Time to Tumor Progression, Study 165

	Taxol/ Cisplatin	HD-Taxol/ Cisplatin	Cisplatin/ Etoposide
Median (months) 95% C.I.	4.3 (3.3-5.1)	4.9 (4.0-5.8)	2.7 (2.2-3.2)
Logrank (p-value) vs. Cisplatin/etoposide (α=0.0125)	0.0504	**0.004**	

Time to progression was also analyzed by considering the 53 patients who were censored for secondary chemotherapy or radiation therapy as being progressed at the date they started the secondary therapy. When analyzed this way, the time to progression in the taxol/cisplatin arm was 3.6 months compared to 2.7 months in the cisplatin/etoposide arm (p=0.027) and 4.3 months for the taxol/cisplatin/G-CSF arm (p=0.004).

Sponsor's Analysis of Tumor Response

Each lesion was classified according to its accessibility. Bidimensionally or unidimensionally measurable lesions were measured by physical examination and radiology scans. Non-measurable lesions such as pleural effusions, lymphangitic or confluent multinodular lung metastases were described as "present" at baseline and "present", "absent", "increased" or "decreased" at each evaluation compared to the previous. Indicator lesions included bi- and unidimensional tumor localizations.

All tumor evaluation data were reviewed by a BMS physician and compared to the assessment made by the study chairman. ECOG assessed indicator lesions selected by the principal investigator to be followed for response whereas BMS assessed all reported disease sites. A final assessment was reached by consensus between BMS and ECOG.

Definition of Response

Complete Response:

Complete disappearance of all clinically detectable malignant disease for at least four weeks. Pathologic complete response may be declared after biopsy.

Partial Response:

For measurable, bidimensional lesions: Greater than or equal to 50% decrease in tumor area (multiplication of the longest diameter by the greatest perpendicular diameter), or a 50% decrease in the sum of the products of the perpendicular diameters of multiple lesions in the same organ site for at least 4 weeks.

For measurable, unidimensional lesions: Greater than or equal to 30% decrease in linear tumor measurements for at least four weeks.

For non-measurable, evaluable lesions: definite improvement in evaluable malignant disease estimated to be in excess of 50% and agreed upon by two independent investigators lasting for at least 4 weeks.

Stable Disease :

No significant change in measurable or evaluable disease for at least 4 weeks , including a decrease in malignant disease of less than 50%, or a decrease in unidimensional measurable disease of less than 30%, or increase in malignant disease of < 25%.

Progression: Significant increase in the size of lesions present at the start of therapy or after a response, or appearance of new metastatic lesions, or stable objective disease associated with a deterioration in performance status of ≥1 level related to malignancy.

For measurable, bidimensional and unidimensional lesions: Greater than or equal to 25% increase in tumor area of any malignant lesions greater than 2 cm. Greater than or equal to 50% increase in the size of the product of diameters if only one lesion is available for measurement and was ≤ 2 cm^2 during start of treatment. Greater than or equal to 25% increase in the sum of the liver measurements below the costal margins and xiphoid.

For nonmeasurable, evaluable lesions: Increase in the area of malignant lesions estimated to be greater than 25%, increase in the size and number of bony metastases and appearance of new lesions

For non-measurable, nonevaluable lesions: definite evidence of new clinically detectable malignant disease

Reviewer's comment**: In the study report, one of the definitions of tumor progression is: (1) an increase of 25% or more in any lesion **or in the sum of the products of the diameters of any lesion 2 cm^2 or greater.

Evaluation of Patient's Total Response

Progression occurs if any previously measurable or evaluable malignant lesions fulfill progression criteria or new malignant lesions develop. Organ site stabilization will not detract form a total patient PR in the presence of other organ site PR's or CR's. Stabilization of evaluable disease does not detract from CR's or PR's in measurable sites,

but the overall response should be a PR. A deterioration in performance status of ≥ 1 level related to malignancy is considered a progression.

***Reviewer's comment**: Response evaluation of "evaluable" lesions was further defined in the study analysis (but was not in the protocol):*

> For bidimensionally measurable lesions at baseline, an evaluation of "decreased" during follow-up was considered to be a minimum of 50% decrease from the previous measurement. A subsequent (≥ 4 weeks) evaluation of "present" was a considered as a confirmation of continued response, with less than a 50% further decrease or less than a 25% increase.

***Reviewer's comment**: Ideally, the assessment of all lesions should be maintained throughout the study. Although it is clinically possible that previously measurable lesions become non-measurable during the course of treatment, the assessment of overall response in such cases was a major problem for the FDA reviewer. When a lesion response evaluation changes from measurable to evaluable, the rules that apply for response assessment also change, allowing for greater subjectivity and limiting one's ability to confirm the findings. In such cases, patients cannot be classified as responders by the FDA reviewer. On the other hand, For lesions with bidimensional measurements that are subsequently given unidimensional measurements, there is growing evidence that there might be good correlation between criteria for response assessments. These patients were considered evaluable for response assessments by the FDA.*

Seventeen of the 599 patients could not be evaluated for response, 11 of which never received study treatment. There were 520 patients with measurable disease who were evaluable for response.

Table No. 11
Clinical Response, Study 165

	Number of Patients (%)		
	Taxol/Cisplatin n=198	HD-Taxol/ Cisplatin n=201	Cisplatin/ Etoposide n=200
Overall Response 95% C.I.	**(46/198) 23%** (18-30%)	**(51/201) 25%** (20-32%)	**(24/200) 12%** (8-17%)

The difference in overall response rates for the treatment comparison of taxol/cisplatin vs. cisplatin/etoposide was statistically significant (odds ratio = 2.3, p=0.003) as was the difference in overall response rates for taxol/cisplatin/G-CSF vs. cisplatin/etoposide (odds ratio = 2.8, p<0.001). Using the logistic regression model, these differences remained statistically significant after adjustment for pre-specified baseline characteristics considered as prognostic factors.

In all treatment arms, patients with Stage IIIB disease had higher response rates. With the exception of patients in the taxol/cisplatin arm who had a response rate of 35% for ECOG PS of 0 and 23% for ECOG PS of 1, response rates for patients with ECOG PS of 0 versus 1 were generally similar. Patients with <5% weight loss appear to have higher response rates compared to patients with > 5% weight loss. Patients who had received prior radiotherapy had comparable response rates except for patients in the taxol/cisplatin/G-CSF arm. In this group, the response rate for patients without prior radiotherapy was 34% compared to 16% for patients who were previously treated with radiation.

Sponsor's Analysis of Time to Response

Time to response corresponded to the period from the first day of treatment until the date of response. The median interval between beginning of study medication and the first observation of an objective response was 8.0 weeks (range: 3.0 to 19.1 weeks) in the taxol/cisplatin arm, 8.1 weeks (range: 2.9 to 25.0 weeks) in the taxol/cisplatin/ G-CSF arm , and 9.2 weeks (range: 3.1 to 20 weeks) in the cisplatin/etoposide arm.

Sponsor's Analysis of Duration of Response

Duration of response was defined as the period from the first day of treatment until the date progression was first noted. Patients who did not relapse prior to this analysis and who were lost to follow-up were censored at their last known alive date and patients who received secondary therapy without documentation of progression were censored at the time of secondary therapy.

Reviewer's comment: *Note that the sponsor used the "first day of treatment" instead of the first day of documentation of a response in their definition of duration of response.*

The median response duration in the taxol/cisplatin arm is 7.1 months (range: 3.3 to 29.4+ months) , 9.2 months (range: 2.2 to 30.2 months) in the taxol/cisplatin/G-CSF arm, and 7.5 months (range 3.0 to 24.7 months) . The difference in response duration for each of the taxol-containing treatment arms were not statistically significant.

Sponsor's Analysis of Quality of Life Assessments

Reviewer's comment: *The statistical analysis of quality of life submitted to the agency in November 1994 proposed using one of two methods depending "on the nature and degree of missingness and dropout for the study". A comparison of change from baseline at each of three time points will be analyzed; or longitudinal methods will be used to model and compare trends over time. The sponsor presented results of their*

analysis based on comparisons of three time points from baseline. The FDA statistician's review includes a longitudinal analysis of quality of life.

Quality of Life (QOL) was evaluated using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and was assessed by evaluation of median change from baseline for seven factors: physical well-being, social/family well-being, relationship with the doctor, emotional well-being, functional well-being, lung cancer symptoms, and total FACT-Lung score. In each of the 37 questions, patients were asked how true each of the statement has in the preceding seven days by choosing one of five different options, valued 0 to 4 ("not at all" to "very much"). Patients were asked to complete the questionnaire at baseline, week 7, 13 and 26.

Quality of life was analyzed by comparing the change from baseline at each of the three time points. Six of the seven QOL factors assessed demonstrated no difference in the change from baseline over time across the treatment arms except for change in lung cancer symptoms (questions under "Additional Concerns"). This section of the questionnaire asked the patients to rate the following during the past seven days. Questions 1-9 were rated from 0 to 4 (each number on the scale with a distinct meaning), while question 10 was rated from 0 to 10 (not at all to very much so) with the patient deciding a particular number designation:

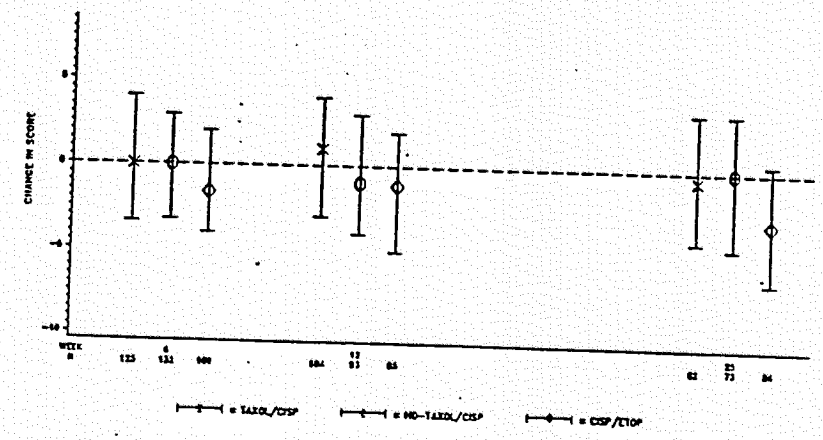
1. I have been short of breath.
2. I am losing weight.
3. My thinking is clear.
4. I have been coughing.
5. I have been bothered by my hair loss.
6. I have a good appetite.
7. I feel tightness in my chest.
8. Breathing is easy for me.
9. I regret my smoking. (for smokers only)
10. How much do these additional concerns affect your quality of life?

There was a significant difference for taxol/cisplatin over cisplatin/etoposide ($p=0.027$). Patients in the taxol/cisplatin arm reported no initial change followed by an improvement in their lung cancer symptoms by the third month; subsequently, patient symptoms approached baseline by the sixth study month. Patients in the taxol/cisplatin/G-CSF arm reported no initial change in their lung cancer symptoms followed by a gradual worsening by the third month and return to baseline by the sixth. In the cisplatin/etoposide arm, patients had an overall worsening of lung cancer symptoms throughout the course of study.

FIGURE 13

FACT-L QOL SCALE: LUNG CANCER SYMPTOMS

CHANGE FROM BASELINE - MEDIAN AND QUARTILES



SPONSOR'S ANALYSIS OF SAFETY RESULTS

All 588 patients who received study therapy were evaluated for safety.

Criteria for Dose Modifications

For all treatment arms, the AGC and platelet nadir, as well as the AGC and platelet count on the day of scheduled retreatment were taken into account for determining the dose modification during the subsequent course summarized in the following table:

Table No. 11
Dose Modifications for Hematologic Toxicities (Study 165)
(summarized from sec 3.4, vol3, p688-689)

	Subsequent Dose of Taxol			Subsequent Dose of Etoposide	
	taxol/cisplatin or HD-taxol/cisplatin	HD-taxol/ cisplatin	taxol/ cisplatin		
AGC/Platelet Nadir of Prior Course	AGC/Platelet On the Day of Retreatment				
	<1500/<100	≥1500/≥100	≥1500/≥100	<1500/ <100	≥1500/ ≥100
>1000/>75	0	250	135	0	100
500-1000/50-75	0	200	110	0	85
<500/<50	0	175	90	0	70

Dose modifications for non-hematologic toxicities were allowed.

Table No. 12
Dose Modifications for Non-Hematologic Toxicities (Study 165)
(summarized from sec 3.4, vol. 3, p 688-690)

	Taxol	Cisplatin	Etoposide
Hepatic (ULN[1])			
SGOT 2-2.5x	↓50%		
>2.5x	hold		
Bilirubin 1.5-2x	↓50%		
>2x	hold		
Renal /Creatinine			
>1.5 but≤2.0		↓50%	
>2.0	hold	hold	hold
Cardiovascular[2]	hold/off study		
Neurologic [3]			
Grade 1	↓25%		
Grade 2	hold		
Hypersensitivity			
moderate	medical treatment, attempt restart		
severe	off study		
Nausea/Vomiting Grade 3	all drugs ↓25%		
Mucositis Grade 3	all drugs ↓25%		
Others			
Grade 3 or 4	hold treatment until ≤Gr. 1, ↓ 50%		
Grade 2	hold treatment until ≤Gr. 1, ↓ 25%		

[1] ULN= upper limit of normal

[2] symptomatic arrhythmia, chest pain, symptomatic hypotension

[3] for ≥Grade 3 neurologic toxicity, dose of cisplatin and taxol were reduced by 50% when patient recovered to grade 1

Reviewer's comment: *Data on dose modifications for Study 165 was not included in the sponsor's analysis of safety and efficacy.*

Discontinuation of Therapy

Patients may be removed from the study for progressive disease, excessive toxicity or greater than 5% weight loss.

Two-hundred fifteen patients discontinued treatment due to adverse events: 75 (38%) in the taxol/cisplatin, 92 (46%) in the taxol/cisplatin./G-CSF and 48 (24%) in the cisplatin/etoposide arm. More patients in the taxol/cisplatin and the taxol/cisplatin/G-CSF came off study for toxicity ($p=0.003$ and $p<0.001$, respectively). Neurotoxicity was the most common reason, followed by gastrointestinal toxicities.

Table No. 13
Off Study Reasons, Study 165
(from sec 6.1, vol 3, p.748)

	Number of Patients (%)		
	Taxol/Cisplatin (n=198)	HD-Taxol/ Cisplatin (n=201)	Cisplatin/ Etoposide (n=200)
Disease Progression[a]	86 (43)	71 (35)	105 (53)
Toxicity	75 (38)	92 (46)	48 (24)
Neurotoxicity	39	62	15
Gastrointestinal[b]	19	14	15
Others[c]	13		
Myelosuppression and Infection	13	5	7
Renal	14	3	4
Ototoxicity	3	1	7
Hypersensitivity	2	5	--
Death	14 (7)	17 (8)	19 (10)
Patient Request	11 (6)	11(5)	13 (7)
Completed/Investigator Decision	8 (4)	4(2)	4(2)
Never Treated	3 (2)	4 (2)	4 (2)

[a] There were significantly more patients who came off study due to progression of disease in the cisplatin/etoposide arm compared to the taxol/cisplatin/G-CSF arm. ($p<0.001$)
[b] nausea, vomiting, stomatitis, diarrhea, anorexia, abdominal pain, ileus
[c] includes weight loss, fatigue, weakness, arthralgia, myalgia, and cardiovascular events

Discontinuation due to Death on Study

A total of 60 patients (10%) died within 30 days of last treatment dose. There were 17 (9%) in the taxol/cisplatin arm, 20 (10%) in the taxol/cisplatin/G-CSF arm, and 23 (12%) in the cisplatin/etoposide arm.

Hematologic Toxicity

Grade IV leukopenia was encountered more frequently in the high dose taxol arm despite the use of G-CSF (Grade IV taxol/cisplatin vs. taxol/cisplatin/G-CSF p=0.002; Grade IV taxol/cisplatin/G-CSF vs. cisplatin/etoposide p=0.007). Grade IV granulocytopenia was more frequently encountered with taxol/cisplatin (144/195, 74%) and taxol/cisplatin/ G-CSF (128/197, 65%) arms compared to the cisplatin/etoposide arms (108/196, 55%). (Grade IV taxol/cisplatin vs. cisplatin/etoposide p<0.001, Grade IV HD-taxol/cisplatin vs. cisplatin/etoposide p=0.051).

Thrombocytopenia of grade IV severity was more frequently encountered in the HD-taxol/cisplatin arm (5%) and in the cisplatin/etoposide arm (5%) as compared to the taxol/cisplatin arm (1%). Grade IV cisplatin/etoposide vs. taxol/cisplatin p=0.020

Reviewer's comment: *Since longer infusion schedules of taxol are thought to be more myelosuppressive, an analysis of the incidence of fever/neutropenia would have been invaluable in assessing its clinical implication. The study report submitted by the sponsor did not contain such an analysis. An analysis of the database was not possible since only worst grade toxicities were reported for each patient and fever/neutropenia was not reported as an event. White blood cell and neutrophil counts per course were available; however, temperature readings were not. Information regarding fever/neutropenia can be gathered from data on hospitalizations but may be incomplete.*

Infection and Fever without Infection:

Approximately one-third of the patients in each arm experienced an infection on study. Fever without infection was encountered more frequently in the taxol treatment arms as compared to the cisplatin/etoposide arm. However, only for the taxol/cisplatin/G-CSF vs. cisplatin/etoposide comparison was the difference significant (p=0.031).

Hypersensitivity Reactions

Grades I-IV and severe reactions (Grade III-IV) were reported most frequently in the taxol/cisplatin/G-CSF arm. The difference among treatment arms was significant (Grade I-IV overall comparison p=0.002; Grade III-IV overall comparison p=0.009).

Cardiovascular Events

Overall, there was a significant difference across treatment arms (p=0.007) in the incidence of cardiovascular events reported as cardiac symptoms, hypotension or hypertension. The difference in cardiovascular events between the taxol/cisplatin and cisplatin/etoposide arms was of borderline significance (p=0.058), while there were significantly more cardiovascular events in the taxol/cisplatin/G-CSF arm as compared to the cisplatin/etoposide arm (p=0.002). Severe cardiovascular events were reported in a similar frequency among the treatment arms.

Neurological Toxicity

Neurosensory toxicity (Grade I-IV) was more frequently reported in the taxol/cisplatin/G-CSF arm (61%) as compared to the taxol/cisplatin (48%) and the cisplatin/etoposide arms (25%). Severe (Grade III-IV) neurosensory toxicity was significantly higher in the taxol/cisplatin/G-CSF arm as compared to the other two treatment arms (p<0.001). There were significantly more severe (Grade III-IV) neuroclinical events reported in the taxol/cisplatin/G-CSF arm as compared to the cisplatin/etoposide arm (p=0.040). There was significantly more Grade I-IV (p=0.041) and Grade III-IV (p=0.047) neuromotor toxicity reported in the taxol/cisplatin/G-CSF arm as compared to the taxol/cisplatin arm.

Constitutional Symptoms

Arthralgia/myalgia of any grade was reported more frequently in the taxol arms as compared to the cisplatin/etoposide arm (overall comparison p<0.001).

Gastrointestinal Manifestations

Nausea (Grade I-III) and severe (Grade III) nausea was reported in a similar frequency among treatment arms. Vomiting (Grade I-IV) and severe (Grade III-IV) vomiting was reported in a similar frequency among treatment arms. Diarrhea (Grade I-IV) was reported in a significantly higher incidence in the taxol treatment arms as compared to the cisplatin/etoposide arm (overall comparison p<0.001). Patients in the taxol/cisplatin /G-CSF arm reported significantly more stomatitis (Grade I-IV) than in either the taxol/cisplatin arm (p=0.031) or the cisplatin/etoposide arm (p=0.005).

Hepatic and Renal Function

There was significantly more hepatic dysfunction (Grade I-IV) in the taxol/cisplatin/G-CSF arm than in the taxol/cisplatin (p=0.008) or the cisplatin/etoposide (p=0.002) arms. Renal impairment (Grade I-V) was reported in a similar frequency among treatment arms.

Sponsor's Discussion (Study 165)

"The study described in this report was initiated by the ECOG in 1993 to determine whether taxol in combination with cisplatin would result in an improved response and/or superior survival in advanced NSCLC patients as compared to the reference regimen cisplatin and etoposide. The reference regimen was chosen by the ECOG based on an analysis of previous ECOG randomized phase III trials in advanced NSCLC that demonstrated the cisplatin/etoposide combination resulted in the highest one year survival rate among several chemotherapy regimens.

The results from this study clearly demonstrate the superiority in response rate and longer time to progression in each of the taxol/cisplatin arms as compared to the standard regimen. While the proportion of one-year survivors with standard therapy was higher in the present study than previously reported by the ECOG for the standard combination of cisplatin/etoposide, a greater number of patients treated with either taxol/cisplatin regimen survived one year. The one year survival rates, approaching 40%, achieved by treatment with either taxol combination represent a clinically meaningful survival improvement for patients with advanced NSCLC. There was strong statistical evidence to conclude that survival in each of the two taxol/cisplatin arms was at least as good or perhaps better than the standard therapy

Additionally, the remarkable efficacy results achieved by either taxol/cisplatin arm was not to the detriment of patients' quality of life. This is demonstrated in five of the seven quality of life factors assessed where there was no difference in the change from baseline across treatment arms. For the remaining factors there was a trend in favor of the taxol/cisplatin/G-CSF arm over standard therapy in terms of emotional well-being, and statistically significant superiority for the taxol/cisplatin arm over standard therapy in terms of lung cancer symptoms.

In this well controlled three arm phase III trial, 599 chemotherapy naive patients with advanced non-small cell lung cancer were stratified by four prognostic factors: disease stage, performance status, weight loss and disease measurability. Patients from 34 centers were randomized by the ECOG to one of three treatment arms: high dose taxol, 250 mg/m^2 given over 24 hours, followed by cisplatin 75 mg/m^2 and G-CSF; low dose taxol, 135 mg/m^2 given over 24 hours, followed by cisplatin 75 mg/m^2; and the standard, cisplatin 75 mg/m^2 day 1, and etoposide 100 mg/m^2 on days 1-3.

The advanced stage of disease in the study population is demonstrated by the fact that 80% of all patients had metastatic disease with two or more involved disease sites, more than two-thirds had an impaired performance status, one-third had weight loss of 5% or greater in the six months preceding study entry, and one-half of the patients had a comorbid chronic disease.

Pretreatment patient characteristics were well balanced among treatment arms, with no statistical difference at baseline. Given the advanced nature of the malignant disease in this study population the response rates achieved in either of the taxol treatment arms are noteworthy. The response rates of 26% in the low dose taxol arm and 30% in the high dose taxol arm are significantly superior when compared to the response rate of 14% in the standard arm ($p=0.003$ and $p<0.001$, respectively). This superiority in response for either taxol/cisplatin treatment compared to the reference regimen was maintained after adjustment for the pre-specified baseline characteristics considered as prognostic factors and the stratification factors.

The median time to disease progression was prolonged by each of the taxol treatments. In the low dose taxol and high dose taxol arms the median time to disease progression was 4.3 months and 4.9 months, respectively, while it was 2.7 months for the standard therapy ($p=0.050$ and $p=0.004$, respectively). Although in the Cox regression model the difference in the median time to progression was of borderline significance for the comparison of low dose taxol to the standard ($p=0.060$), the median time to progression remained significantly longer for treatment with high dose taxol as compared to the standard ($p=0.005$).

Both taxol-containing combinations resulted in a trend for longer survival. The median survival for patients in the low dose taxol and high dose taxol arms was 9.3 months and 10.0 months, respectively, as compared to 7.4 months for the standard ($p=0.125$ and $p=0.079$, respectively). The primary statistical analyses based on the hazard ratio estimates and the lower bound of the confidence intervals strongly support the conclusion for this study that survival in each of the two taxol arms was not likely to be worse than the survival in the standard arm.

After adjustment for predefined covariates of potential prognostic value in a stratified Cox regression model, these survival results were generally maintained. In addition, the model identified a normal baseline LDH as a significantly favorable independent predictor of improved median survival, a finding consistent with other reports in the literature.

A further analysis from this study presented by the ECOG during the 1996 Annual Meeting of the American Society of Clinical Oncology (ASCO) demonstrated that the survival for the patients from the two taxol treatment arms pooled was significantly longer as compared to standard therapy, with a median survival of 9.7 months for the pooled taxol-containing arms vs. 7.4 months for standard therapy ($p=0.049$).

The high dose taxol treatment resulted in more severe toxicity than the low dose taxol treatment. In many instances, the low dose taxol arm and the standard therapy resulted in a similar toxicity profile, with the exception of adverse events typically associated with taxol treatment; arthralgia/myalgia, neurosensory toxicity, and hypersensitivity reactions were reported more frequently with either taxol treatment as compared to the reference regimen.

The use of G-CSF in the high dose taxol arm ameliorated granulocytopenia as demonstrated by the fact that the low dose taxol arm resulted in significantly more Grade IV

granulocytopenia than the standard. There was less severe thrombocytopenia reported in the taxol/cisplatin arm as compared to the other two treatments and overall, there was no difference in the incidence of severe anemia.

Overall and severe hypersensitivity was reported more frequently in the high dose taxol arm as compared to either of the other treatments. This may, in part, be due to the method used in our analysis: e.g., rash occurring at any time during treatment was considered as hypersensitivity, even if remote from study drug administration and more likely related to G-CSF.

The higher incidence of cardiovascular events reported in patients on the high dose taxol/cisplatin treatment as compared to the cisplatin/etoposide treatment may be a result of the close monitoring of vital signs instituted only for patients receiving taxol. This is further supported by the fact that there was no difference across treatment arms in the incidence of severe cardiovascular events.

As expected, neurological toxicity was reported more frequently with taxol treatment than with standard therapy. Neurosensory toxicity was more common in the high dose taxol arm as compared to the low dose taxol arm, and for either taxol arm as compared to standard. While neuromotor toxicity was reported more frequently with high dose taxol as compared to low dose taxol, there was no significant difference in neuromotor toxicity between low dose taxol and the standard. Additionally, there was more arthralgia/myalgia reported in the high dose taxol arm than in the low dose taxol arm, and for either taxol treatment as compared to standard.

Diarrhea, stomatitis and hepatic dysfunction were more severe in the high dose taxol treatment arm compared to either of the other treatments. While there was more diarrhea in the low dose taxol arm as compared to standard, the incidence of stomatitis and hepatic dysfunction was similar for low dose taxol and standard.

None of the described toxicities impacted negatively on the patients' quality of life as measured by the self-administered FACT-L questionnaire. The change from baseline over time did not differ for patients on either taxol treatment as compared to the reference regimen for the assessments of physical, social/family, and functional well-being, as well as for the patient-doctor relationship and the total FACT-Lung score. Moreover, patients treated with high dose taxol had an improvement in emotional well-being that approached statistical significance when compared to patients treated with the standard. The most striking differences were recorded by the patients' assessment of change in lung cancer symptoms. While patients in the reference arm tended to have an overall worsening of lung cancer symptoms throughout the course of the study, patients in the low dose taxol arm had an initial tendency to have their lung cancer symptoms improve. The difference in the change from baseline over time for lung cancer symptoms between low dose taxol and standard was significant in favor of the low dose taxol arm.

Clearly, taxol in combination with cisplatin demonstrated impressive antitumor activity against advanced non-small cell lung cancer in this large, multicenter, randomized phase III trial. Similar results have been reported in abstract form by the Lung Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC). The EORTC trial was a multicenter, randomized phase III trial that reported superior response rates for taxol in combination with cisplatin as compared to their standard therapy, teniposide/cisplatin.

In the present study, the two taxol/cisplatin treatment arms were more efficacious as compared to the reference regimen. The real promise of a substantial patient benefit is further demonstrated by the considerable delay in disease progression and the trend towards an overall survival improvement in patients treated with taxol in combination with cisplatin as compared to the reference. The survival in either of the taxol treatment arms was at least as good or better than the reference regimen of cisplatin/etoposide.

In the palliative setting of advanced non-small cell lung cancer the higher level of toxicity associated with the high dose taxol treatment as compared to the low dose taxol treatment is worthy of consideration. The increase in taxol dose in the taxol/cisplatin/G-CSF arm did not translate into a magnitude of improved efficacy over taxol/cisplatin that would clearly justify the use of this more toxic regimen.

Therefore, taxol, given at a dose of 135 mg/m^2 administered over 24 hours in combination with cisplatin 75 mg/m^2 has been demonstrated to be safe and effective for the treatment of advanced non-small cell lung cancer."