Discontinuation due to Death Within 30 Days

The number of patients who died within 30 days after last drug administration was 18 (11%) in the teniposide/cisplatin arm and 10 (6%) in the taxol/cisplatin arm.

Table No. 21
Death Within 30 Days- Study 103
(from Sec 8/10, vol. 5, p. 1538)

	Number of Patients (%)	
	Teniposide/cisplatin n=165	Taxol/cisplatin n=160
Number of Deaths within 30 days	18 (11)	10 (6)
Cause of Death		
Toxicity	8 (5)	4 (3)
Disease	5 (3)	1 (1)
Other	4 (2)	4(3)
Unknown	1 (1)	1 (1)

Dose Reduction and Treatment Delay

The dose of a particular drug is considered reduced when it is less than the mid value between the two dose levels. A course was considered delayed when given more than two days later than the planned first day.

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There were significantly more patients with dose reduction or dose discontinuation in the teniposide/cisplatin arm (33%) compared to the taxol/cisplatin arm (20%) (p=0.008). A total of 141 courses (21%) were reduced or discontinued in the teniposide/cisplatin arm as compared to 62 courses (8%) in the taxol/cisplatin arm. Hematologic toxicity was the main reason for dose reduction in the teniposide cisplatin arm while it was nonhematologic toxicity for the taxol/cisplatin arm as shown in the following table:

Table No. 22
Reason for Dose Reduction- Study 103

	Number of courses (%)	
	Teniposide/cisplatin n=68	Taxol/cisplatin n=38
Hematologic	**43 (63)**	**3 (8)**
Febrile nuetropenia	20	2
Leuco/neutropenia w/o fever	17	1
Thrombocytopenia ± anemia	6	-
Nonhematologic	**16 (24)**	**30 (79)**
Renal	13	13
Neurotoxicity	-	12
Allergy	-	2
Cardiac toxicity	2	1
Other]	1	2
Other	**9 (13)**	**5 (13)**
Incorrect calculation	7	3
Other reasons	2	2

Delay in study therapy was analyzed for 511 courses for teniposide/cisplatin and 633 courses for taxol/cisplatin, which correspond to all the courses administered after the first. Of the 633 courses of taxol/cisplatin, 81% (533/633) was given on time compared to 40% (202/511) courses of teniposide/cisplatin. The most frequent reason for dose delay is hematologic toxicity (63%) for the teniposide/cisplatin arm and nonhematologic toxicity for the taxol/cisplatin arm (15%).

Table No. 23
Treatment Delays - Study 103

	Number of courses (%)	
	Teniposide/cisplatin n=511	Taxol/cisplatin n=633
Courses given on time	**202 (40)**	**511 (81)**
Reason for delay		
Hematologic	**195 (63)**	**10 (8)**
Leuc/neutropenia w/o fever	162	8
Febrile neutropenia	14	0
Others	19	2
Nonhematologic	**25 (8)**	**18 (15)**
Renal	10	2
Infection	6	6
GI	5	2
Other	4	8
Other Reasons	**89 (29)**	**94 (77)**
Not drug related	29	41
Administrative reason	30	37
Disease related	17	10
Patient request	9	4
Reason not reported	4	2

Reviewer's comment: *There were 309 courses delayed (60%) in the teniposide/cisplatin arm, and 122 courses (19%) in the taxol/cisplatin arm.*

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ON ORIGINAL

Hematologic toxicity:

Neutropenia (course 1 and worst course) was significantly more frequently reported in the teniposide arm than in the taxol/cisplatin arm (p<0.0001). Severe neutropenia was reported at course 1 in 75% of patients receiving teniposide/cisplatin as compared to only 19% of patients receiving taxol/cisplatin (p<0.0001). When considering worst course values, again the teniposide-containing arm caused significantly more severe neutropenia (p<0.0001).

Table No. 24
Neutropenia
(from Sec 8/10, vol. 5, p.1510 and 1511)

	Number of Patients (%)			
	FIRST COURSE[a]		WORST COURSE[b]	
	ten/cis n=146	tax/cis n=145	ten/cis n=156	tax/cis n=156
Neutropenia				
Grade 0	22 (15)	73 (50)	10 (6)	31 (20)
Grade 1	5 (3)	22 (15)	4 (3)	20 (13)
Grade II	10 (7)	23 (16)	8 (5)	20 (13)
Grade III	27 (18)	22 (15)	26 (17)	41 (26)
Grade IV	82 (56)	5 (3)	108 (69)	44 (28)
Grade III + IV	**109 (74)**	**27 (18)**	**134 (86)**	**85 (54)**
Thrombocytopenia[c]				
Grade III	16 (10)	- (-)	30 (18)	2 (1)
Grade IV	16 (10)	- (-)	30 (18)	2 (1)
Grade III + IV	**32 (20)**	**- (-)**	**60 (36)**	**4 (2)**

[a]any neutropenia/thrombocytopenia p<0.0001 severe neutropenia/thrombocytopenia p<0.0001
[b]any neutropenia/thrombocytopenia p<0.0001 severe neutropenia/thrombocytopenia, p<0.0001
[C] only worst grade thrombocytopenia shown

Thrombocytopenia was significantly more frequently observed in the teniposide/cisplatin arm (course 1: p<0.0001; worst course: p<0.0001). Severe thrombocytopenia was also significantly more frequently reported in the teniposide-containing arm (course 1: p<0.0001; worst course: p<0.0001).

Overall anemia was observed in 93% of the patients receiving teniposide/cisplatin and 77% of patients receiving taxol/cisplatin. This difference was statistically significant (p<0.0001). Severe anemia (worst course) was also observed significantly more frequently in the teniposide/cisplatin arm (37/163 patients- 23%) compared to the taxol/cisplatin arm (15/159 patients- 9%), (p=0.001).

Neutropenic fever

Neutropenic fever was reported when a febrile episode was reported with a Grade IV neutrophil count. More patients developed febrile neutropenia in the cisplatin/teniposide (60 patients- 36%) arm compared with the taxol/cisplatin (8 patients- 5%) combination ($p<0.0001$). In the cisplatin/teniposide arm, there were 71/676 courses (11%) with febrile neutropenia compared to 9/793 (1%) courses in the taxol/cisplatin arm.

A total of 50 courses with infections were reported in 39 patients (24%) in the teniposide/cisplatin arm and 40 courses with infection in 30 patients in the taxol/cisplatin arm. ($p=0.342$)

Bleeding and Blood Transfusions

Most of the bleeding episodes reported were localized and not associated with clinical consequences. In the teniposide/cisplatin arm, 35 patients (21%) experienced bleeding episodes versus 35 patients (22%) in the taxol/cisplatin arm. However, the number of patients requiring red cell transfusions was significantly higher in the teniposide/cisplatin arm than in the taxol/cisplatin arm (65 patients-39% versus 21 patients-13%). ($p<0.0001$)

Hypersensitivity reactions:

Hypersensitivity reactions occurred more frequently in the taxol/cisplatin arm (8 patients-5%) compared to the teniposide/cisplatin arm (2 patients-1%). ($p=0.058$) Severe hypersensitivity reactions resulted in drug discontinuation in 3 patients: 1 in the teniposide/cisplatin arm and 2 in the taxol/cisplatin arm.

Cardiovascular events

Cardiovascular events other than hypotension and bradycardia occurred in 23 patients (14%) in the teniposide/cisplatin arm and 16 patients (10%) in the taxol/cisplatin arm. Severe cardiovascular events were reported in 10 patients in the teniposide/cisplatin arm and 12 patients in the taxol/cisplatin arm. Severe events led to treatment discontinuation in 1 patient in the teniposide/cisplatin arm and 2 patients in the taxol/cisplatin arm.

Peripheral neuropathy

Peripheral neuropathy were mostly Grade I or II, was observed in 28% of patients enrolled in the teniposide/cisplatin arm as compared to 68% in the taxol/cisplatin arm ($p<0.0001$). Severe events (Grade III) were reported in 14 patients receiving the taxol combination and 1 patient receiving the teniposide combination ($p=0.0003$). Peripheral neuropathy led to

treatment discontinuation in 13 patients enrolled in the taxol/cisplatin arm versus none in the teniposide/cisplatin arm.

Arthralgia/myalgia

Arthralgia/myalgia was reported by 38 patients (23%) in the teniposide arm and 88 patients (55%) in the taxol arm ($p<0.0001$). Six taxol-treated patients developed severe symptoms as compared to one teniposide-treated patient.

Asthenia

Asthenia was reported by about half of the patients in each arm.. Grade III to IV asthenia was reported by 16 patients in the teniposide arm and 8 patients in the taxol arm.

Alopecia

Only a small number of patients did not experience alopecia (13% in the teniposide and 11% in the taxol arm). The number of patients who reported alopecia were similar in both arms.

Gastrointestinal Manifestations

Gastrointestinal complaints were reported evenly in the two treatment arms. Severe (grade III and IV) nausea and vomiting was reported by 32 patients (19%) in the teniposide arm and 22 patients (14%) in the taxol arm ($p=0.183$). Diarrhea was reported by 50 patients in the teniposide arm and 49 patients in the taxol arm. grade III mucositis was reported by 1 patient in the teniposide arm and 2 in the taxol arm.

Renal function

Renal function was evaluated using serum creatinine, creatinine clearance and investigator reported adverse event terms. A similar number of patients reported renal toxicity ($p=0.622$). Severe events occurred in 3 patients enrolled in the teniposide/cisplatin arm and 2 in the taxol/cisplatin arm.

Sponsor's Discussion (Study 103)

"The Phase III study described in this report was initiated in 1993 by the EORTC Lung Cancer Cooperative Group (LCCG). The Group had just completed study 08875 which compared 2 schedules of single agent teniposide to 2 schedules of the combination of teniposide and cisplatin [19]. The cisplatin-containing arms were superior to teniposide alone in terms of response rate (22% versus 6%, $p<0.001$) and survival (median of 7.2 months versus 5.9 months, $p=0.008$). Consequently, the EORTC LCCG decided to compare their standard combination of teniposide and cisplatin to a new promising combination of taxol and cisplatin.

This multicenter prospective randomized and well controlled Phase III trial was designed for patients with locally advanced or metastatic NSCLC previously untreated with chemotherapy. Between 26Aug93 and 29Feb96, a total of 332 patients from 19 centers were centrally randomized at the EORTC Data Center. Pretreatment characteristics were well balanced between the two groups. Of note, however, more patients had visceral and bone involvement in the taxol/cisplatin arm as compared to the teniposide/cisplatin arm.

The combination of taxol and cisplatin proved to be much easier to deliver than the teniposide/cisplatin combination. There were significantly more dose reductions and treatment delays in the teniposide/cisplatin arm, mostly due to severe hematologic toxicity. This resulted in a significantly higher cisplatin dose intensity in the taxol/cisplatin arm.

The taxol/cisplatin treatment was more efficacious than the standard therapy: significantly more patients achieved a clinical response in the taxol/cisplatin arm (37%, 58/157) than in the teniposide/cisplatin arm (26%, 41/156) ($p=0.041$). This difference favoring the taxol/cisplatin combination was statistically significant after adjustment for a number of potential prognostic factors in a logistic regression model.

This superiority in clinical response did not translate into significant differences in time to progression and survival. However, the median time to progression (5.1 months) and the median survival (9.5 months) for the taxol/cisplatin arm in this advanced NSCLC population must be considered as a significant improvement as compared to the natural history of this disease, as proven by the results obtained in several prospectively randomized trials which compared cisplatin-containing regimes to best supportive care.

In this study, patients receiving the combination of teniposide/cisplatin achieved a median TTP of 5.0 months and a median survival of 9.9 months. These median values are longer than these previously reported by the same EORTC-LCCG group with the same regimen (TTP=4.3 months; survival=7.2 months) and may reflect the selection of different patient population [19]. Of note, the previous EORTC LCCG study enrolled less female patients (20% versus 30%), more patients with a 5% weight loss (37% versus 27%), more patients

with ECOG PS = 2 (18% versus 10%) and more patients with metastatic disease (71% versus 63%) as compared to the current study.

The taxol/cisplatin combination had an unquestionably better safety profile than the teniposide/cisplatin combination. As compared to teniposide/cisplatin combination, the taxol/cisplatin combination was associated with significantly less leukopenia, neutropenia, thrombocytopenia and anemia. In addition, severe hematologic toxicity was also significantly more frequent in the teniposide/cisplatin arm . This resulted in more complications (i.e. febrile neutropenia, severe infections, RBC transfusions) in the teniposide/cisplatin arm.

Nonhematological toxicity was similar between both treatment arms with the exception of peripheral neuropathy and arthralgia/myalgia which were more frequent in the taxol/cisplatin arm. Most of these events were, however, mild to moderate in severity.

Overall, the number of patients who discontinued therapy due to drug-related adverse events and those who died on study was slightly higher in the teniposide/cisplatin arm.

The superior tumor response rate as well as excellent safety profile of the taxol/cisplatin combination translated into a significantly better quality of life for patients receiving this treatment. Patients enrolled in the taxol/cisplatin arm reported statistically better global health status, physical, role and social functioning scores. Moreover, taxol-treated patients reported significantly less fatigue but more peripheral neuropathy. Finally, dyspnea, appetite loss, hemoptysis and diarrhea scores almost reached statistical significance in favor of the taxol arm.

Some differences appear when the BMS database presented in this report is compared with the data presented in the EORTC publications. Most of these discrepancies are due to the fact that all randomized patients have been analyzed in this report, whereas EORTC excluded ineligible patients from their analysis. Also, the WHO criteria for clinical response were strictly applied by the BMS reviewers resulting in downgrading of 15 responses (9 in the taxol/cisplatin arm and 6 in the teniposide/cisplatin arm). Safety results were consistent with the EORTC publications.

Study CA139-103 is a large, randomized and well-conducted Phase III trial which provides evidence of an overall superiority for a taxol/cisplatin regimen over standard therapy in patients with advanced NSCLC. The taxol combination produced a better clinical response and safety profile which translated into a significantly better quality of life for these patients. Thus, the administration of taxol, given at a dose of 175 mg/m^2 over 3 hours in combination with cisplatin 80 mg/m^2, can be recommended for the treatment of patients with advanced NSCLC."

Study Protocol CA 139-208

Reviewer's comment: *During the Pre-NDA meeting of May 5, 1997, it was decided that study 208 would be included as one of the studies in the NDA application; however, due to the proximity to the planned submission date (June 1997) it was agreed that the full study report and primary data in electronic format will be submitted at a later date. The full study report was received by the agency on January 22,1998. The sponsor's overall analysis of safety and efficacy was not revised to include study 208.*

Title

Randomized Multicentric Comparative Study of Cisplatin Versus Cisplatin and Paclitaxel in Patients With Non-Small Cell Lung Cancer (NSCLC)

Investigator, Location of Trial

Thirty-five sites in ten European countries, Israel and Russia.

Publications

None

Study Period

11 Jan 95 - 2 Apr 96 (Study enrollment period).

Number of subjects:

414

Amendments:

- October 1994 (before trial activation): to clarify the means of diagnosis of NSCLC, acceptance of patients with asymptomatic brain metastases, and guidelines for dose reduction/ discontinuations in case of neurotoxicity were defined

Objectives:

Primary: survival
Secondary: response rates, time to progression, tolerability and quality of life

Study Design - Methodology:

Prospective multicenter, open-label, randomized study comparing cisplatin alone (100 mg/m^2) to a combination of taxol (135 mg/m^2 , 3-hour infusion) and cisplatin (80 mg/m^2) in patients with previously untreated non-small cell lung cancer. Patients were stratified by institution, performance status (Karnofsky 80-100 versus 60-70) and stage of disease (IIIB versus IV). Randomization was performed centrally by BMS using a Pocock minimization procedure. The accrual goal of 400 was believed to provide at least 85% power to detect a 50% relative difference in one-year survival rate in the taxol/cisplatin arm compared to cisplatin alone (i.e. an absolute increase of 12.5% in one-year survival rate or a difference in median survival of 2.5 months).

Diagnosis and Main Criteria for Entry:

Patients must fulfill all of the following criteria for eligibility:

- histologically proven diagnosis of non-small cell lung carcinoma
- no prior chemotherapy
- stage IIIB (not amenable to radical radiotherapy) or stage IV
- Palliative radiotherapy (to not more than 30% of marrow bearing bones) may have been given more than four weeks prior to study entry; but should have evidence of progressive disease prior to study entry. Indicator lesions should be outside a previously irradiated field.
- have radiologically or clinically documented disease

Exclusion Criteria

- past or current history of other neoplasms
- history of arrhythmias of CHF, even if well controlled
- pre-existing neurotoxicity ≥ grade 2
- active infections, allergy to taxol, teniposide or cyclosporine
- altered mental states/dementia
- need for urgent radiotherapy

Therapy, dose, route of administration:

Taxol was supplied by BMS (Batch no. C4B00, K4B00, L4B04, C5B00, G4B00, S92F021M, S93H013M) and cisplatin was obtained through commercial sources. Patients received a combination of taxol 175 mg/m^2 (3-hour IV infusion) followed one hour later by cisplatin 80 mg/m^2 (30 min. infusion) on day 1 repeated every 21 days. Standard premedication with dexamethasone (po), cimetidine (iv) and diphenhydramine (iv), or their equivalent, was given prior to taxol. Patients enrolled in the control arm received cisplatin (100 mg/m^2) on day 1 every 21 days with pretreatment and post-treatment hydration.

Treatment Duration:

Patients remained on study for a minimum of three courses in the absence of disease progression or intolerable toxicity. Patients who achieved stable disease received up to six courses. Patients continued up to two additional courses of treatment after best response.

Patients were removed from treatment for unacceptable toxicity, intercurrent illness, patient request, pregnancy or for other reasons which affected assessment of clinical status to a significant degree.

Study Parameters

Table No. 25

Patient Evaluation- Study 208
(Sec. 3.5, vol. 99.1, p30)

Parameters	Pretreatment	After each cycle
History and P.E.	x	x
Performance Status	x	x
Tumor measurement by P.E.	x	x
Quality of Life	x	every cycle and off study
Hematology	x	x
Chemistry	x	x
Creatinine Clearance	x	if indicated
Chest X-rays	x	x
Other Imaging	x	after C3 and C6/off study
ECG	x	if indicated
Toxicity Assessment	x	continuous

Statistical Considerations

Fisher's exact test was used to compare response rates between treatment arms. And comparison between treatment arms for safety and efficacy parameters were carried out using two-sided tests (alpha level of 5%). Kaplan -Meier estimates were used in the analysis of all time to event variables. A 95% confidence interval for the median time to event was computed using the method of Brookmeyer and Crowley. The primary comparison for survival and time to progression was a Logrank test stratified by performance status and disease stage.

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

Data were prospectively collected on case report forms and reviewed by clinical research associates from BMS for consistency and completeness, and verified against medical records, clinical charts and source documents. The data were then entered into the BMS database. BMS performed an audit of six sites representing 121 patients (29%).

SPONSOR'S STUDY RESULTS

Patients characteristics

Pretreatment characteristics were balanced between the two arms. The diagnosis of NSCLC was confirmed in 411 patients (99%). The median age was 60 years in both treatment arms. A total of 396 patients (96%) had measurable disease with lung, mediastinum, bone and lymph nodes outside the thorax as the most common sites of disease. Cell type was evenly distributed among treatment arms. Approximately 36% of patients had squamous cell carcinoma.

Table No. 26
Pretreatment Patient Characteristics, Study 208
(Sec 5.1 and 5.3, vol 99.1, pp52 and 57)

	Number of Patients (%)		
	Cisplatin n=207	Taxol/cisplatin n=207	Total n=414
Stage			
IIIA	0 (0)	1 (<1)	1 (<1)
IIIB	63 (30)	61 (29)	124 (30)
IV	144 (70)	145 (70)	289 (70)
Performance Status			
80-100	170 (82)	170 (82)	340 (82)
60-70	37 (18)	37 (18)	74 (18)
Weight loss in last 6 mos			
<5%	115 (55)	101 (49)	214 (52)
5-10%	44 (21)	48 (23)	92 (22)
>10%	25 (12)	27 (13)	52 (13)
Not reported	25 (12)	31 (15)	56 (14)
Gender			
Male	168 (81)	166 (80)	334 (81)
Female	39 (19)	41 (20)	80 (19)
Extent of Disease			
Intrathoracic	92 (44)	85 (41)	177 (43)
Visceral ± soft tissue± intrathoracic	94 (45)	96 (46)	190 (46)
Softtissue± intrathoracic	21 (10)	26 (13)	47 (11)

Prior therapy

Thoracotomy /lung resection was performed in 14% of all patients (13% in the cisplatin arm and 15% in the taxol/cisplatin arm. Radiotherapy was administered as adjuvant or primary therapy in 11 patients (3%), six patients in the cisplatin arm and five patients in the taxol/cisplatin arm.

Number of courses administered:

Patients enrolled in the cisplatin arm received a total of 759 courses (median=3) while those in the taxol arm received 889 courses (median=5). (p=0.0002) The median treatment duration was also significantly shorter in the cisplatin arm=9.9 weeks compared to the taxol/cisplatin arm, 14.9 weeks. (p=0.0014).

SPONSOR'S EFFICACY RESULTS

Sponsor's Analysis of Survival

At the time of analysis, 81% of patients have died. Survival was calculated from the day of randomization to the day of death. Otherwise, the patient was censored on the last day known to be alive. The median survival for patients enrolled in the cisplatin arm was 8.6 months (95% C.I. 7.1-10.3 months) as compared to 8.1 months (95% C.I. 7.3-9.2 months) for patients enrolled in the taxol/cisplatin arm (p=0.862; hazard ratio 0.98, 95% C.I. 0.79-1.22). The Kaplan-Meier estimated percentage of patients alive at one year was 36% in the cisplatin arm and 30% in the taxol/cisplatin arm.

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Time to progression:

Time to progression was calculated from the day of randomization until the date progressive disease was first reported or date of death if progression was not documented. Patients who did not progress were censored to their last day of follow-up. Patients who received secondary therapy without a progression date were censored at the day of the start of the second therapy. Patients who were lost to follow-up were censored at the last known alive date. Patients who were never treated or had a wrong histology were censored on the day of randomization.

Median time to progression was 3.2 months (95% C.I. 2.4-3.9 months) in the cisplatin arm as compared to 4.3 months (95% C.I. 3.5-4.6 months) in the taxol/cisplatin arm (p=0.085, hazard ratio of cisplatin over taxol/cisplatin =1.21).

Table No. 27
Time to Progression Analysis- Study 208
(summarized from sec. 7.1, vol 99.1, p.103)

	Number of Patients (%)	
	Cisplatin n=207	Taxol/cisplati n n=207
Patients who have progressed	**168 (81)**	**174 (84)**
Documented Progression On-Study	101	89
Progression during follow-up	44	64
Death	23	21
Reason for censoring		
Secondary therapy	**35 (17)**	**25 (12)**
Radiotherapy	19	16
Chemotherapy	14	8
Surgery	2	1
Other reasons	**4 (2)**	**8 (4)**
Not relapsed	2	0
Never treated	1	5
Others	1	3

When the 57 patients who received salvage chemotherapy or radiotherapy were considered to have progressed at the time of start of therapy, the median time to progression was 2.7 months in the cisplatin arm as compared to 4.1 months in the taxol/cisplatin arm (p=0.026).

***Reviewer's comment**: Some patients in the cisplatin arm were taken off due to toxicity and subsequently given salvage therapy. Patients in the taxol + cisplatin arm who experienced the same cisplatin-related toxicities had cisplatin stopped but continued to receive taxol instead of an alternative therapy. This might explain the apparent widening of the difference in time to progression when the first date of secondary therapy is considered as an event.*

***Reviewer's comment**: Actual tumor measurements were entered in on-treatment case report forms but not after patients were taken off study. During follow-up,(which is every two months) documentation of progression/relapse is entered into follow-up case report forms by indicating the site and date of progression only.*

Chemotherapy, radiotherapy and surgery were given to patients after treatment on study. The most frequently used second line chemotherapy agents were vinorelbine, carboplatin, etoposide, ifosfamide and cisplatin. Five patients originally randomized to the cisplatin arm received taxol.

Table No. 28
Subsequent Therapy- Study 208
(summarized from sec. 7.2, vol 99.1, p.112)

	Number of Patients (%)	
	Cisplatin n=207	Taxol/cisplatin n=207
# Patients with follow-up therapy	122 (59)	109 (53)
Surgery	5 (2)	3 (1)
Radiotherapy	71 (34)	76 (37)
Chemotherapy	76 (37)	57 (28)

Clinical response:

A total of 387 patients could be evaluated for clinical response. Each lesion site was classified as either measurable or non-measurable. Non-measurable lesions were described as "present" or "absent" at baseline. Only uni- or bidimensional measurable sites were considered as indicator lesions for response evaluation.

Criteria for response evaluation in patients with measurable disease (bi- or unidimensionally measurable)

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 lasting for at least 4 weeks

without appearance of any lesions or without progression in any of the sites. Non-measurable lesions must remain stable or regress for this category.

Stable Disease (SD) Steady state or response less than partial response of at least four weeks duration without appearance of new lesions.

Progressive Disease (PR) an increase in >25% of the product of diameters of measurable lesions and/or appearance of new lesions.

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.

***Reviewer's comment**: A total increase of ≥ 25% in the sum of lesion areas is considered a progression in studies 165 and 208. In study 103, the criterion is more stringent in that a 25% increase in even a single lesion will be considered a progression of disease.*

BMS response rates were reported for evaluable patients with measurable disease and for all randomized patients. Patients with non-measurable disease were not considered in the response analysis. .

***Reviewer's comment:** In the protocol, patients with non-measurable disease were to be assigned a response category using estimates of lesion measurements similar to the WHO criteria.*

Among the 414 patients randomized, 200 had measurable disease in the cisplatin arm and 196 in the taxol/cisplatin arm. For patients with measurable disease in the cisplatin arm, there were one complete response (1%) and 33 partial responses (17%) for an overall clinical response rate of 17% (34/197, 95% C.I. 12-23%). In the taxol/cisplatin arm for patients with measurable disease, three patients achieved a complete response (2%) and 47 patients had a partial response (25%) for an overall clinical response rate of 26% (50/190, 95% C.I. 20-33%). The difference in overall response was statistically significant in favor of the taxol/cisplatin arm (p=0.028).

Time to response:

Time to response corresponded to the period from the first day of treatment until a response was documented. The median time to first response for patients receiving cisplatin was 8.9 weeks (range 2.6-18.7 weeks) versus 8.6 weeks (range 3.0-17.9 weeks) for patients receiving taxol/cisplatin. (p=0.329)

Duration of response:

The duration of overall response was calculated for all responders with measurable disease and defined as the period between the day of first study drug administration and the date progressive disease was first noted. The median duration of overall response for clinical