

MEDICAL OFFICER EVALUATION

FDA Reviewer's Efficacy Analysis

The following table summarizes the efficacy results from the three pivotal trials according to the sponsor's analysis. The shaded areas represent comparisons with significant differences against the corresponding control arms.

Table No. 37
Efficacy Results- Taxol Pivotal Studies

	Number of Patients (%)						
	Study 165			Study 103		Study 208	
	taxol/ cisplatin (n=198)	HD-taxol/ cisplatin (n=201)	cisplatin/ etoposide (n=200)	taxol/ cisplatin (n=166)	teniposide /cisplatin (n=166)	taxol/ cisplatin (n=190)	cisplatin (n=197)
Response rate (%) (95% C.I.)	26% (20-34) (p=.003)	30% (23-38) (p<.001)	14% (9-20)	35% (29-44) (p=.046)	25% (19-33)	26% (20-33) p=0.028	17% (12-33)
Time to Progression Median (months) (95% C.I.)	4.3 (3.3-5.1) (p=.0504)	4.9 (4.0-5.8) (p=0.004)	2.7 (2.2-3.2)	5.1 (4.3-5.9)	5.0 (3.7-5.8)	4.3 (3.5-4.6)	3.2 (2.4-3.9)
Survival Median (months) (95% C.I.)	9.3 (8-10.4)	10.0 (8.9-11.7)	7.4 (6.5- 8.6)	9.5 (8.2 -11.7)	9.9 (8.2 - 12)	8.1 (7.3-9.2)	8.6 (7.8- 10.3)
One Year Survival % Patients (95% C.I.)	36 (30-43)	40 (34-47)	32 (26-39)	41 (33-49)	41 (33-49)	30 (24-36)	36 (29-42)

Regardless of infusion schedule, response rates in all the taxol-containing treatment arms were superior to the control arms in all the studies. Time to tumor progression was superior in the HD-taxol/cisplatin arm compared to cisplatin/etoposide in study 165, where taxol was given as a 24-hour infusion. In the 3-hour taxol infusion studies (103 and 208), there were no

differences between the taxol arms and the corresponding controls (teniposide/cisplatin and cisplatin alone, respectively) in time to tumor progression, median and one-year survival.

FDA Analysis of Overall Survival

The electronic data was reviewed for the analysis of overall survival. In each study, survival was calculated from the day of randomization to death or censored at the last day the patient was known to be alive. Seventy-five to eighty-five percent of patients have died at the time of analysis in all three studies, leaving a minority of censored survival dates. Survival analyses by the FDA for studies 165, 103 and 208 are identical to that of the sponsor's.

Table No. 38
FDA Analysis of Survival

	Median/ 95% C.I. (months)	One Year Survival/ 95% C.I.
STUDY 165		
taxol/cisplatin	9.3 (8.0 to 10.4)	36% (26 to 39%)
HD-taxol/cisplatin	10.0 (8.9 to 11.7)	40% (34 to 47%)
cisplatin/etoposide	7.4 (6.5 to 8.6)	32% (26 to 39%)
STUDY 103		
taxol/cisplatin	9.5 (8.2 to 11.7)	41% (33-49%)
cisplatin/teniposide	9.9 (8.2-12.0)	41% (33-49%)
STUDY 208		
taxol/cisplatin	8.1 (7.3-9.2)	30% (24-36%)
cisplatin	8.6 (7.1-10.3)	36% (29-42%)

It may be noted that median and one-year survival rates are lower in study 208 compared to study 103, which both used the same doses and infusion schedule of taxol. Although this may be explained by chance, the difference may also be attributed to variation in pretreatment characteristics of patients enrolled in the studies. The proportion of patients with more favorable attributes in studies 103 compared to study 208, respectively are as follows: Stage IIIA disease (10% vs. 0%), Performance Status (ECOG 0-1, 90% vs KPS 90-100, 47%) , Weight loss <5% during the last three months (71% vs. 52%).

Neither a survival advantage nor disadvantage was shown with taxol in combination with cisplatin as a 24-hour or 3-hour infusion compared to what was believed as the "best" control arms for studies 165 and 103, and for cisplatin alone in study 208.

FDA Analysis of Time to Tumor Progression

Time to progression was defined as the period from date of randomization until first documentation of tumor progression, or date of death for patients without such documentation. At the time of analyses, a majority of the patients (about 77%-87%) have been assigned a progression date. Patients who received secondary therapy were censored on the first day of therapy while a minority of patients who either never received therapy or had a wrong primary cell type were censored on the day of randomization. A secondary analysis of time to progression included the first day of secondary therapy as an event. The following table summarizes the sponsor's analysis of time to tumor progression:

Table No. 39
Summary of Time to Tumor Progression

	median/ 95% C.I. (months)	p-value ^b	median/ secondary analysis ^a	p-value/ secondary analysis
STUDY 165				
taxol/cisplatin	4.3 (3.3-5.1)	0.0504	3.6	0.027
HD-taxol/cisplatin	4.9 (4.0-5.8)	0.004	4.3	0.004
cisplatin/etoposide	2.7 (2.2-3.2)		2.7	
STUDY 103				
taxol/cisplatin	5.1 (4.3-5.9)	0.723	4.6	
cisplatin/teniposide	5.0 (3.7-5.8)		4.7	
STUDY 208				
taxol/cisplatin	4.3 (3.5- 4.6)	0.085	4.1 (3.3-4.4)	0.026
cisplatin	3.2 (2.4-3.9)		2.7 (2.3-3.2)	

^a time to progression was analyzed including the first day of secondary therapy

^b p-values entered for each line drawn after comparison with the control arm in each study, those with significant differences are in bold font

A statistically significant difference in time to tumor progression was seen between the cisplatin/etoposide and HD-taxol/cisplatin arms in favor of the HD-taxol arm. When first day of secondary therapy was considered, significant differences were also seen in the taxol/cisplatin arm vs. cisplatin/etoposide in study 165 and in the taxol/cisplatin vs. cisplatin alone in study 208.

In practice, documentation of disease progression oftentimes antedates the start of secondary therapy and is usually the reason for discontinuing treatment. In most research settings, a new therapy can only be started after at least four weeks from the last cycle of prior therapy. On the other hand, secondary therapy may start without disease progression in patients who do not tolerate a prior regimen. Finally, there may be other medical and personal reasons that may either cause a delay or early start of secondary therapy in relation to the actual date of progression. Therefore, the accuracy and clinical relevance of the first day of secondary therapy to the actual time of progression is questionable.

For study 165, 517 of 599 patients (86%) who either progressed or died were considered for the analysis of time to progression by the sponsor (See Table No.10, p.22). Tumor progression dates were not confirmed by the FDA reviewer for 7 patients, 2 treated with HD-taxol/cisplatin and 5 with cisplatin/etoposide.

Table No. 40
BMS versus FDA Assessment
of Tumor Progression-Study 165

Subject	Treatment Arm	BMS Assessment	FDA Assessment
	HD taxol-cisplatin	PD on 9/7/94	no documentation of PD
	HD taxol-cisplatin	PD on 11/27/94	no documentation of PD
	cisplatin/etoposide	PD on 3/1/94	no documentation of PD
	cisplatin/etoposide	PD on 12/16/93	no documentation of PD
	cisplatin/etoposide	PD on 5/3/94	no documentation of PD
	cisplatin/etoposide	PD on 1/27/95	no documentation of PD
	cisplatin/etoposide	PD on 10/11/93	no documentation of PD

The patients in study 165 listed above were noted to have disease progression by the investigators on follow-up case report forms; but actual documentation of tumor measurements on the specified dates were missing. Although this may have affected the quality of data, the FDA agrees with the sponsor's analysis of tumor progression in this study.

In study 103, there were three differences in opinion between the sponsor and the FDA analysis of progression which did not significantly affect the comparison between the two treatment arms.

Table No. 41
BMS versus FDA Assessment of Tumor Progression-Study 103

Subject	BMS Assessment	FDA Assessment
	PD on 10/30/95 PD on 5/22/95 PD on 1/25/96	PD on 1/3/96 PD on 7/6/95 no documentation of PD

Several patients in Study 208 had tumor progression during follow-up; but actual tumor measurements were not found in the electronic submission. As mentioned in an earlier section of the review, documentation of progression/relapse was entered into follow-up case report forms by indicating only the site and date of progression for 28 patients in the cisplatin arm and 44 patients in the taxol/cisplatin arm who progressed during follow-up. In the absence of actual tumor measurements and specification of whether or not a lesion is new, verification of progression was not possible. Nevertheless, after reviewing line listings and actual case report forms, the FDA agrees with the sponsor's analysis of time to tumor progression in study 208.

There was no statistically significant difference in time to tumor progression between the control and experimental arms in all three studies except for the HD-taxol + cisplatin arm in study 165. In this particular situation where there is no improvement in median survival, but time to treatment progression is superior, one can speculate that this may be evidence of clinical benefit. However, additional information from the toxicity profile and/or change in quality of life should also be considered. On the other hand, the burden of proving additional clinical benefit is more with the taxol/cisplatin arm of 165, 103 and 208 since no improvement in either survival and time to progression was observed.

FDA Analysis of Response Rate

The significance of response rates as evidence for efficacy and/or clinical benefit in NSCLC is unsettled and merits further discussion. It is uncertain whether overall survival is improved, or if there is correlation between response rates and survival in patients with NSCLC treated with cisplatin combination regimens. In the 612 patient, three arm, European study with navelbine + cisplatin (Arm1) versus vindesine + cisplatin (Arm 2) versus navelbine (Arm 3), significantly higher response rates and longer survival times (28% and 40 weeks, respectively) were seen in Arm 1 compared to Arm2 (19% and 32 weeks, respectively). An ECOG study comparing three different cisplatin-containing regimens with

CAMP (cyclophosphamide, adriamycin, methotrexate and procarbazine) showed no difference in survival (23-25 weeks) even though the cisplatin-containing regimens tended to have higher response rates than the 16% achieved with the non-cisplatin containing regimen. Also, the median survival of these patients were not much different from a comparable historical group of patients (VA Lung Group) who were treated with supportive care alone. On the other hand, there are two studies in which superior response rates with platinum-containing regimens were associated with worse survival. One such study was published by Ruckdeschel, et al (J. Clin. Oncol 7:1602-113, 1986) using MVP (mitomycin, vinblastine and cisplatin) in patients with advanced NSCLC. In a five-arm study by Bonomi, PD (J. Clin. Oncol. 7:1602-1613, 1989) one of the five treatment arms using carboplatin alone resulted in the lowest response rate (9%) but the longest median survival (7 months versus 5-6 months). The correlation of response rates with survival is at best, inconsistent.

Patients with advanced NSCLC have lesions classified as measurable (bidimensional and unidimensional), or evaluable/non-measurable. The response assessments may not always be simple and at times can be quite tedious. One of the major problems encountered in the assessment of tumor response with this NDA application is the occasional absence of measurements during treatment on tumors that were measured at baseline. It is unclear whether the absence of data was due to disappearance of tumor or failure to record observations. In the FDA response assessment, only patients with tumors that were present from baseline and during follow-up could be classified as responders.

Another major problem identified was investigators changing the status of tumors from being bidimensionally or unidimensionally measurable at baseline to evaluable/non-measurable at some point during treatment. For measurable lesions, actual tumor measurements are recorded; while non-measurable lesions were evaluated as being present, absent, increased or decreased. These changes presented as problems for the reviewer. For example, a patient with four lesions measured at baseline may have a 50% decrease in the sum of the areas in two lesions while the other two were "decreased" during treatment. These patients were not considered as responders by the FDA reviewer.

A similar but less problematic situation was encountered when tumors changed from bidimensionally to unidimensionally measurable. In some protocols, a 30% change in the longest diameter in either direction define response or progression in unidimensionally measured lesions; while in others, they are converted into bidimensional measurements simply by multiplying the longest diameter by itself. Squaring the diameter is a conservative and probably acceptable method to deal with such changes. On the other hand, there is mounting evidence showing good correlation between the classical bidimensional tumor response assessments with the 30% rule for assessment of unidimensional tumor measurements. In patients where this situation was encountered during review, response assessments were followed as specified in the protocol.

The differences between FDA analysis and the sponsor's analysis of tumor response are as follows:

Study 165:

Table No. 42
Differences between BMS versus FDA Assessment of Tumor Response - Study 165

Subject	BMS Assessment	FDA Assessment
<u>Taxol + Cisplatin</u>	PR PR PR PR PR	measurable lesions changed to evaluable, not a PR measurable lesions changed to evaluable, not a PR measurable lesions changed to evaluable, not a PR measurable lesions changed to evaluable, not a PR no confirmation of PR, not a PR
<u>HD-Taxol + Cisplatin</u>	PR PR PR	measurable lesions changed to evaluable, not a PR measurable lesions changed to evaluable, not a PR no confirmation of PR
<u>Cisplatin + Etoposide</u>	PR	no confirmation of PR

Study 103:

Table No. 43
Differences between BMS versus FDA Assessment of Tumor Response - Study 103

Subject	BMS Assessment	FDA Assessment
<u>Taxol + Cisplatin</u>	PR PR PR PR PR PR	measurable lesions changed to evaluable, not a PR measurable lesions changed to evaluable, not a PR no confirmation of PR, not a PR
<u>Teniposide + Cisplatin</u>	PR PR PR PR PR PR PR	two lesions at baseline, only one lesion followed for PR, not a PR no follow-up of lesions at baseline, no confirmation of PR, not a PR no documentation of PR, not a PR no documentation of PR, not a PR no confirmation of PR, not a PR no confirmation of PR, not a PR no confirmation of PR, not a PR

Study 208:

Table No. 44
Differences between BMS versus FDA Assessment of Tumor Response - Study 208

Subject	BMS Assessment	FDA Assessment
<u>Cisplatin</u> none	--	--
<u>Taxol + Cisplatin</u>	PR	measurable lesion changed to evaluable, not a PR

Using response rates obtained after FDA analysis, Fisher's exact test showed significant differences in favor of the taxol treatment arms that were consistent with the sponsor's analysis.

Table No. 45
Summary of BMS and FDA Analysis of Tumor Responses - Pivotal Studies

	Response Rate (%)		
	# of Patients	BMS Analysis (%) (95% C.I.)	FDA Analysis (%) (95% C.I.)
STUDY 139-165			
Taxol + Cisplatin	198	46/198 (23%) (18-30%)	41/198 (21%) (15-27%) (p=0.012)
HD-Taxol + Cisplatin	201	51/201 (25%) (20-32%)	48/201 (24%) (18-30%) (p=0.001)
Cisplatin + Etoposide	200	24/200 (12%) (8-17%)	23/200 (12%) (8-16%)
STUDY 139-103			
Taxol + Cisplatin	157	58/157 (37%) (29-45%)	52/157 (33%) (26-40%) (p=0.017)
Cisplatin + Teniposide	156	41/156 (26%) (20-34%)	33/156 (21%) (15-27%)
STUDY 139-208			
Taxol + Cisplatin	190	50/190 (26%) (20-33%)	49/190 (26%) (p=0.041)
Cisplatin	197	34/197 (17%) (12-33%)	34/197 (17%)

FDA Discussion on Quality of Life Assessment:

Reviewer's comment: For a more detailed analysis of Quality of Life, refer to the biostatistics review.

Demonstration of significant improvement in certain aspects of quality of life may be interpreted as important clinical benefit especially when a positive correlation with other efficacy endpoints is observed. However, a significant improvement in quality of life in conjunction with a slight decrement efficacy may still be perceived as significant clinical benefit.

According to the sponsor's analysis of study 165, there was a significant improvement in lung cancer associated symptoms in patients enrolled in the taxol/cisplatin arm compared to patients in the cisplatin/etoposide arm. These results should be interpreted with caution. First, there was significant attrition of patients due to noncompliance by the third study month. Secondly, other medical conditions, concomitant medications, etc. may have affected the occurrence and severity of symptoms included in the questionnaire. Two longitudinal approaches performed by the biostatistics reviewer did not show any statistically significant differences in the quality of life assessments between any of the taxol arms and the cisplatin/etoposide arm. ($p=0.026$ for dropouts and $p=0.021$ for completers with nominal $\alpha=0.0125$) However, patients treated in the taxol arm either improved or remained stable while there was deterioration from baseline in patients treated with cisplatin/etoposide in the Lung Cancer Symptom Subscale.

Patient compliance is the major problem with quality of life testing in study 103 with only 100 patients (50 in each arm) responding at baseline. Since the analysis was centered on changes from baseline measurements, further drop in compliance during treatment argues against the accuracy by which the test results represented the whole patient population. However, a longitudinal analysis of the QOL subscales performed by the biostatistics reviewer showed a statistically significant difference in physical functioning favoring the taxol arm.

A significant change in physical functioning was seen in patients treated in the taxol/cisplatin arm compared to cisplatin alone in study 208. 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 ($p<0.0001$). These differences in symptom scales were consistent with incidence of toxicities observed in each treatment

Several questions in the symptom scales of quality of life analysis relate to patient's symptoms which may be influenced by toxicity from chemotherapy (e.g. nausea and vomiting, neuropathy, alopecia, etc.). Severity of toxicity are based on a different set of standards which, unlike QOL scales, do not often reflect patient's functional status or its

effect in other aspects of daily living. A difference in timing with respect to treatment administration, or how and who asks the questions, could also cause variations in responses. Despite consistency of the results in some symptoms, one should be careful in making generalizations regarding the correlation of toxicity with results of quality of life tests.

**APPEARS THIS WAY
ON ORIGINAL**

FDA Reviewer's Safety Analysis

Reviewer's comment: Specific safety analyses done by the FDA reviewer for study 165 were not included in the sponsor's review and were derived primarily from electronic data which was submitted by the sponsor on January 1998 as an addendum. According to the sponsor, the additional electronic data which the FDA requested was "not clean" and unaudited.

FDA Analysis of Death within 30 Days of Last Dose

In study 165, 60 patients (10%) died within 30 days of last treatment dose. Patient summaries and circumstances surrounding death were reviewed to establish causality. Deaths due to toxicity were attributed to the treatment combination since the contribution of individual drugs was difficult to establish.

There were 17 (9%) deaths in the taxol/cisplatin arm, 20 (10%) in the taxol/cisplatin/G-CSF arm, and 23 (12%) in the cisplatin/etoposide arm. Deaths were caused by treatment-related toxicity, complications from disease progression, related medical conditions or a combination. Toxicity from treatment were related to 5% (10/198) and 6% (12/201) of deaths within 30 days of last treatment in the taxol/cisplatin and HD-taxol/cisplatin arms respectively, and 2% (5/200) in the cisplatin/etoposide arm.

**APPEARS THIS WAY
ON ORIGINAL**

Table No. 46
Deaths within 30 Days of Last Treatment Dose-Study 165

Cause of Death	Taxol/ Cisplatin (%) n=198	HD-Taxol/ Cisplatin (%) n=201	Cisplatin/ Etoposide (%) n=200
Toxicity	10 (5%)	12 (6%)	5 (2%)
Renal	1	1	--
Neutropenia/ Infection	4	10	5
Cardiac	4	1	--
Neurotoxicity	1		
Disease Progression	1(<1%)	5 (2%)	10 (5%)
Other Medical Conditions	6 (3%)	3 (1%)	8 (4%)
TOTAL	17	20	23

Using Fisher's exact test to compare each of the taxol-containing regimens with the cisplatin/etoposide arm, the difference between deaths due to toxicity were not statistically significant between cisplatin/etoposide vs. taxol/cisplatin ($p=0.2$) and HD-taxol/cisplatin ($p=0.135$).

In study 103, more patients died within 30 days of treatment in the teniposide/ cisplatin arm (11% vs. 6%); however, the proportion of patients dying from drug-related toxicity was similar in both arms. In study 208, more patients died in the cisplatin arm (12% vs 6%) mostly from progressive disease.