent cycle of therapy (cycle 3, n = 178 and n = 215; cycle 4, n = 148 and n = 184 in the bexarotene and control arms, respectively). The most common reason for early withdrawal was disease progression, which occurred in 79 patients in the bexarotene arm, and 77 patients in the control arm. Overall, 18.8% of patients in the bexarotene arm withdrew due to bexarotene toxicity, the most frequent toxicity being hypertriglyceridemia (10.6%). Hypertriglyceridemia was also the most common cause for dose suspension and dose reduction in bexarotene-treated patients.

DISCUSSION

This study, unfortunately, joins a long list of recent clinical trials in which the addition of a third experimental agent to standard chemotherapy doublets has not demonstrated a survival benefit (Appendix Table A2, online only). However, this was not due to the study design, the drug dose, or any known heterogeneity in the study population. Notably, retrospective analysis demonstrated a significantly prolonged survival in a large subpopulation that experienced bexarotene-induced, grade 3/4 hypertriglyceridemia. This represents well over one third (~40%) of the bexarotene study population. Overall survival in these patients exceeded 12 months, which has only been observed in one other phase III clinical trial in advanced NSCLC.[14] Furthermore, these results support the concept that sensitivity to bexarotene—determined by the degree of induced hypertriglyceridemia—may define the subpopulations of NSCLC patients who are likely to have distinct survival benefit.

A similar correlation between bexarotene-induced hypertriglyceridemia and survival has been noted in several other studies, including the SPIRIT I study.[7a] Retrospective analyses of the two first-line phase I/II studies[7,9] that led to the design and enabled the conduct of the SPIRIT studies also revealed either significant or numeric correlations between bexarotene-induced hypertriglyceridemia and improved survival (A. Negro-Vilar, unpublished data, 2006). Recently, a significant correlation between bexarotene-induced hypertriglyceridemia and survival was reported in a phase II bexarotene monotherapy trial in chemotherapy-refractory advanced NSCLC patients.[11]

This phase III study demonstrates that bexarotene treatment is associated with survival benefit in patients who develop rapid and high-grade hypertriglyceridemia and who are male, have stage IV disease, are smokers, and who have experienced ≥ 5% weight loss in the 6 months immediately preceding study entry. It is important to note that NSCLC patients with these characteristics typically have an unfavorable prognosis. Interestingly, these patients represent a group with characteristics opposite to those patients who appear to benefit from targeted therapies or even standard chemotherapeutic agents.

Although the hypertriglyceridemia observed in this study was anticipated,[15] the association between triglyceride elevation and prolonged survival in bexarotene-treated patients was not expected. Equally surprising was the observation that bexarotene-treated patients with low-grade triglyceride elevation had a shorter mean survival than patients who did not receive bexarotene; these results warrant further investigation. Several possible explanations could account for these observations. Thus far, a separate analysis to be published elsewhere has not found any pharmacokinetic explanations. Pharmacogenomic effects, as well as any impact of lipid signaling and metabolism pathways on tumor progression, may provide some insight and will be presented in a separate report. In the interim, these results suggest that grade 3/4 hypertriglyceridemia may serve as a biochemical marker for survival advantage of bexarotene treatment in NSCLC, whereas grade 0 to 2 hypertriglyceridemia is indicative of a lack of response or possibly poor prognosis. In control patients in whom triglyceride levels were slightly increased during the study compared with baseline (data not shown), hazard-ratio analysis

showed a trend but no statistically significant correlation between increased triglyceride levels and survival in control patients. Whether hypertriglyceridemia is a prognostic factor that identifies patients with a higher probability of survival regardless of bexarotene treatment, or a predictive factor that identifies an important subgroup of patients who should benefit from bexarotene treatment, and whether development of hypertriglyceridemia can be used for patient selection in first-line NSCLC studies remain to be determined.

In conclusion, bexarotene did not improve overall survival when added to carboplatin and paclitaxel in first-line treatment of NSCLC in the ITT population. However, a subset analysis indicated that a bexarotene-treated subpopulation of patients with high-grade triglyceride elevation had improved survival. Notably, this subpopulation included patients with typically unfavorable characteristics (stage IV disease, male, smoker, and substantial prior weight loss). Whether hypertriglyceridemia is a predictive biomarker of bexarotene sensitivity leading to potential survival benefit in this population of patients, or just a prognostic factor, warrants further study specifically designed to address this question. Ongoing biomarker analyses from the SPIRIT trials may help identify likely responders and possibly determinants of survival to better select patients for future studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).