Study Protocol CA 139-103:

Title:

A Randomized Trial of Two Cisplatin-Based Combination Chemotherapies in Advanced Non-Small Cell Lung Cancer

Investigator, Location of Trial: Study Chairman:

Principal Investigators: Drs. Postmus and Giaccone. The study was conducted in 18 centers located in 6 European countries (Belgium, Italy, the Netherlands, Czech Republic, Poland and Spain).

Publications:

Giaccone G, Splinter TAW, Postmus P, et al. Teniposide-Cisplatin vs paclitaxel-cisplatin in advanced non-small cell lung cancer (NSCLC). Results of a randomized phase II study of the EORTC-LCCG. Proceedings ASCO, 1995; 14:356(A1082).

Postmus PE, Giaccone G, Splinter TAW, et al. Teniposide/cisplatin Versus Paclitaxel-Cisplatin in Advanced Non-Small Cell Lung Cancer: Interim Results of a Randomized Phase III Study of the EORTC-LCCG. Emerging Concept in Clin. Oncol., 1995; 7.

Postmus PE, Giaccone G, Debruyne C, et al. Results of the Phase II EORTC Study Comparing Paclitaxel/Cisplatin With Teniposide/Cisplatin in Patients With Non-Small Cell Lung Cancer. Sem. In Oncol., 1996; 23 (suppl. 12): 10-13.

Giaccone G, Splinter T, Postmus P, et al.: Paclitaxel-cisplatin versus teniposide-cisplatin in advanced non-small cell lung cancer (NSCLC). Proceeding ASCO, 1996; 15:373(A1109).
Scagliotti GV, Giaccone G, Postmus P, et al. Teniposide/Cisplatin Versus Paclitaxel/Cisplatin in Advanced Non-small Cell Lung Cancer: Interim Results of a Randomized Phase III Study of the EORTC Lung Cancer Cooperative Group. European Respiratory Journal, 1996; 9 (suppl 23): 399s (A2510).

Giaccone G, Postmus P, Debruyne C, et al. Final results of a EORTC Phase III study of paclitaxel versus teniposide, in combination with cisplatin, in advanced NSCLC. Proceedings ASCO,1997;16:406a (A1653).

Giaccone G, Postmus PE, Splinter TAW, et al. Preliminary results: Cisplatin/Paclitaxel vs Cisplatin/Teniposide for Advanced Non-Small-Cell Lung Cancer. Oncology, 1997;11-4 (Suppl 3):11-14.

Study Period:

August 26, 1993 to February 29, 1996 (last patient randomized)

Number of subjects: 332

Amendments:

- June 1993: amendment to add BMS staff and BMS standard sections in the protocol
- January 1995: expansion of the study to Phase III , added as a new objective the evaluation of Quality of Life and recognized the use of the Common Toxicity Criteria scale for the evaluation of toxicity

Objectives:

To compare the efficacy (i.e. overall survival, response rates and progression free survival) and the tolerability of taxol and cisplatin versus teniposide and cisplatin in patients with advanced previously untreated non-small cell lung carcinoma (NSCLC).

Study Design - Methodology:

Prospective, multicenter, open-label, centrally randomized study, designed initially as a two-step phase II trial which expanded to a phase III. Patients in the Phase II portion were incorporated in the statistical analysis of the Phase III comparative trial. Enrollment of an additional 288 patients over 30 months in the phase III would allow detection of a three-month increase in survival with 80% power. Patients were stratified prior to randomization by institution, performance status (ECOG 0 versus 1- 2) and by disease extent (locally advanced versus metastatic).

Diagnosis and Main Criteria for Entry:

- histologically proven NSCLC
- locally advanced or widespread disease, not amenable to radical surgery
- evaluable or measurable disease, with progression within two months prior to study entry
- performance status ≤ 2 and life expectancy of ≥ 2 months
- age >18 and <76 years
- adequate hematologic, renal, and hepatic function
- no sign of cardiac failure or rhythm disturbances requiring medication
- no prior chemotherapy
- radiotherapy should not include all target lesions for evaluation
- no brain involvement or leptomeningeal disease, no previous malignancies, no acute infections

Therapy, dose, route of administration:

Patients receive a combination of taxol, 175 mg/m^2 as a three hour intravenous infusion and cisplatin, 80 mg/m^2 on day 1 or a combination of teniposide, 100 mg/m^2 on days 1, 3 and 5 and cisplatin 80 mg/m^2 on day 1. All patients randomized to the taxol/cisplatin arm received a standard taxol premedication regimen consisting of dexamethasone, diphenhydramine and cimetidine.

Criteria for Dose Modification

The following dose levels were identified:

Table No. 14
Dose Modification for Study 103

	Dose (mg/m^2)		
Level	Teniposide	Taxol	Cisplatin
0	100	175	80
-1	80	135	60
-2	60	100	-

For granulocyte counts <0.5x 10^9/L and/or platelets <50 x 10^9/L, febrile neutropenia and severe bleeding, the dose of teniposide or taxol should be decreased by one level. For severe paresthesias and/or weakness (CTC≥ Grade 2 neurologic toxicity) reduce cisplatin dose by one level, if severe paresthesias or mild weakness persist, reduce teniposide or taxol dose by one level.

Treatment discontinuation is required for failure of hematologic recovery (granulocyte count ≥ 1.5x10^9/L and platelet count ≥ 100x10^9/L within 35 days, intolerable paresthesia or marked motor loss (CTC Grade III Neurological Toxicity), paralysis (Grade IV)

Treatment Duration:

Therapy was given for at least 1 course and discontinued for disease progression or severe toxicity. Patients who responded or achieved stable disease received up to 6 courses. Patients randomized to the taxol and cisplatin arm could receive an additional 4 courses of single-agent taxol after 6 courses of the combination chemotherapy.

Disease monitoring and Criteria for Response:

Up to eight representative lesions were selected at baseline and followed. Each lesion was classified as measurable (bidimensionally measurable), evaluable (unidimensionally measurable) and nonmeasurable. Only measurable and evaluable lesions were considered in the analysis of indicator lesions and imaging techniques took precedence over physical examination for response evaluation. WHO criteria were used to assess tumor response (complete, partial response, stable disease and progressive disease).

Study Parameters

Table No. 15

Study Parameters-Study 103

	PRIOR TO THERAPY	WEEKLY	BEFORE EACH CYCLE
H&P	x		x
Weight	x		x
Vital Signs[1]	x		x
Tumor Measurement	x		x[a]
Performance Status	x	x	x
CBC	x	x	x
Creatinine ± creatinine clearance	x		x
Bilirubin, SGOT, SGPT, alk phos	x		x
Electrolytes	x		x
Total protein/albumin	x		x
Urinalysis	x		x
CXR	x		x
ECG	x		x
Liver UL/CT Scan	x		x
QOL Questionnaire	x		x

[a] after 2,4,6,8,10 cycles and thereafter every 6 weeks or when indicated

[b] at 5 points in time, namely at randomization and every six weeks thereafter (only in patients enrolled in the phase III of the study.

Drug Formulation

Taxol was supplied by Bristol-Myers Squibb (Batch no. S92K032M, S92K031M, S92F021M, S93F008M, S93H013M, C4B00, C4B07, G4B00, K4B00, L4B04, J3F39, C5B00). Teniposide and cisplatin were obtained through commercial sources. Standard premedication with dexamethasone, cimetidine and diphenhydramine was given prior to taxol.

Statistical Considerations

Kaplan-Meier estimates were used in the analysis of all time to event variables (survival, time to progression and duration of response) using a 95% confidence interval. The primary comparison of survival and time to progression was a logrank test stratified by performance status (ECOG 0 vs. 1-2) and extent to disease (locally advanced vs. metastatic). A secondary analysis was a Cox proportional hazards regression. P-values from a stratified

logrank test (unadjusted) and from the Cox model (adjusted) were reported, along with hazard ratios and their 95% confidence intervals as estimated from the Cox models. For evaluable patients with uni- or bidimensionally measurable disease, the odds ratio between treatment arms and a 95% confidence interval of the odds ratio was given.

Reviewer's comment: *The sample size estimation and statistical analyses that were prospectively defined in the protocol were carried out and were consistent with the analyses performed by the sponsor at the end of the study.*

Data Collection and Management

For Study 139-103, data were collected prospectively on case report forms (CRF) that were specifically designated for this study by the EORTC Data Center. The CRF's were completed at the study site by the local investigator and/or data manager and signed by the investigator before transferring into the BMS Clinical database .

The BMS medical team reviewed all efficacy data from EORTC CRF's and discrepancies in analyses were brought to the attention of the EORTC and study chairman. Consensus between the BMS assessment and the EORTC assessment was not reached in all cases, however, the study report was based on the efficacy analysis established by the BMS medical team. Adverse events that were considered not to be related to study therapy were not entered in the EORTC database and BMS designated these events as disease related.

SPONSOR'S STUDY RESULTS

Eighty patients randomized between August 1993 to October 1994 during the phase II portion of the trial were included in the analyses. A clinical response was assessed in 26% (10/38) of the eligible patients who received teniposide/cisplatin and in 40% (14/35) of those who received taxol/cisplatin.

Patients characteristics

A total of 332 patients were randomized from 19 participating institutions. The diagnosis of NSCLC was confirmed in 329 patients (99%). Seventy percent (234/332) of patients enrolled were male. The median age was 58 in both treatment arms. A total of 318 patients (96%) had measurable disease with lung, mediastinum, lymph nodes outside the thorax and bone as the most common sites of disease. Radiotherapy was administered as initial therapy in 18 patients (11%) in the teniposide/cisplatin arm and 21 patients (13%) in the taxol/cisplatin arm. No patients received chemotherapy.

Patient pretreatment characteristics are summarized in the table below:

Table No. 16
Pretreatment Patient Characteristics at Baseline - Study 103

	Number of Patients (%)		
	Teniposide/cisplatin (n=166)	**Taxol/cisplatin** (n=166)	**Total** (n=332)
Stage			
IIIA	15 (9)	18 (11)	33 (10)
IIIB	47 (28)	41 (25)	88 (27)
IV	101 (61)	106 (64)	207 (62)
Undetermined	3 (2)	1 (1)	4 (1)
Performance Status			
0	59 (36)	58 (35)	117 (35)
1	93 (56)	88 (53)	181 (55)
2	14 (8)	20 (12)	34 (10)
Weight loss in last 3 mos			
<5%	115 (69)	120 (72)	235 (71)
>5%	48 (29)	43 (26)	91 (27)
Not reported	3 (2)	3 (2)	6 (2)
Gender			
Male	117 (70)	117 (70)	234 (70)
Female	49 (30)	49 (30)	98 (30)
Extent of Disease			
Intrathoracic	85 (51)	68 (41)	153 (46)
Visceral ± soft tissue± intrathoracic	41 (35)	65 (39)	106 (32)
Softtissue± intrathoracic	35 (21)	30 (18)	65 (20)
Unknown	5 (3)	3 (2)	8 (2)

Forty-three (13%) of the 332 randomized patients did not meet all eligibility criteria, 22 patients (13%) in the teniposide/cisplatin arm and 21 patients (13%) in the taxol/cisplatin arm. The number and type of reasons for ineligibility were similar in both arms.

Number of courses administered, dose reduction, dose delays and dose intensity:

In study 103, treatment duration in the teniposide/cisplatin arm was restricted to 6 courses while patients enrolled in the taxol/cisplatin arm could receive an additional 4 courses of taxol as single agent after completing 6 courses of the combination.

There were a total of 676 courses of teniposide/cisplatin administered to 165 patients and 793 courses of taxol/cisplatin given to 160 patients. The median number of courses given in both arms was 5. The overall percentage of patients with dose reductions was 33% in the teniposide/cisplatin arm and 20% in the taxol/cisplatin arm (p=0.008). Treatment delays were also more frequent in the teniposide/cisplatin arm with only 40% of all courses given on time as compared to over 80% in the taxol/cisplatin arm. Hematologic toxicity was the most frequent reason for dose reduction and dose delays in the teniposide/cisplatin arm. Dose reductions and dose delays in the teniposide/cisplatin arm resulted in a significantly higher cisplatin dose intensity in the taxol/cisplatin arm (p=0.0001).

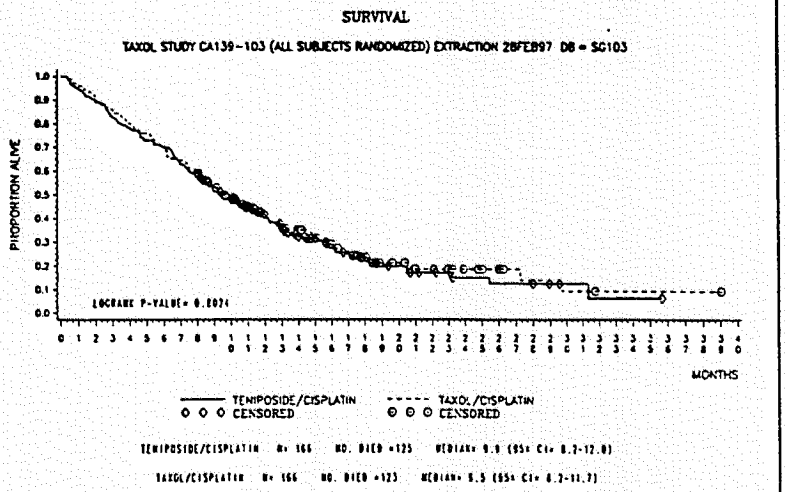
SPONSOR'S EFFICACY RESULTS

A total of 313 patients (94%) could be included in the analysis of clinical response. All 332 randomized patients were included in the analysis of time to progression and survival.

Sponsor's Analysis of Survival

Survival was calculated from the date of randomization to death; otherwise, patients were censored on the last day known to be alive. At the time of this analysis, a total of 248 patients had died, 125 (75%) in the teniposide/cisplatin arm and 123 (74%) in the taxol/cisplatin arm. The median survival for patients enrolled in the teniposide/cisplatin arm was 9.9 months (95% C.I. 8.2-12.0) with a range of 0.36 to 35.7 months as compared to 9.5 months (95% C.I. 8.2 to 11.7) with a range of 0.36 to 39.0 months for patients enrolled in the taxol/cisplatin arm. The difference is not statistically significant (p=0.802), hazard ratio of 1.03 (95% C.I. 0.80 - 1.33). The Kaplan-Meier estimated percentage of patients alive at one year was 41% in the teniposide/cisplatin arm and 41% in the taxol/cisplatin arm.

Figure 3


SURVIVAL
TAXOL STUDY CA139-103 (ALL SUBJECTS RANDOMIZED) EXTRACTION 28FEB97 DB = SG103
PROPORTION ALIVE
LOGRANK P-VALUE= 0.0024
MONTHS
TENIPOSIDE/CISPLATIN
CENSORED
TAXOL/CISPLATIN
CENSORED
TENIPOSIDE/CISPLATIN N= 166 NO. DIED =125 MEDIAN= 9.0 (95% CI= 8.2-12.0)
TAXOL/CISPLATIN N= 166 NO. DIED =123 MEDIAN= 9.5 (95% CI= 8.2-11.7)

Sponsor's Analysis of Time to Progression:

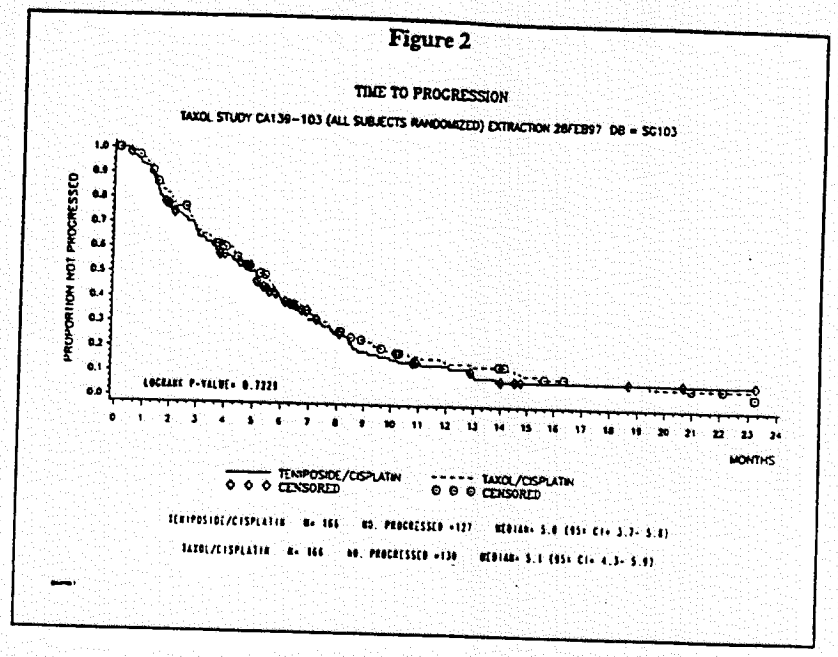
Time to progression was calculated from the date of randomization until the date progressive disease was first reported. Patients who did not progress were censored to their last day of follow-up. Patients who were off therapy and who received secondary therapy for a reason other than disease progression were censored at then start of the secondary therapy. Patients who were lost to follow-up were censored at the last known alive date. Patients who were never treated were censored on the day of randomization.

Table No. 17
Time to Progression Analysis- Study 103

	Number of Patients (%)	
	Teniposide/cisplatin n=166	Taxol/cisplatin (n=166)
Patients who have progressed	127 (77)	130 (78)
Death	16	10
Documented Progression	111	120
Reason for censoring		
Secondary therapy	27 (16)	18 (11)
Radiotherapy	21	8
Surgery	6	4
Chemotherapy	0	6
Not relapsed	10 (6)	11 (7)
Never treated	1 (1)	6 (4)
Other	1 (1)	1 (1)

Median time to progression was 5.0 months in the teniposide/cisplatin arm (95% C.I. 3.7-5.8) as compared to 5.1 months in the taxol/cisplatin arm (95% C.I. 4.3-5.9) (p=0.723).

Figure 2



Analysis of time to progression, considering the 35 patients who were censored for chemotherapy and radiotherapy as progressing on the day they start the secondary therapy was 4.7 months (95% C.I. 3.6-5.1) for the teniposide/cisplatin arm compared to 4.6 months (95% C.I. 3.9-5.6) for patients in the taxol/cisplatin arm.

Clinical response:

Responses were defined according to WHO criteria as :

Complete Remission (CR): disappearance of all evidence of active tumor for a minimum of 4 weeks.

Partial Remission (PR): 50% or greater decrease in the sum of the product of the longest perpendicular diameters of all measurable lesions (or an estimated decrease of 50% for all nonmeasurable lesions) lasting for at least 4 weeks without appearance of any lesions or without progression in any of the measurable and nonmeasurable sites.

Stable Disease (SD) a decrease of less than 50% or an increase of <25% in the sum of the products of the longest perpendicular diameters of all measurable sites or estimation in nonmeasurable sites, without appearance of new lesions or evidence of progression

Progressive Disease (PR) an increase in >25% of the product of diameters of any measurable lesion or in estimated size of nonmeasurable lesions or

appearance of new lesions. Deterioration of the ECOG performance status attributed to disease was considered as clinical progression.

Early death and early toxicity were considered as treatment failures. Patients were considered non-evaluable if they have no tumor measurements available, wrong histology or were never treated.

When all randomized patients are considered, response rates were 25% (41/166, 95% C.I. 18-32%) and 35% (58/166, 95% C.I. 28-43%) respectively for the teniposide/cisplatin arm and the taxol/cisplatin arm (p=0.046). Only 320 of the 332 patients were evaluable for tumor response. There were 161 evaluable patients in the teniposide/cisplatin arm with no complete responses and 41 partial responses for an overall clinical response rate of 26% (41/156). A total of 159 patients were evaluable in the taxol/cisplatin arm; 2 patients achieved a complete response (1%) and 56 patients had a partial response (36%) for an overall clinical response rate of 37% (58/157). The difference in overall response was statistically significant in favor of the taxol/cisplatin arm (p=0.041, odds ration of taxol/cisplatin over teniposide/cisplatin: 1.67: 95% C.I. 1.02-2.72).

Sponsor's Analysis of Time to Response:

Time to response corresponded to the period from the first day of treatment until the first response was documented. The median time to first response for the teniposide/cisplatin combination was 7.1 weeks (range: 5.0-15.4) versus 6.1 weeks (range: 1.1-18.1) for patients receiving taxol/cisplatin (p=0.215).

Sponsor's Analysis of Duration of response:

Duration of response was defined as the period between the day of first study drug administration until progressive disease was first noted. Patients who did not relapse prior to this analysis were censored to their last day of follow-up. The median duration of response for clinical responders was identical in both arms: 8.1 months.

Quality of life (QOL)

Quality of life was evaluated using the EORTC core questionnaire QLQ-C30 and the lung module LC-13. The QLQ-30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social-functioning), a global health status/QOL scale, 3 symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptoms, and perceived financial impact of the disease. The lung cancer module is composed of 13 questions assessing specific symptoms associated with lung cancer. Both questionnaires were administered at randomization and every six weeks thereafter.

A subset of 100 patients (50 in each arm), randomized after February 1, 1995, participated in the QOL evaluation at baseline. Patients enrolled in the taxol/cisplatin arm reported

statistically better global health status (p=0.027), physical (p=0.002), role functioning (p=0.021) and social functioning scores (p=0.030). Taxol-treated patients reported significantly less fatigue but more peripheral neuropathy. Dyspnea, hemoptysis, appetite loss and diarrhea scores approached statistical significance in favor of the taxol arm.

Compliance to the quality of life testing is shown in the following table (summarized from Sec. 8/10 vol. 5, p.1477)

Table No. 19
Quality of Life Questionnaire Compliance-Study 103

	# of Patients with questionnaire/ # of patients per period (%)[a]	
	Teniposide/cisplatin	Taxol/cisplatin
Baseline (prior to day 1)	50/86 (58)	50/82 (61)
Week 6 (prior to day 64 after randomization)	53/85 (62)	46/79 (58)
Week 12 (prior to day 106 after randomization)	37/74 (43)	37/71 (52)
Week 18 (prior to day 148 after randomization)	23/66 (35)	22/66 (33)
Week 24 (prior to day 190 after randomization)	16/62 (26)	14/63 (22)

[a] number o fpatietns filling a QOL questionnaire over the number of patietns alive at the start of the period (randomized after February 1, 1995)

Reviewer's comment: *Patient compliance seems to be a major problem with quality of life testing for study 103. If QOL data was collected for only 100 patients at baseline and decreased to a total of 45 patients by week 18, this represents a small proportion and may not truly represent quality of life for the whole population.*

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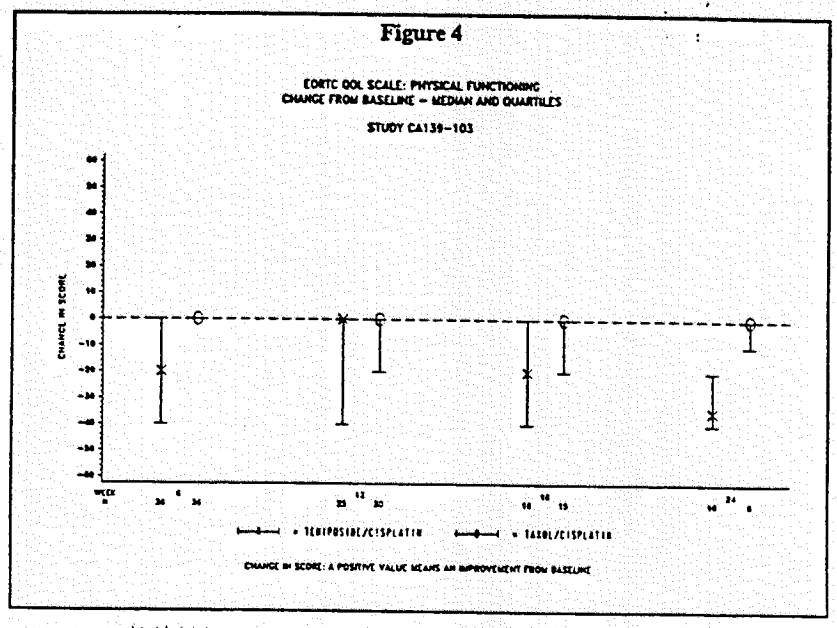
ON ORIGINAL

Overall, patients in the taxol/cisplatin arm reported significantly better results in the following scales:

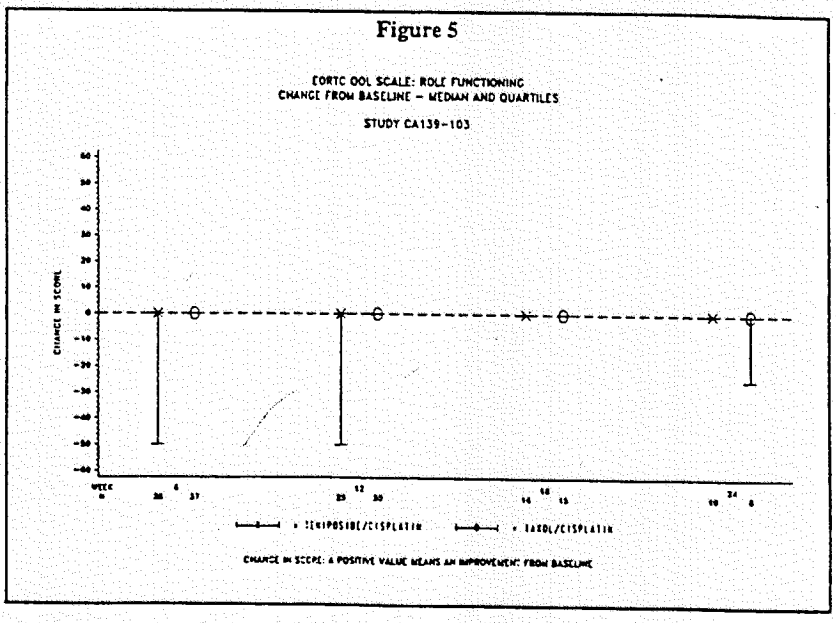
1. Physical Functioning (p=0.002)

Figure 4



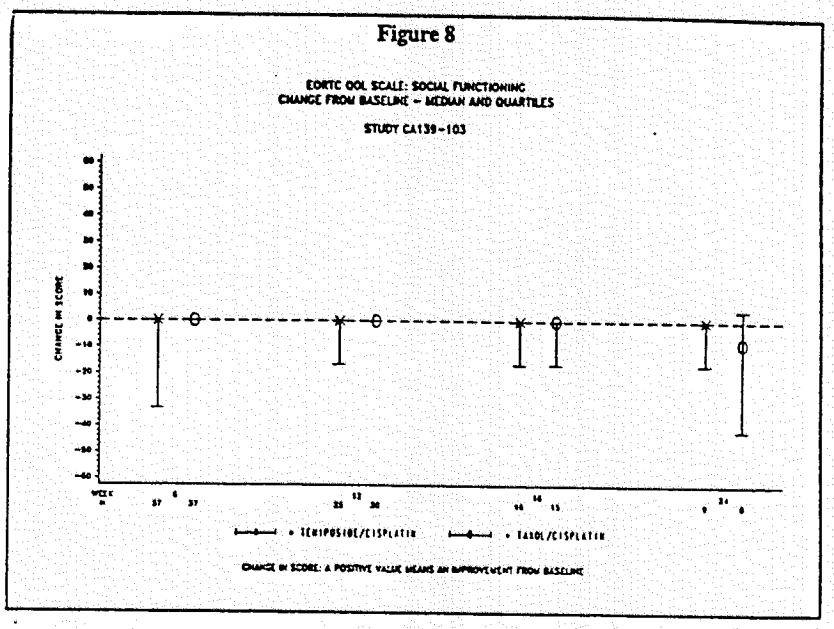
2. Role Functioning (p=0.021)

Figure 5



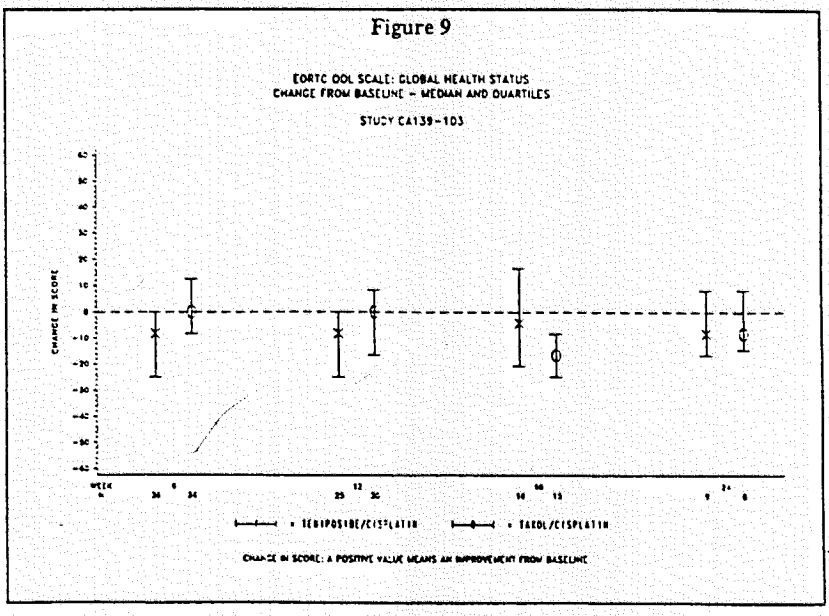
3. Social Functioning (p=0.030)

Figure 8

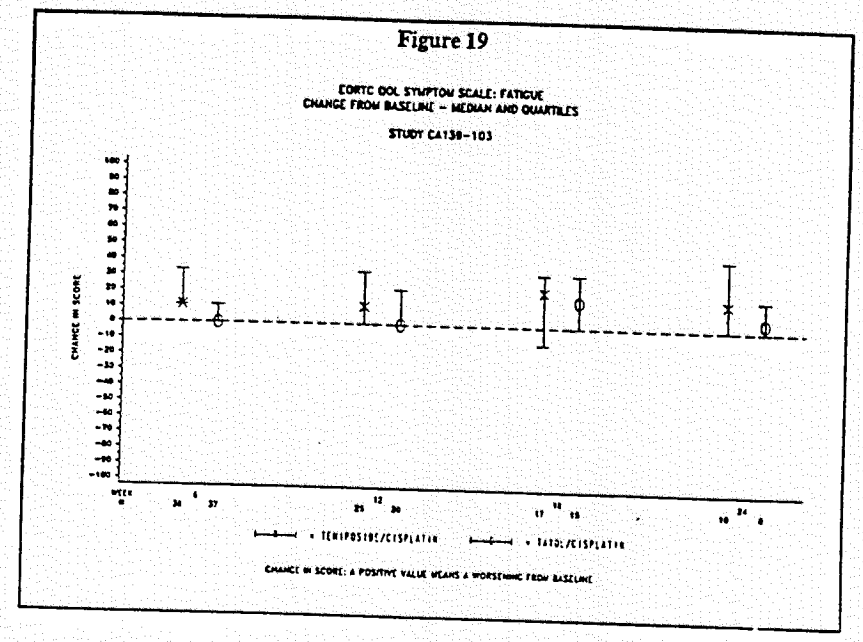


4. Global Health Status (p=0.027)

Figure 9



5. Fatigue (p=0.017)



SPONSOR'S SAFETY RESULTS

The NCIC-CTC expanded common toxicity criteria (CTC) were used to assess toxicity. Each patient who received at least one dose of the study drug was considered evaluable for safety. A total of 325 patients were included in the analysis: 165 patients in the teniposide/cisplatin arm and 160 patients in the taxol/cisplatin arm.

Discontinuation of Therapy

Criteria for treatment discontinuation are progression of disease, toxicity, patient refusal, completion of protocol treatment, death, protocol violation, lost to follow-up and others.

Overall, there was no difference in the reason for off-treatment (p=0.663). Twenty-six patients in the teniposide/cisplatin arm and 30 patients in the taxol/cisplatin arm discontinued treatment due to treatment-related toxicity. The following table lists the primary reason for off therapy:

Table No. 20
Primary Reason Off Study- Study 103

	Number of Patients (%)	
	Teniposide/cisplatin n=166	Taxol/cisplatin n=166
Disease Progression	**59 (36)**	**65 (39)**
Completed Treatment	**55 (33)**	**46 (28)**
Toxicity (drug related)	**26 (16)**	**30 (19)**
Peripheral neuropathy	0	13
Hematologic	9	1
Gastrointestinal	6	2
Infection	3	1
Cardiovascular	2	2
Asthenia/malaise	1	3
Arthralgia/myalgia	0	3
Ototoxicity	3	0
Nephrotoxicity	2	1
Hypersensitivity	0	2
Pulmonary	0	2
Patient Request	**11 (7)**	**9 (5)**
Death	**10 (6)**	**7 (4)**
Intercurrent Disease	4	4
Treatment related toxicity	4	2
Unknown cause	1	1
Disease progression	1	0
Other Reasons	**5 (3)**	**9 (5)**