responders was 7.5 months (range 3.2-24.9$^+$ months) in the cisplatin arm and 6.5 months (range 3.1$^+$-20.2 months) in the taxol/cisplatin arm.(p=0.237)

Quality of life (QOL)

Quality of life was evaluated using the EORTC core questionnaire QLQ-C30 and the lung module LC-13. This evaluation was to be performed at baseline, before each treatment course at off-study and during follow-up every two months until disease progression.

At baseline, QOL evaluation was available in 368 patients overall, 190 patients (92%) in the cisplatin arm and 178 patients (86%) in the taxol/cisplatin arm. Compliance was approximately 60% of all the patients remaining on-study up to Day 120. Questionnaires were completed during 685 on-study periods in the taxol/cisplatin arm as compared to 584 in the cisplatin arm. Throughout the time testing was done, the participants were well balanced for pretreatment characteristics such as disease stage, baseline PS, weight loss, etc.. The following functional scales were tested: (1) physical functioning, (2) role functioning, (3) emotional functioning; (4) cognitive functioning; (5) social functioning and (6) global health status. The following symptoms were tested: dyspnea, cough, hemoptysis, nausea and vomiting, appetite loss, constipation, diarrhea, sore mouth, trouble swallowing, pain, pain in chest, pain in shoulder, pain elsewhere, pain medication consumption, pain medication effect, fatigue, insomnia, hair loss, peripheral neuropathy, and financial difficulties.

In comparing the changes from baseline, more patients in the taxol/cisplatin arm reported an improvement in physical functioning during the first five QOL evaluation periods. (p=0.054) Significant differences in favor of the taxol/cisplatin combination were seen in three QOL scales: nausea/vomiting (p=0.0003), loss of appetite (p=0.020) and constipation (p=0.032) . On the other hand, patients in the taxol/cisplatin arm reported significantly more alopecia (p<0.0001) and peripheral neuropathy (p<0.0001).

Reviewer's comment: The significant differences in the QOL symptom scales (nausea/vomiting, alopecia and neuropathy) are consistent with the difference in incidence and severity of these adverse events during monitoring of toxicity while on treatment.

Physical functioning was evaluated with five yes/no questions in the QLQ-C30 questionnaire. These questions assess the patients' ability to perform daily activities. At baseline, the median score for physical functioning was better for patients in the cisplatin arm than for patients in the taxol/cisplatin arm. The following figure depicts the median change from baseline in physical functioning over the first seven time periods. (from sec 8.1,vol 99.1, p 126) The number of patients who completed questionnaires at a given time point are noted on the x-axis and the vertical line represents changes from baseline for the 25th to 75th percentile of all patients.

EORTC QOL SCALE: PHYSICAL FUNCTIONING
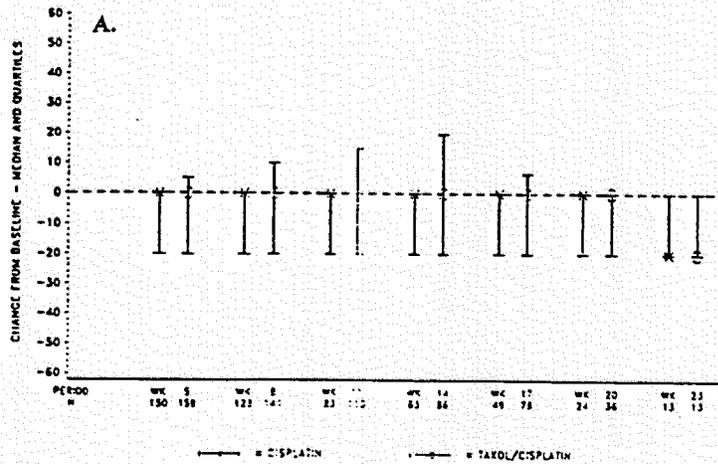
The following figure depicts the results in a different way. (from sec 8.1, vol 99.1, p 126) For example, at week 5 in the cisplatin arm, about 15% of patients assessed an improvement in physical functioning while an additional 50% assessed no change. In the taxol/cisplatin arm during the same period, 25% assessed an improvement while 40% assessed no change.
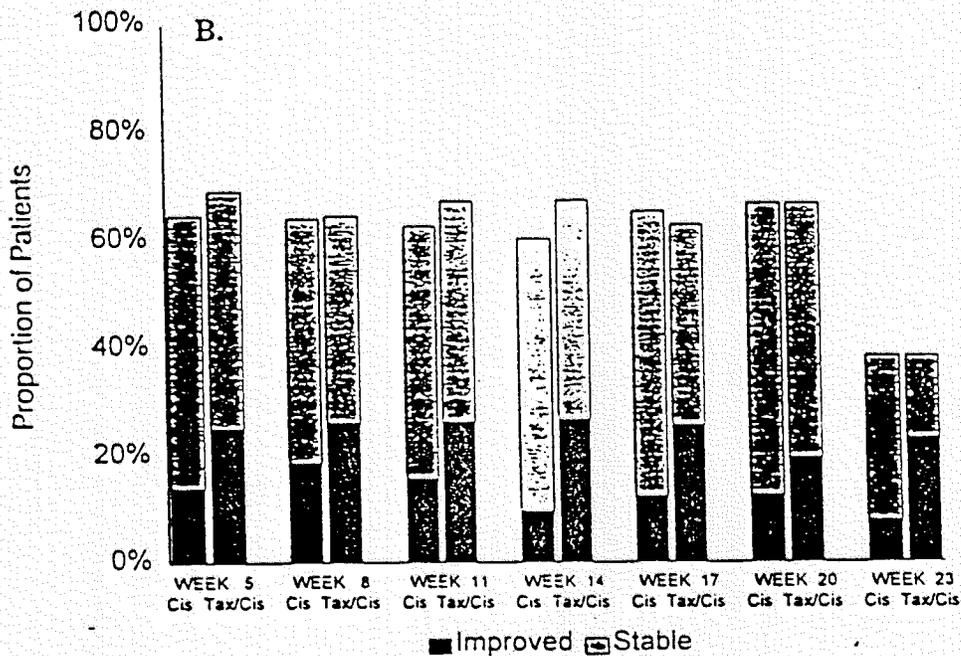
SPONSOR'S SAFETY RESULTS

The number of courses administered per patient was significantly lower in the cisplatin arm (median 3) as compared to the taxol/cisplatin arm (median 5) (p=0.0002). There were 759 courses of cisplatin administered to 206 patients and 889 courses of taxol/cisplatin given to 202 patients.

Criteria for Dose Modification

The following dose levels were identified:

Table No. 29
Dose Levels- Study 208
(Sec 3.3.4, vol 99.1, p.28)

Dose Level (mg/m^2)		0	-1	-2
Arm A	Cisplatin	100	75	50
Arm B	Cisplatin	80	60	40
	Taxol	175	150	135

Dose reduction of cisplatin in Arm A and of cisplatin and taxol in Arm B were required for subsequent treatment courses, based on the following criteria:

- ANC <0.5 x 10^9 cells/L lasting more than 7 days;
- any episode of febrile neutropenia;
- WHO grade IV thrombocytopenia if requiring platelet transfusion or associated with bleeding;
- grade III mucositis

Discontinuation of cisplatin was required for

- grade II neurological toxicity, severe paresthesias and/or mild weakness;
- clinical hearing loss;
- grade I Nephrotoxicity

Both taxol and cisplatin were discontinued for:

- hematologic recovery not achieved within 36 days (ANC ≥ 1.5 x 10^9 cells/L and platelet count ≥100 x 10^9 cells/L;
- grade II neurological toxicity,
- grade II nephrotoxicity ;

- symptomatic arrhythmia or heart blocks other than first degree;
- other major organ toxicity >grade II

Reviewer comment: The protocol required discontinuation of cisplatin (regardless of treatment arm) for grade II peripheral neuropathy, clinical hearing loss and grade I nephrotoxicity. This meant discontinuation from protocol treatment for patients in the cisplatin arm while patients enrolled in the taxol arm may continue to receive taxol alone. This may partly explain the greater median number of treatment courses received by patients in the taxol/cisplatin arm.

A dose reduction occurs when the actual dose delivered was less than midvalue between the starting dose and the next lower dose level. Dose reductions were more frequent in the taxol/cisplatin combination arm than in the cisplatin arm. In the cisplatin arm, 13/202 patients (6%) had a dose reduction, compared to 30/202 (15%) in the taxol/cisplatin arm.

Table No. 30
Reason for <u>First</u> Dose Reduction- Study 208
(summarized from Sec 6.1, vol 99.1, p 85)

	Arm 1 Cisplatin	Arm 2	
		Cisplatin	Taxol
# Patients with Dose Reduction	13	11	19
Hematologic	4	4	6
Nonhematologic	7	6	7
Other	2	1	6

A course was considered delayed when given more than 23 days after the start of the prior course. Treatment delays were more frequent in the cisplatin arm than in the taxol/cisplatin arm.

Table No. 31
Treatment Delays - Study 208
(summarized from Sec. 6.1.4, vol 99.1, p 87)

	Number of courses (%)	
	Cisplatin	Taxol/cisplatin
# of Courses Analyzed	553	687
Courses Delayed	128 (23)	108 (16)
Reason for delay		
Hematologic	**57 (45)**	**17 (16)**
Nonhematologic	**2 (2)**	**8 (7)**
Other Reasons	**69 (54)**	**83 (77)**
Administrative reason	30	38
Disease related	11	9
Patient request	11	15
Reason not reported	17	21

Reviewer's comment: *Overall, there were more treatment delays in the cisplatin arm and proportionately more delays due to hematologic toxicity.(45% vs 16%) However, a majority of patients in both treatment arms had delays for "other" reasons which were unclear.*

Treatment-related toxicity was the reason for study discontinuation in 89 patients; 51 (25%) of patients enrolled in the cisplatin arm and 38 (18%) of patients enrolled in the taxol/cisplatin arm. Renal toxicity was the most frequently cited reason for drug discontinuation (26 patients in the cisplatin arm and 11 patients in the taxol/cisplatin arm); another ten patients in the taxol/cisplatin arm had cisplatin discontinued due to renal toxicity.

Table No. 32
Primary Reason Off Study- Study 208
(summarized from Sec 6.3, vol. 99.1, p91)

	Number of Patients (%)	
	Cisplatin n=207	Taxol/cisplatin n=207
Disease Progression	**86 (42)**	**81 (39)**
Completed Treatment	**27 (13)**	**48 (23)**
Toxicity (drug related)	**51 (25)**	**38 (18)**
Nephrotoxicity	26	11
Peripheral-neuropathy	4	10
Nausea/vomiting	9	2
Ototoxicity	7	0
Cardiovascular	2	5
Asthenia	2	4
Hematologic	1	0
Arthralgia/myalgia	0	1
Hypersensitivity	0	2
Death	21 (10)	15 (7)
Disease-related	18	10
Treatment related toxicity	3	5
Patient Request	15 (7)	12 (6)
Other Reasons	6 (3)	8 (4)

Reviewer's comment: *Overall, more patients enrolled in the cisplatin arm were taken off treatment due to treatment related toxicity, and less patients completed the prescribed treatment.*

Discontinuation due to Death Within 30 Days

Twenty-four patients (12%) in the cisplatin arm and 13 (6%) in the taxol/cisplatin arm died within 30 days of last drug administration. Death in the cisplatin arm were mostly due to disease.

Table No. 33
Death Within 30 Days- Study 208
(from Sec 9.13, vol 99.1, p. 206)

	Number of Patients (%)	
	Cisplatin n=206	Taxol/cisplatin n=202
Number of Deaths within 30 days	24 (12)	13 (6)
Cause of Death		
Toxicity	3	5
Disease	21	8

Hospitalizations

The incidence of hospitalizations during therapy were similar in both arms: the most frequent reasons being drug administration, infection, and administrative reasons.

Table No. 34
Treatment Delays - Study 208
(summarized from Sec. 9.12, vol 99.1, p 202)

	Cisplatin n=206	Taxol/cisplatin n=202
# of Patients Hospitalized (%)	80/206 (39)	80/202 (40)
# of Courses with Hospitalizations	134/59 (18)	170/889 (19)
Reason for Hospitalization		
Drug Administration	40	70
Documented Infection	14	14
Administrative	12	12
Tumor Progression	11	13
Study drug toxicity	15	4
Cardiovascular Event	12	12
Others (<10 courses)	44	48

Reviewer's comment: *More treatment courses of taxol/cisplatin required admission to the hospital. It is unclear whether these admissions to administer therapy were due to problems from prior course administration or may have been for other reasons (e.g. premedication and prolonged total treatment infusion time).*

HEMATOLOGIC TOXICITY

Neutropenia (worst course) was significantly more frequent in the taxol/cisplatin arm than in the cisplatin arm (p<0.0001). Severe neutropenia was reported in 45% of the patients receiving taxol/cisplatin as compared to 17% of patients receiving cisplatin (p<0.0001). Thrombocytopenia occurred at a similar frequency and severity in both study arms, severe thrombocytopenia was observed rarely. Overall, anemia was observed in 68% of the patients receiving cisplatin and 67% of patients receiving taxol/cisplatin. In most cases, anemia was mild to moderate.

Table No. 35
Worst Course Hematologic Toxicity- Study 208
(from Sec 9.1, vol. 99.1, -172-174)

	Number of Patients (%)	
	Cisplatin (n=204)	Taxol/cisplatin (n=200)
Neutropenia		
Grade III	30 (15)	41 (21)
Grade IV	4 (2)	49 (25)
Grade III + IV	**34 (17)**	**90 (46)**
Thrombocytopenia[c]		
Grade III	3 (1)	1 (<1)
Grade IV	1 (<1)	1 (<1)
Grade III + IV	**4 (2)**	**2 (1)**
Anemia		
Grade III	13 (6)	17 (8)
Grade IV	0 (0)	3 (1)
Grade III + IV	**13 (6)**	**20 (10)**

Reviewer's Comment: *According to the sponsor, the higher incidence of hematologic toxicity in the taxol/cisplatin was possibly due to the higher median number of courses received. An analysis of the first course hematologic toxicities will be included in the FDA safety review for study 208.*

Neutropenic fever

Febrile neutropenia was defined as an adverse event with the primary term "febrile neutropenia" or a fever event with the last neutrophil count of Grade IV in the period from 10 days before this fever event until the day of fever onset; a grade IV neutrophil count in the

period from onset day +1 until resolution of the fever event. Febrile neutropenia was reported in 8/202 patients in the taxol/cisplatin arm (4%) compared to 1/206 patients in the cisplatin arm (<1%). (p=0.019) Infections were reported in a similar number of patients and courses in both arms.

Infections

The incidence of infections was similar in both arms. In the cisplatin arm, 64 courses (8%) of infections were reported in 49 (24%) of patients; while in the taxol/cisplatin arm, there were 90 courses (10%) of infections in52 patients (26%). Severe infections were rare, occurred in 13 patients (6%) in the cisplatin arm and nine patients (4%) in the taxol/cisplatin arm (p=0.512).

Bleeding and Blood Transfusions

There was no difference in incidence and severity of bleeding . In the cisplatin arm, bleeding was reported in 43 courses (6%) in 33 (16%) patients; while in the taxol/cisplatin arm, bleeding was experienced in 57 courses (6%) in 34 patients (17%). The number of blood transfusions were similar in both arms.

NON-HEMATOLOGIC TOXICICTIES

As outlined in the following paragraphs, the combination of taxol/cisplatin caused more hypersensitivity reactions, hypotension, peripheral neuropathy, arthralgia/myalgia, diarrhea and alopecia, while cisplatin caused more nausea/vomiting and ototoxicity. One patient in the taxol/cisplatin arm died due to a cerebrovascular accident and one patient in the cisplatin arm due to renal failure.

Hypersensitivity reactions:

Hypersensitivity reactions were reported in five patients (2%) in the cisplatin arm and 15 patients (7%) in the taxol/cisplatin arm (p=0.022). One patient enrolled in the taxol/cisplatin arm suffered from a severe hypersensitivity reaction.

Cardiovascular events

Cardiovascular events other than bradycardia and hypotension occurred in 15% of patients enrolled in the cisplatin arm and 21% of patients enrolled in the taxol/cisplatin arm

(p=0.155). Severe cardiovascular events were reported in six patients in the cisplatin arm and ten patients in the taxol/cisplatin arm (p=0.319).

Peripheral neuropathy

Peripheral neuropathy, mostly Grade I or II, was observed in 25% of patients enrolled in the cisplatin arm and in 54% of patients enrolled in the taxol/cisplatin arm (p<0.0001). Severe events (Grade III) were reported in two patients receiving cisplatin and eight patients receiving the taxol/cisplatin combination (p=0.060).

Arthralgia/myalgia

Arthralgia/myalgia was reported in 20% of patients treated with cisplatin and in 46% of patients treated with the taxol/cisplatin combination (p<0.0001). Ten patients treated with taxol/cisplatin and four patients receiving cisplatin developed severe (Grade III) arthralgia/myalgia (p=0.109).

Ototoxicity

Significantly more patients developed ototoxicity in the cisplatin arm (33 patients, 16%) than in the taxol/cisplatin arm (nine patients, 4%). (p=0.0001). Severe ototoxicity (Grade III) was reported in three patients, all enrolled in the cisplatin arm (p=0.248).

Asthenia

Developed in 63% of patients in the cisplatin arm versus 68% in the taxol arm. (p=0.349)

Alopecia

Alopecia (19% of patients in the cisplatin arm versus 87% of patients in the taxol/cisplatin arm; (p<0.0001).

Gastrointestinal Manifestations

Nausea and vomiting was experienced more frequently by patients treated with cisplatin (80%) as compared to the taxol/cisplatin combination (67%; p=0.004); it was severe in 32 and 24 patients respectively (p=0.315). Diarrhea was less frequently reported by patients on the cisplatin arm (11% versus 20%; p=0.014) but was generally mild to moderate in severity.

Renal function

More patients enrolled in the cisplatin arm (90 patients, 44%) than in the taxol/cisplatin arm (73 patients, 36%) developed renal toxicity (p=0.130). Severe events occurred in three cisplatin patients as compared to one taxol/cisplatin treated patient (p=0.623). Twenty-six patients (13%) in the cisplatin arm and 11 patients (5%) in the taxol/cisplatin arm had to discontinue treatment due to nephrotoxicity.

APPEARS THIS WAY
ON ORIGINAL

SPONSOR'S DISCUSSION (Study 208)

"The phase III study described in this report was initiated in January 1995 to show that the combination of taxol and cisplatin was safe and effective compared to high-dose cisplatin in a population of advanced NSCLC patients. Given the study design with a different cisplatin dose in the two treatment arms, this study was not to address the contribution of taxol to cisplatin in the treatment of advanced NSCLC. This multicenter randomized and prospectively monitored phase III trial was designed for patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC previously untreated with chemotherapy.

A total of 414 patients from 35 centers in ten European countries, Israel and Russia were centrally randomized at the BMS Biostatistics and Data Management Department (Waterloo, Belgium). Pretreatment characteristics were well balanced between the two groups, except for number of disease sites.

The combination of taxol/cisplatin proved to be easier to administer than high-dose cisplatin. The median number of courses in the high-dose cisplatin arm was three as compared to five in the taxol/cisplatin arm. This resulted in a higher median cumulative dose of cisplatin in the taxol/cisplatin arm despite higher individual dose of cisplatin in the single agent arm. In addition, there were more treatment delays in the high-dose cisplatin arm.

The taxol/cisplatin combination was more efficacious that the high-dose cisplatin regimen: significantly more patients achieved a clinical response in the taxol/cisplatin arm (26%, 50/190) than in the high-dose cisplatin arm (17%, 34/197) (p=0.028). This difference favoring the taxol/cisplatin arm remained statistically significant after adjustment for a number of potential prognostic factors in a logistic regression model.

Median time to progression was also favored in the taxol/cisplatin arm (4.3 months versus 3.2 months, p=0.0846). When patients were considered to have progressed, rather tha being censored, at the time of salvage therapy, the median time to progression was significantly prolonged in the taxol/cisplaltin arm (4.1 months versus 2.7 months, p=0.026). This more conservative analysis seems justified because the majority of those patients were taken off study for treatment related toxicities and subsequently received salvage therapy. After adjusting for the same set of prognostic factors the advantage for the taxol/cisplatin treatment was maintained (p=0.056 and p=0.016 respectively for the two analyses.

The median survival was 8.1 months and 8.6 months for patients enrolled inn the taxol/cisplatin and the high-dose cisplatin respectively. Although this trial failed to demonstrate a statistically significant superiority for the combination over high-dose cisplatin in terms of survival, the study provided sufficient statistical evidence to state that the survival in the two groups was comparable. In fact the survival curves were superimposable over the two-year period.

In this study, more patients in the high-dose cisplatin then in the taxol/cisplatin arm received salvage chemotherapy prior to or after disease progression was assessed. A crossover to taxanes in the high-dose cisplatin arm was uncommon.

The protocol was written to avoid severe and irreversible toxicities in the palliative setting and required discontinuation of cisplatin in case of renal toxicity (WHO Grade I), clinical hearing loss or severe paresthesias and/or mild weakness (WHO Grade II neurological toxicity). This and the significantly higher number of courses administered to patients in the taxol/cisplatin arm as compared to the high-dose cisplatin arm have to be considered when comparing the safety profile of the two treatment arms.

The combination of taxol/cisplatin caused more severe leukopenia and neutropenia as compared to the high-dose cisplatin. However, this resulted in a limited number of febrile neutropenia episodes and in a similar number of infections as compared to the high-dose cisplatin arm.

As expected, hypersensitivity reactions, peripheral neuropathy, arthralgia/myalgia, diarrhea and alopecia were more frequent in the taxol/cisplatin arm. However, there was no difference in terms of severe (Grade III) events between the two arms. High-dose cisplatin did produce significantly more nausea and vomiting as well as ototoxicity.

Overall, patients in the taxol/cisplatin arm reported a better quality of life. Statistically significant differences favoring the taxol/cisplatin combination were noted in the three QOL scales: nausea/vomiting, loss of appetite and constipation. In addition, patients in the taxol/cisplatin arm reported an improvement in physical functioning. In contrast, patients in the high-dose cisplatin arm reported less alopecia and less peripheral neuropathy, in agreement with the results of the safety analysis.

Study CA 139-208 is a large, randomized and prospectively monitored phase III trial which provides some evidence of superior activity for a taxol/cisplatin regimen over high-dose cisplatin in patients with advanced NSCLC. The taxol/cisplatin combination produced a better clinical response and increased time to progression, whereas survival was clearly not inferior as compared to high-dose cisplatin.

Thus the administration of taxol given as a dose of 175 mg/m^2 over three hours in combination with cisplatin 80 mg/m^2 can be recommended for the treatment of patients with advanced NSCLC."

<div style="background:black;color:white">SUPPORTING PHASE II SINGLE AGENT CLINICAL TRIALS</div>

Four prospective phase II studies were conducted to determine the efficacy and safety of taxol as a single agent in patients with advanced non-small cell lung cancer. There were three single arm phase II studies and one randomized phase II study in which taxol and two experimental agents were administered.

– The study design are as follows: (from Section 2.2.2, vol. 86.2, p.51)

Study Design - Single Agent Studies

	Study 029			Study 027	Study 127	Study 201
	TAXOL	Piroxantrone	Merbarone	TAXOL	TAXOL	TAXOL
Initial dose (mg/m^2):	250	150	1000	200	200	225
⁻ion duration:	24 hrs	1 hr	5 days	24 hrs	3 hrs	3 hrs
ment schedule:		every 3 weeks		every 3 weeks	every 3 weeks	every 3 weeks
ɔse intensity (mg/m^2/wk):	83	50	1667	67	67	75
Dose reduction:	for hematologic toxicity > Grade II & for non-hematologic ≥ Grade III			for hematologic toxicity Grade IV; or Grade III nonhematologic	for significant hematological or non-hematological effects	for Grade III neutropenia, Grade I-II thrombocytopenia or Grade III non-hematologic toxicity
Dose escalation:	n/a			if < Grade III neutropenia or < Grade I-II thrombocytopenia	n/a	n/a

Overall, 224 patients with advanced non-small cell lung cancer were enrolled to receive taxol in the four studies.

The following table summarizes the efficacy results from the single agent studies:

Table No. 36
Efficacy Results- Single Agent Taxol Studies

	Number of Patients (%)			
	Study 029 (n=24)	Study 027 (n=26)	Study 127 (n=20)	Study 201 (n=53)
Response rate (%)	4/24 (17%)	5/26 (19%)	4/20 (20%)	10/53 (19%)
Time to Progression Median (months) (95% C.I.)	2.1 (1.5-4.4)	2.7 (1.6-4.7)	4.5 (2.6-5.6)	4.0 (2.1-5.6)
Survival Median (months) (95% C.I.)	4.4 (3.0-16.2)	8.1 (4.8-13)	11.7 (7.3-16.8)	9.0 (5.9-11.4)
One Year Survival % Patients (95% C.I.)	40% (21-59)	33% (16-48)	43% (22-64)	35% (23-48)