This unplanned comparison of patients alive at one year the yielded a significant difference between the docetaxel 75 mg and control arms, p = 0.046. The survival rates derived from the numbers of patients either known to be alive 365 days or to have died before 365 days are as follows:

Docetaxel 100 mg : 21 ÷ (96+21) = 17.9%
Docetaxel 75 mg : 32 ÷ (83 + 32) = 27.8%
Control : 20 ÷ (20 + 98) = 16.8%

The chi-square test is a commonly used test for comparing proportions and is an approximate method. It is not a comparison of one year Kaplan-Meier curve estimates. It is not recommended in situations of low expected frequencies. In such a situation the Fisher's exact test is recommended because it incorporates the probabilities of frequencies more extreme than those observed. The FDA chose to repeat the comparison of the two arms with this more conservative test to check how robust the Chi-Square results were. The FDA found that the p value for the comparison of the same two arms (docetaxel 75 mg vs. control) utilizing the more conservative Fisher's Exact test was **0.0587**. When the docetaxel 100 mg arm was compared to the control using the Fisher's Exact test the p = 0.8650.

The FDA statistical reviewer requested clarification of the sponsor's chi-square methodology utilized in their other randomized, controlled trial (TAX317) analysis. Review of that methodology revealed that, in the analysis of that study, the sponsor had incorporated censoring in the comparison, deriving rates from the Kaplan-Meier curves. When that same methodology was applied to the comparison of rates of 1-year survival in TAX 320, the statistical reviewer determined that the p-value for the comparison of 1-year survival between the docetaxel 75 mg/m^2 arm and the control arm was p=0.025.

Reviewer Comment: The sponsor submitted an updated safety analysis by fax dated November 5, 1999. The probability of one year survival at one year, according to the Kaplan-Meier curves, is now reported with minor changes: docetaxel 100 mg/m^2 = 23% (CI=15, 30); docetaxel 75 mg/m^2 = 30% (CI = 22, 39); and control = 20% (CI = 13, 27). The sponsor used Chi-Square again to compare the docetaxel 75 mg/m^2 arm to the control arm, p=0.05. The sponsor utilized the valid Chi-Square methodology that incorporated censoring in this analysis.

Who were the patients that survived ≥365 days in this study? The clinical characteristics of these 73 patients are summarized by treatment arm in the table below. The percentage of the 1-year survivors that had IIIB disease was highest on the docetaxel 100 mg arm, (even though that arm had the highest proportion of poor prognosis IIIB disease based on performance status, response to prior therapy and number of prior regimens prior to study entry). The control arm had the highest percentage of 1-year survivors with the combination of non-PD response to prior therapy + PS <2. The docetaxel 75 mg arm had the highest proportion of 1-year survivors with PD as best response to prior platinum-based chemotherapy. In general the patients with >1 year survival had baseline characteristics that included non-PD response to prior platinum, PS <2, and <10% weight loss. Most experienced NC as a best response on TAX 320. The control arm had the highest percentage of one year survivors who had experienced PD as the best response on study. All long-term survivors with PD as best response went on to further therapy.

Table 16 TAX 320 Clinical Characteristics of Patients with Survival ≥365 Days

	Docetaxel 100 mg	Docetaxel 75 mg	Control
Total No. Patients	**21**	**32**	**20**
Stage IIIB	6/21 (29%)	6/32 (19%)	3/20 (15%)
Stage IV	15/21 (71%)	26/32 (81%)	17/20 (85%)
Best Response on Study = PR (No. Censored for Further Chemotx)	7 = 33% (6/7= 86%)	5 = 16% (5/5=100%)	0
Best Response on Study = NC (No. Censored for Further Chemotx)	10 = 50% (9/10 = 90%)	17 = 53% (14/17=82%)	11 = 55% (10/11=91%)
Best Response on Study = PD (No. Censored for Further Chemotx)	2 = 11% (2/2=100%)	7 = 22% (7/7=100%)	8 = 40% (8/8=100%)
Best Response on Study = IMP (No. Censored for Further Chemotx)	1 (0/1)	1 1/1	0
Best Response on Study = NE (No. Censored for Further Chemotx)	1 (0/1)	2 (2/2)	1 (0/1)
Best Response to Prior Cisplatin non-PD + PS <2	16 (76%)	24 (75%)	17 (85%)
Best Response to Prior Cisplatin = PD	4 (19%)	8 (25%)	3 (15%)
PS = 2 (at study entry)	2 (10%)	2 (6%)	1 (5%)

The following table summarizes the differences of distribution of clinical characteristics between overall study population's ≥365 day survivors and <365 day survivors.

Table 17 TAX 320 Comparison of Clinical Characteristics of Those Participants Surviving ≥365 Days

	≥365 day Survivors	<365 day Survivors
PS =2	7%	19%
Prior Platinum Response = PD	21%	32%
Prior Platinum Response = CR/PR	47%	31%
Prior Platinum Response = CR	12/73 = 17%	?17/300 = 6%
Progressed While on Prior Platinum Treatment	19/73 = 26%	129/300 = 43%
Progressed Within 3 months of prior platinum treatment	10/73 = 14%	64/300 = 21%
III B disease	21%	9%
PS<2 + Prior Platinum Response Non-PD	75%	58%
PS<2 + PR to Prior Platinum	44%	27%
PS<2 + IIIB disease	19%	8%
No. Organs Involved =1 =2	 44% 43%	 25% 38%
Best Response on Study PR NC PD NE	 16% 52% 23% 6%	 3% 28% 53% 15%
Weight loss ≥ 10% at study entry	1%	11%

Those patients who lived ≥365 days and were treated with further chemotherapy (censored for further chemotherapy in the sponsor's exploratory survival analysis) included 9 who experienced a response of PR to that further chemotherapy – 1 on the docetaxel 100 mg arm, 3 on the docetaxel 75 mg arm, and 5 on the control arm. (The characteristics of those patients are summarized in Table 22 below, in the discussion of further chemotherapy.) Only two had achieved a PR on study. All but one had metastatic disease. All but two had a performance status of <2. Only one of the group of responders had a prior platinum response of PD, and that patient responded to cisplatin + toremifene in subsequent chemotherapy.

The reviewer has summarized a comparison of the 1-year survivors on study vs. the non - 1-year survivors in the following table, in terms of their response to study treatment and their exposure to post-study chemotherapy. The table shows that a higher proportion of ≥1 year survivors were censored for further chemotherapy. A lower proportion of the NC's and PD's among the non-

survivors (1-year) went on to further therapy. There were more patients with a NE and PD response in the non-survivor subgroup.

Table 18 TAX 320 Comparison of Censoring for Further Therapy According to Study Treatment Response Between Survivors of ≥ 1 year and Non-Long Term Survivors.

	≥365 day survivors			<365 day survivors		
	Docetaxel 100 mg	Docetaxel 75 mg	Control	Docetaxel 100 mg	Docetaxel 75 mg	Control
Overall Censored	**81%**	**91%**	**90%**	**39%**	**34%**	**32%**
PR's censored	86% (6/7)	100% (5/5)	0	83% (5/6)	76% (2/3)	0%
NC's censored	90% (9/10)	82% (14/17)	97% (10/11)	47% (14/30)	41% (11/27)	52% (14/27)
IMP's censored	0	100% (1/1)	0	0	100% (1/1)	0
PD's censored	100% (2/2)	100% (7/7)	100% (8/8)	39% (21/54)	28% (14/51)	29% (16/55)
NE's censored	0 (0/1)	100% (2/2)	0 (0/1)	0 (0/14)	36% (4/11)	16% (3/19)

Although a higher proportion of one year survivors were censored for further chemotherapy, only 9/73 (12%) of those survivors were known responders (PR) to that further chemotherapy. The fact that there was a difference between groups (survivors vs. non-survivors) in percentage who went on to further chemotherapy may say something about the overall prognostic status of those patients.

The sponsor submitted a further unplanned analysis of survival that included censoring for subsequent chemotherapy. The proposed justification for this unplanned analysis was "a large proportion of patients received a potentially effective post-study chemotherapy and the drug exposure...post-study...is substantially different between treatment groups." The Kaplan-Meier curves that result from this censored analysis differ from the original in that the docetaxel 100 mg and 75 mg group curves no longer separate. All three curves remain overlying until approximately 8 months, and it is not until late that the control curve separates. The median survivals are still not found to be significantly different for the docetaxel 100 mg , 75 mg, and control arms, respectively: 6.6 months (95% CI = 5.0, 7.9), 5.8 months (95% CI = 5.2, 8.0), and 5.4 months (95% CI = 4.2, 7.9). The log rank yields a p = 0.25 in the comparison of the docetaxel 100 mg to control arm, and p = 0.12 in the comparison of the docetaxel 75 mg to control. In a further unplanned analysis, the sponsor combined the censored for further chemotherapy data from the two docetaxel arms and compared it to the control. The log rank test of this combined comparison yields a p value of 0.08, which the sponsor interpreted as "a favorable trend" in median survival for docetaxel. The unplanned 1-year survival analysis utilizing this unplanned censored data does not change the 1-year survival noted in the docetaxel 75 mg group – 32%. The %1-year survival of the docetaxel 100 mg group increases to 32% and that of the control decreases to 10% from 19%. The sponsor performed the Chi-Square analysis of the single point - one year, a further unplanned analysis of an unplanned analysis, and combined the data from the two docetaxel arms (again another unplanned analysis) for the comparison to the control arm. The resulting p value was significant, p=0.012.

Reviewer Comment: In its November 5 survival analysis update, the sponsor reports that these unplanned analyses remain statistically significant. With censoring for further chemotherapy the one year survival probabilities are 33% and 30% for the docetaxel 100 mg and 75 mg arms, respectively, while that of the control arm is 11%. The Chi-square comparison yields a p value of <0.006.

Reviewer Comment: Of all the unplanned survival analyses presented, the FDA could be persuaded that the analysis of the percentage of one year survival was a clinically relevant endpoint to be examined, particularly given the separation seen at the tail of the curve in this population of patients who would be expected to have a poor expected one year survival. The selection of Chi-Square to analyze this endpoint instead of the log rank test seems to follow from the reason for retrospectively selecting this endpoint - the late separation of the curves. This was, however, an analysis performed after and prompted by looking at the data, so it would seem prudent to temper interpretation of the significance of the difference found in the comparison by considering how much Type I error should have been "spent" going through this process. The p value that results from the Chi-Square analysis is not dramatic, p=0.046, and the use of a more conservative method to take a second look at how robust that finding is seems justified, even though the Chi-Square estimate analysis in a prospectively defined setting might be viewed as appropriate given the fact that the expected frequency of events would <u>not</u> have been low. The Fisher's Exact test yielded a p value that generally would not be viewed as significant, p= 0.0587 (docetaxel 75 mg vs. control). At best there appears to be a trend for improved survival with time, but this observation in this study cannot be decisively argued as having not occurred other than by chance.

The unplanned exploratory analysis that was performed utilizing censoring for subsequent chemotherapy involved a confluence of multiple unplanned analyses and cannot be accepted. The sponsor justified this censoring on the basis of differences among treatment groups in "potentially effective post-study chemotherapy". The percentage of patients on each arm who were treated with chemotherapy post-study was similar across treatment arms: 36% (D100), 39% (D75), and 39% (V/I). The sponsor's concern is that on the control arm 24/48 patients (20% of the total control arm patient population) who were treated with subsequent chemotherapy, were treated with a taxane. The reviewer explored the potential impact of further therapy by summarizing the data provided on chemotherapy and the responses recorded. These findings are summarized in tables found in the <u>Appendix</u> of this review, where they are organized by specific subsequent chemotherapy drug, and patients in each TAX 320 treatment arm treated with that drug are tabulated separately, including dividing the control arm into those treated with vinorelbine and those treated with ifosfamide on study. Patients who were administered the drug in combination with another are noted in the table, and are duplicated in the subsequent table devoted to the additional chemotherapeutic drug in the regimen. The response to a drug (or the combination containing the drug) is listed, along with number of subsequent chemotherapy regimens delivered to the patient and the response associated with the further regimens. The number of cycles of each subsequent chemotherapy drug is listed. ("UK" = Unknown)

The following table summarizes the patients who were reported to have experienced a PR in subsequent therapy. It should be noted that in many patients the response to further therapy was reportedly unknown, so there may have been more actual responses to therapy. There were 14 control arm patients who had treatment responses reported as unknown, 14 docetaxel 100 mg/m^2 patients, and 19 docetaxel 75 mg/m^2 patients.

Table 19 TAX 320 Patients Who Achieved a PR on Subsequent Chemotherapy

Pt. No.	Treatment Arm	Active 3rd Line Reg.	No. of Cycles	Cycle(s)	Best Response	No. Other Regimens	Best Response Other Reg.
10489	Control (Vinorelb)	Paclitaxel	2	061, 062	PR	3	PD, PD, PD
10407	Control (Ifosfamide)	Gemcitabine	3	062, 063, 064	PR	1 (+1 H)	NC
10381	Docetaxel 75mg	Gemcitabine	5	063 - 067	PR	0	
10442	Control (**Vinorelb**)	**Vinorelbine**	1	061	PR	2	UK
10437	Control (Ifosfamide)	Vinorelbine	1	066	PR	0	
10478	Docetaxel 75mg	Vinorelbine+ Carboplatin	6	061-065	PR	0	
10668	Docetaxel 75mg	Vinorelbine+ Carboplatin	4	061-064	PR	0	
10348	Control (Vinorelbine)	Cisplatin + Toremifene	3	061-063	PR	1 (+estramu)	PD (PD)
10663	Control (Vinorelbine)	Cisplatin + Toremifene	2	061-062	PR	0	
10488	Docetaxel 100mg	Cisplatin + Toremifene	3	061-063	PR	1 (+ estramu)	PD (PD)
10048	Docetaxel 75mg	Cisplatin + Toremifene	4	061-064	PR	0	

Only one patient (on the control arm) was known to respond to a taxane in post-study therapy. The response was unknown in 8 control arm patients that were treated with paclitaxel or docetaxel. Two of the control arm patients responded to control arm therapy, post-study. Of the carboplatin or cisplatin-containing regimens that yielded a PR in subsequent therapy (N = 6), four were administered to docetaxel treatment arm patients (75 mg = 3; 100 mg = 1) and two to the patients treated on the Control arm. Two of the six responders on the control arm responded to a platinum-containing combination regimen. Four of the five responders on the combined docetaxel arms were treated with a platinum based combination regimen. There were 30 patients treated in subsequent therapy with a carboplatin/cisplatin-based regimen. Thirteen had experienced at least a PR to prior platinum therapy and 11 had experienced PD to that prior therapy.

The characteristics of the six patients who responded to further treatment with a cisplatin/carboplatin based regimen (after participating in this study that required a history of prior treatment with cisplatin/carboplatin) are summarized in the table below.

Table 20 TAX 320 Characteristics of the Patients who Experienced PR on Subsequent Platinum-Based Chemotherapy

	Stage	No. Prior Regimens	Prior Platinum Response	Prior XRT	Prior Taxane	TTP Censored	Survival (days)
10048 Docetaxel 75 mg	IV	1	PD	Yes	No	No (285 d)	532
10348 Control (Vinorelbine)	IV	1	PR	Yes	Yes	No (111 d)	414
10478 Docetaxel 75 mg	IV	1	PR	Yes	No	No (49 d)	387
10488 Docetaxel 100 mg	IV	1	PR	Yes	Yes	No (232 d)	468
10663 Control (Vinorelbine)	IV	1	NC	Yes	Yes	No (94 d)	352
10668 Docetaxel 75mg	IV	1	PR	Yes	No	No (96 d)	313

The known responses to further therapy can be summarized by treatment arm as follows:

No. of Patients Treated With and Responding to Further Therapy by Treatment Arm: (Chemotherapy Listed in Further Therapy Table 26B; Volume 62.50)

Control: **RR= 6/48 = 12.5%**

(One of the control arm vinorelbine responses was to vinorelbine)

Docetaxel 100 mg: **RR= 1/45 = 2.2%**

Docetaxel 75 mg: **RR= 4/49 = 8.2%**

The reviewer attempted to examine the relative distribution of performance status at the time of last cycle on treatment among the arms in those patients who went on to further chemotherapy. Performance status at last cycle was not available in all patients (39/45 on the docetaxel 100 mg arm; 47/49 on the docetaxel 75 mg arm, and 43/48 on the control). The distribution for those available patients is summarized in the table below:

Table 21 Relative Distribution of Performance Status at the End of Study Treatment in Patients Who Received Further Chemotherapy with an Alternative Regimen

Performance Status	Docetaxel 100 mg N=39/45	Docetaxel 75 mg N=47/49	Control N=43/48
0	4 (10%)	10 (21%)	3 (7%)

Performance Status	Docetaxel 100 mg N=39/45	Docetaxel 75 mg N=47/49	Control N=43/48
1	26 (67%)	28 (60%)	32 (74%)
2	9 (23%)	6 (13%)	5 (12%)
3	0	3 (6%)	3 (7%)

Of those patients with available PS data at last cycle, the majority who went on to further chemotherapy had a PS = 1. The docetaxel 75 mg arm had the highest percentage of PS=0 patients who went on to further chemotherapy.

3.10.2 Response

The sponsor's analysis of overall response, ORR, included a sum of CR's + PR's. The protocol specified that PR's were defined by bidimensionally measurable disease, and that unidimensionally measurable/ evaluable-only disease could not by itself provide the basis of a PR assessment of disease response. Unidimensionally measurable disease that decreased by at least 50% in the sum of the largest diameter of all lesions, and non-measurable evaluable disease that decreased by at least 50% in estimated area (not to include pleural effusions) were to be designated "Improvement" (IMP). The sponsor indicates in the Study Report that it proceeded with inclusion of such IMP's as PR's in their analysis of ORR, contrary to protocol plan, "for consistency with other studies in the NDA submission". Response percentages in the ITT population were based on a total of 124 patients on each of the docetaxel arms and 122 on the control arm. One patient in each arm was not included in the ITT analysis on the basis of their not having a diagnosis of non-small cell lung carcinoma. (One patient on the docetaxel 100 mg arm had small cell lung carcinoma, one patient on the docetaxel 75 mg arm had no tumor, and one patient on the control arm had renal cell carcinoma.)

The sponsor found the response rates in both docetaxel arms to be significantly higher than that on the control arm – 10.5% (95% CI = 5.9, 17.6) on the docetaxel 100 mg arm and 6.5% (95% CI = 3.0, 12.7) on the docetaxel 75 mg arm vs. 0.8% (95% CI = 0.0, 5.2) on the control arm. Comparison of the docetaxel 100 mg/m^2 arm to control was significant using the Fisher's Exact test, p=0.001, as was the comparison of the docetaxel 75 mg/m^2 arm to control, p=0.036.

*Reviewer Comment: The reviewer checked the response assignments made on each arm utilizing the sponsor's table, **23B. Data Flow-Tumor Lesions Assessment and Response as Per CRF** in volume 48 of the application, and utilized the same total N per treatment arm that the sponsor did for the ITT population (not counting the single patient on each arm who did not have non-small cell lung carcinoma). This review found that of the 6 patients - two docetaxel 100 mg patients (Pt. 10389 and 10659), 3 docetaxel 75 mg patients (Pt. 10026, 10677, and 10687), and one control (Pt. 10015) - that the sponsor considered to have a response of IMP (evaluable-only and/or unidimensional disease), only 2 were converted to PR for the response analysis – Pt. 10659(a docetaxel 100 mg patient) and Pt. 10687 (a docetaxel 75 mg patient). As shown below, the reviewer could not confirm that Pt. 10687 had actually achieved an IMP. The following tables summarize the review of the response assignments.*

Table 22 TAX 320 Reviewer's List of Response Assignment Errors

Control	**Assigned**	**FDA**
10483	PD	NC
10500	PD	NC
10511	NC	PD (only 4 weeks from baseline)
10676	*PD*	*NC*
Docetaxel 100 mg	**Assigned**	**FDA**
10062	PD	NC
10103	NC	PD a baseline bi-dimensionally measurable lesion by CT becomes NE on CT in 002, and bidimensionally measurable and the basis for PD in cycle 004
10391	**PR**	**NC**
10409	NC	PD Not all lesions reassessed from baseline on study (bidimensional) before PD occurs
10434	*NC*	*PD* *Baseline uni-dimensional brain lesion was not reassessed until the brain became the site of PD*
10477	NC	PD
10486	NC	IMP (evaluable only dz)
10519	*NC*	*PD* *Baseline evaluable lesion was never reassessed prior to PD*
10654	NC	PD Baseline evaluable lesion was never reassessed prior to PD
10659	PR	IMP (evaluable only disease)
Docetaxel 75 mg	**Assigned**	**FDA**
10098	*NC*	*PD*
10165	PD	Can't confirm PD
10329	*NC*	*PD*
10438	**NE**	**PD**
10510	**PR**	**NC**
10687**	PR	NE (baseline evaluable lesion

		never reassessed)

** this patient also had evaluable only disease (evaluable and unidimensional)

The sponsor responded to these proposed response revisions in correspondence dated November 5, 1999. They agreed with the FDA assessment in all but 8 patients (One on the Control arm, **10676**; 3 on the docetaxel 100 mg arm – **10391, 10434, 10519**; and 4 on the docetaxel 75 mg arm – **10098, 10329, 10438, and 10510**.) After reviewing the sponsor's comments, the FDA reviewer concurred with the PD assignment made to control patient **10676** and the NC assignments in docetaxel 75 mg patients **10434 and 10519**. The reviewer also concurred with the NC assignment to docetaxel 75 mg arm patients **10329 and 10098**. In a team meeting with the sponsor before ODAC on December 3, 1999, the FDA reviewer agreed to accept the PR assessment of patients **10391 and 10510**. These changes are summarized below. In the table above, those revisions that the FDA ultimately reversed on the basis of the sponsor's comments are in italics. Those that the sponsor disagreed with, but the FDA did not believe their comments supported their response assignments are bolded. The remaining patients were those that the sponsor concurred with FDA changes. (They concurred with two docetaxel revisions from PR to IMP, but disagreed with two other docetaxel PR revisions to NC.)

Table 23 TAX 320 Summary Impact of Response Assignment Changes by FDA Reviewer

Control			
PR	**NC**	**PD**	**NE/IMP**
0	+2 -1 Net = +1	+1 -2 Net = -1	0
Docetaxel 100 mg			
PR	**NC**	**PD**	**NE/IMP**
+0 - 1 Net = -1	+2 –4 Net = -2	+4 –1 Net = +3	+ 1 IMP
Docetaxel 75 mg			
PR	**NC**	**PD**	**NE/IMP**
+0 –1 Net = -1	+1 –0 Net = +1	+1 –0 Net = +1	+1 –1 Net = 0

The resulting responses by treatment arm are shown below broken into two groups. The first table utilizes the protocol specified division of PR's and IMP's based on whether patients had bidimensionally measurable disease. The second table converts the IMP's to PR's.

Table 24 TAX 320 Summary of Reviewer's Revised Response Rates Utilizing Separate PR and IMP Response Categories (NE Category Not Shown)

	Docetaxel 100 mg	**Docetaxel 75 mg**	**Control**
PR	9.7% (12/124)	5.7% (7/124)	0.8% (1/122)

NC	32.3% (40/124)	35.5% (44/124)	30.9% (38/123)
IMP	1.6% (2/124)	1.6% (2/124)	0.8% (1/122)
PD	45.2% (56/124)	46.8% (58/124)	51.6% (63/122)

Table 25 TAX 320 Summary of Reviewer's Revised Response Rates Combining PR's and IMP's in One Response Category

	Docetaxel 100 mg	**Docetaxel 75 mg**	**Control**
PR	11.3% (14/124)	7.3% (9/124)	1.6% (2/122)

Using the pre-specified response definition of overall response = CR + PR and the reviewer changes of the responses, the response rate on the docetaxel 100 mg/m^2 arm remains significant using the Fisher's Exact test, p=0.005. The docetaxel 75 mg/m^2 arm response rate, however, favored docetaxel, p=0.04. Even without making the FDA changes in response assignments, the FDA statistical reviewer found that when the analysis of response rates was adjusted for multiple comparison with the Bonferroni adjustment, the difference between the docetaxel 75 mg/m^2 and control arms was not statistically significant, p=0.072.

The sponsor did an exploratory subgroup analysis to compare responses among the treatment arms in different prognostic categories. There were no responses across the arms in patients with ≥ 10% weight loss in the 3 months prior to study entry (docetaxel 100 mg = 14, docetaxel 75 mg = 9, and control = 12), ≥3 prior regimens of chemotherapy (docetaxel 100 mg = 11, docetaxel 75 mg = 9, and control = 5), or prior ifosfamide treatment (docetaxel 100 mg = 4, docetaxel 75 mg = 3, and control = 2). The response rate in all other prognostic categories was always higher on the docetaxel 100 mg arm (based on sponsor's response assignments), except for Stage IIIB disease (docetaxel 100 mg = 5.9% vs. docetaxel 75 mg = 8.3%), PD as best response to prior cisplatin chemotherapy (docetaxel 100 mg = 2.5% vs. docetaxel 75 mg = 6.7%), and history of prior paclitaxel therapy (docetaxel 100 mg = 7.7% vs. docetaxel 75 mg = 11.8%).

Reviewer Comment: Examining the characteristics of the patients with reviewer-confirmed PR's and IMP's (N=23) revealed that all responders had Stage IV disease at study entry, except two patients on a docetaxel arm, and all but two had a PS of ≤1 at study entry (both on the docetaxel 100 mg arm). Ten of the 23 patients had experienced a PR on prior cisplatin chemotherapy and 4 had experienced PD as a best response to prior cisplatin. The latter 4 patients were distributed among the treatment arms as follows: Docetaxel 100 mg = 1; Docetaxel 75 mg = 2; and Control = 1. Two of these responders treated on the docetaxel 100 mg arm were censored in the TTP analysis – one for further chemotherapy.

Another secondary endpoint, duration of response, was <u>not</u> found to be significantly different among the arms by log rank test, p=0.33, in the comparison of the docetaxel 100 mg arm to control, and p=0.28 in the comparison of the docetaxel 75 mg arm to control. The median

duration of response of the arms was 32.1 weeks on the docetaxel arm, 39.3 weeks on the docetaxel 75 mg arm and 25.6 weeks on the control arm. The control arm's duration of response was based on the sponsor analysis of one patient with PR. (There was one additional patient with an IMP on the control arm.)

3.10.3 Time to Progression

Time to progression, TTP, was a protocol specified secondary endpoint that was to be measured from the date of randomization to the date of disease progression. As noted in this review's **section 3.9 Endpoints/Statistical Considerations**, comparisons were to be made utilizing the log rank test. The statistical analysis plan dated January 15, 1998 stated censoring would be done if a patient was lost to follow-up, if no PD or death had occurred prior to cut-off date, if death occurred ≥3 months beyond last tumor assessment, and if further therapy including radiotherapy, chemotherapy, surgery , or immunotherapy was initiated before documentation of PD. The final study report indicates that the actual analysis of TTP included censoring for all of these, except radiotherapy. The reviewer found no patients with a well-documented PD date who would have qualified for censoring on the basis of further radiotherapy (the dates of radiotherapy appeared to follow the dates of PD).

Ultimately, 9 docetaxel 100 mg arm patients, 7 docetaxel 75 mg, and 8 control patients were censored. (A study total of 13 were coded as censored for further chemotherapy.) The sponsor excluded the single patient on each arm who did not have non-small cell lung carcinoma from this analysis. The prospectively defined analysis of TTP found no significant differences in median TTP: docetaxel 100 mg = 8.4 weeks (95% CI= 6.7, 11.0), docetaxel 75 mg = 8.5 weeks (95% CI = 6.7, 11.0), and control = 7.9 weeks (95% CI = 6.9, 11.0). Again, the Kaplan-Meier curves separate after first overlying one another until approximately 16 weeks. The log rank test was used in the analysis and was found to be significant in the comparison of the docetaxel 100 mg arm to the control, p=0.044, but the docetaxel 75 mg comparison to the control was not, p=0.093. In an unplanned analysis, the sponsor pooled the TTP data from the docetaxel arms. Again the median TTP was not found to be significantly different from that of the control: docetaxel = 8.4 weeks (95% CI = 7, 11) and Control = 7.6 weeks (95% CI = 6.7, 10.1), but the log rank comparison of the combined (unplanned) docetaxel arm data was found to be significantly longer than that of the control arm, p=0.046.

The sponsor's exploratory analysis to examine impact of prognostic factors on TTP revealed that the percentage of patients who did not experience PD by week 26 on both docetaxel arms was essentially the same across the prognostic factors utilized for stratification, with the exception of performance status >1. In that subgroup, the docetaxel 75 mg non-PD rate at 26 weeks was lower than that of the docetaxel 100 mg arm – 6% vs. 22%.

Reviewer Comment: The majority of censoring in the TTP analysis on the docetaxel 75 mg and the control arms was for further chemotherapy – 5/7 on docetaxel and 5/8 on control. The nine censored patients on the docetaxel 100 mg arm were more evenly distributed among chemotherapy (n=3), no PD documented before last assessment (n=4), and no assessment after baseline (n=2).

Time to progression is an endpoint that is subject to bias, particularly in on open label trial. That bias can be introduced by differences in patterns of performing tumor assessments. If those assessments are not performed as directed by the protocol, PD may be documented later in

patients that have delayed evaluations than if performed when as directed. The reviewer examined the tumor assessments and timing of PD determination in the study arms, and found that such delays did occur. The tables tabulating those patients in which altering the assessment timing could have altered the PD date can be found in the Appendix .

In the process of conducting the time to progression review, the FDA reviewer identified 20 control arm patients, 18 docetaxel 100 mg arm patients, and 23 docetaxel 75 mg arm patients for whom she was unable to confirm their PD date assigned with the tumor assessment data provided in the application. In response to the FDA's request for clarification of these PD dates, the sponsor submitted information on these patients in question in correspondence dated November 5, 1999. Their explanation for the PD dates selected follows in the table below. The number of patients falling into each category is tabulated by treatment arm. After reviewing the correspondence, there remained patients that the FDA reviewer could not confirm or concur with the PD date assigned. Those patient numbers have a short narrative included in the table. Despite the statistical analysis plan to censor patients with no documented PD prior to further therapy at the date of last assessment before the start of further therapy, the sponsor used the date of further therapy (chemotherapy and radiotherapy) as an event date in 9 patients (docetaxel 100 mg= 1; docetaxel 75 mg = 3; control = 5).

Table 26 TAX 320 Summary of Sponsor Responses to FDA Questions Regarding Specific Patients' PD Date Assignments

	Docetaxel 100 mg N= 18	Docetaxel 75 mg N=23	Control N=20
PD not Documented; PD date = Date of Death	12/18	14/23	8/20
Error in PD date Assignment		2 10165 – PD should have been Date of Death instead of Date of cycle 1; Date of death was 2/3/96; Date of event in dataset was 11/14/95.) 10341 – Date of PD should be date of documented progression on chest x-ray – 2/13/96 instead of the date in the electronic dataset of 7/13/96. – That CXR does not appear in tumor listings for reviewer to confirm	
PD not Documented;	0	0	3

	Docetaxel 100 mg N= 18	Docetaxel 75 mg N=23	Control N=20
PD date = Date of Further Chemotherapy			
PD not Documented; PD date = Date of Further Radiotherapy	1	3	2
PD date attributed to date of further therapy, but no further therapy documented in Further Therapy Dataset		1 (10163)	
Response states patient was counted as an event on date of death, but electronic Efficacy dataset states the patient was censored	1 10484 Death = 11/28/97 Censored for PD = 10/28/96 (Randomization Date)		
Response indicates the date of PD is Not Applicable as there was no documented PD, no further therapy, and death was not due to malignant event. The **event** date assigned was date of death.	1 10004 (11/11/95)	1 10664 (5/28/97)	1 10362 (2/5/96)
Unverifiable	2 10070 = PD on Chest X-ray not included in dataset 10054 = "Sponsor table has been corrected to support date of documented progression"	2 10044 = PD is based on clinical assessment of PD on chest x-ray without objective measurements. 10341* - see above in PD Error 10370 – Date of PD is provided by investigator with no supporting documentation.	6 10093 = Date of PD is "per a query form the date of clinical progression noted in cycle 3" 10414 = Date of PD provided on follow-up form without supportive X-ray documentation 10437 = Date of PD taken from a "PD" assignment to a CXR without measurements assessment of previously bidimensionally documented dz on CT's

	Docetaxel 100 mg N= 18	Docetaxel 75 mg N=23	Control N=20
			10459 = Date of PD is based on a follow-up CT not included in data set that reportedly showed PD in atelectasis. 10500 = Date "per query form is demonstrated on CT 10672 = Date is reported but supportive documentation not provided
Keying Error prevented listing from supporting PD	1 10078		

The reviewer also submitted revised TTP dates to the sponsor, based on her review of the tumor assessment and dates. The list of these patients can be found in the Appendix. The sponsor agreed with 3/4 control arm revisions proposed by the reviewer (+5d, +6d, -21 d), and the reviewer concurred with their reasons for maintaining the PD date on the fourth patient (who had CR in the lesion that sponsor called PD in cycle 002 subsequently in cycle 004). On the docetaxel 100 mg arm the sponsor concurred with 4/7 FDA revisions of PD dates. The reviewer did not agree with the sponsor's justification of the PD dates selected in the remaining 3, as these patients had met the PD response criteria on the date assigned by the reviewer. (Resulting changes: -21d, -152 d, -185 d, +13d, -6d, +16 d, -59d.) On the docetaxel 75 mg arm, the sponsor concurred with 4/7 of the reviewer's changes. One of the patients they disagreed on was justified on the basis of a keying error, which the reviewer accepted. The reviewer concurred with the sponsor on the other two patients as well. (Resulting changes: -205d, +122d, +9d, -95d). This resulted in 11 patients having their date of PD changed. There were two additional PD date errors noted in the table above in the docetaxel 75 mg arm (+81d, -150d).

The FDA statistical reviewer re-ran the TTP analysis with these PD date changes and changing censoring for further chemotherapy to events at the time of further therapy. The Agency's TTP analysis performed with those changes yielded a median time to progression that was no longer statistically significant for either dose level examined. The comparative results of the sponsor and FDA TTP analyses are shown in the table below:

Table 27 Comparison of Sponsor and FDA Time To Progression Analyses

	Docetaxel 100 mg/m²		Docetaxel 75 mg/m²		Control	
	RPR	FDA	RPR	FDA	RPR	FDA
% Censored	7.3%	4.8%	5.6%	1.6%	6.6%	2.5%

Median TTP	8.4 weeks	8.4 weeks	8.5 weeks	8.3 weeks	7.9 weeks	7.6 weeks
95% CI	(6.7, 11.0)	(7.0, 10.1)	(6.7, 11.0)	(7.0, 11.7)	(6.9, 11.0)	(6.7, 10.1)
26 week K-M estimate	19%	16%	17%	15%	8%	7%
95% CI	(12,26)	(10, 23)	(10, 24)	(9,22)	(3, 13)	(2, 11)
Log Rank	P=0.044	P=0.064	P=0.093	P=0.074		

3.10.4 Quality of Life

The quality of life instrument utilized in this study was the LCSS (Lung Cancer Symptoms Scale). It is composed of two subscales – one a patient scale and one an observer scale. The patient scale includes 9 descriptors that are rated by marking a 100 mm horizontal line visual analog scale. The nine descriptors include six targeting specific symptoms and 3 global questions. The symptoms assessed are appetite, fatigue, cough, dyspnea, hemoptysis and pain. The global questions examined patents' perceived impact of illness on their activity level, their assessment of overall symptoms related to their tumor, and their overall rating of quality of life. The **observer scale** included 6 symptom descriptors (loss of appetite, fatigue, cough, dyspnea, hemoptysis, pain) measured on a 5 point ordinal scale (0, 25, 50, 75, 100; where 100 = none and 0= severe). The observer scale was to be filled out based on an interview of the patient. Its directions stated "Direct the interview to assess lung cancer symptoms using the time frame of during the past day."

Reviewer Comment: The LCSS was to be completed before starting dexamethasone premedication. There were 39 patients identified by the FDA statistical reviewer, whose LCSS was completed after having started dexamethasone. Many of these patients had more than one QoL assessment performed while taking dexamethasone (total assessments = 130). The sponsor indicated in correspondence dated November 15, 1999 that it concurred with that number, except for 3 QoL assessments, and stated that there were five assessments that were completed on the same day that dexamethasone was initiated.

An evaluable assessment was one that was completed. "Completed" was defined as missing ≤3 descriptors. Patients were excluded from the quality of life analysis if they had no baseline assessment, an incomplete baseline assessment, no on-treatment assessment, or if the only on-treatment assessment was incomplete. Baseline assessments were performed in >70% of the study patients: docetaxel 100 mg = 84%, docetaxel 75 mg = 73%, and control = 73%. The most common reason for non-evaluability in the QoL analysis, "no on-treatment assessment", occurred in greatest frequency on the docetaxel 75 mg arm = 19.2% vs. 18.7 % (control arm) and 11.2% (docetaxel 100 mg arm). The comparison of the number of patients available for QoL evaluation at each study period to the percentage with evaluable assessments in that period is summarized in the table below. Those periods in which there was a group with ≥10% difference compared to the others are highlighted.

Table 28 TAX 320 Distribution of Evaluable LCSS QoL Assessments Over the Study Periods

Period	**Docetaxel 100 mg** No. of Patients Available for Assessment (Percentage with Evaluable QoL Assessment)	**Docetaxel 75 mg** No. of Patients Available for Assessment (Percentage with Evaluable QoL Assessment)	**Control** No. of Patients Available for Assessment (Percentage with Evaluable QoL Assessment)
Baseline	125 (84)	125 (73)	123 (73)
1	121 (74)	121 (69)	119 (65)
2	104 (55)	99 (61)	96 (65)
3	69 (62)	69 (70)	61 (66)
4	54 (69)	58 (62)	49 (59)
5	43 (70)	48 (67)	32 (56)
6	35 (57)	37 (59)	24 (75)
Follow-up #1	125 (13)	123 (10)	122 (11)
Follow-up #2	125 (0)	123 (2)	121 (1)

One of the sponsor's QoL analyses is an analysis of covariance, "ANCOVA". This is a paired analysis of the difference between the baseline and the last available assessment on study for each patient. The FDA does not consider this a valid QoL analysis as it ignores what may have happened between those two points. The Agency prefers longitudinal analysis and use of pattern mixture modeling. The latter examines completers and non-completers for evidence of informative missingness. If the means of the two groups do not differ, there is evidence that the mechanism of missing data is ignorable.

The longitudinal analysis performed by the sponsor comparing each docetaxel arm to the control found no significant difference in patient and observer total scores and subscores, except for a favorable trend toward docetaxel 100 mg in the OBSERVER Total Score, p=0.048. The only patient score that approached significance was the Lung Cancer QoL Today score, favoring the docetaxel 75 mg arm, p=0.058.

Reviewer Comment: *The sponsor explored the existence of a relationship between response on study and QoL benefit with an analysis comparing totaled patient LCSS subscale scores at various periods to baseline totals among the response groupings PR + IMP, PR + IMP + NC and PD. The best total score from 9 subscales, each with a best score equal to 100 mm, is 900 mm. The sponsor found that the subgroup defined as best response of PR + IMP, had totaled best response subscores that were 10% better (90 mm of 900 mm possible) than the baseline totals on the docetaxel 100 mg treatment arm, 9% better (83 mm of 900 mm possible) on the docetaxel 75 mg arm, and 1% on the control arm. It was not clear to the reviewer that an improvement of 90mm/900mm was clinically meaningful and use of totaled subscales was not a clearly validated methodology.*

The statistical reviewer repeated the QoL longitudinal analysis with pattern mixture focusing on the patient pain subscale and the patient "QoL Today" subscale. The patient pain subscale was selected because the sponsor found statistical significance favoring docetaxel in this subscale in TAX 317, and in TAX 320 the sponsor believed that clinical benefit was shown in decreased analgesic use in the docetaxel 100 mg/m^2 arm. The patient QoL Today subscale was selected because the sponsor's longitudinal analysis showed this approached statistical significance

favoring docetaxel 75 mg/m^2. In addition, this patient scale was a global scale that allows the patient to "weigh" the various other components into one composite quality of life score. The reviewers avoided the observer scales as they appeared to be more vulnerable to bias. The statistical reviewer found no significant differences among treatment arms, although the rate of decline in the QoL today patient scores was slower on the docetaxel arms. See Statistical Review.

The reviewer attempted to explore the same issue by limiting the examination to individual subscales. The reviewer selected the patient global quality of life subscale ("How would you rate the quality of your life today") as the "sentinel" subscale for examination, since this subscale allows the patient to determine the "weight" he/she gives to the various components that make up his/her quality of life as he/she finds pertinent to his/her individual situation. This was also the patient subscale for which differences approached significance (favoring docetaxel 75 mg arm, p=0.058) in the longitudinal analysis presented by the sponsor. A minimum change of +20 mm was selected as a change that might be more indicative of a significant perceived change in status. The electronic dataset was utilized to determine the percentage of each treatment groups' response category (PR, NC, PD, IMP) that achieved that minimum change (20mm) in the global quality of life subscale. That percentage was determined both for the sponsor's reported response assignments and the reviewer's revisions of response assessments across treatment groups. Once patients with a minimum of 20 mm change in the global Q0L category in each response category were identified, the reviewer examined how many of those patients had experienced an improvement of at least 30 mm, 40 mm and ≥50 mm. Additionally, in those same patients who had experienced at least a 20mm improvement in reported global QoL, the reviewer examined the concurrent changes in the two other global patient subscores - symptoms ("How bad are your symptoms from lung cancer?") and impact on normal activities ("How much has your illness affected your ability to carry out normal activities?") - to see how many also reported improvements in at least one of the other two subscales of a minimum of 20 mm, 30 mm, 40 mm, or ≥50 mm. These results are listed in the table below. "Completers" are as defined by the sponsor in their longitudinal QoL analyses (those treated for more than 3 cycles).

Table 29 TAX 320 Exploratory Analysis of Response/Quality of Life Relationship – Reviewer's Response Assignments

Docetaxel 100 mg	*Range of # assessments	QoL Today			Additional Two Global Questions			
		≥30	≥40	≥50	≥20	≥30	≥40	≥50
PR (N=4; 36%) Completer: 4/4	2-6 #1-10	3/4	2/4	1/4	4/4	4/4	4/4	3/4
NC (N= 8; 27%) Completer: 5/8	1-5 #1-5	3/8	3/8	1/8	4/8	4/8	2/8	1/8
PD (N=12; 20%) Completer: 2/12	1-2 #1-6	11/12	7/12	2/12	9/12	4/12	1/12	1/12
IMP (N=0/2) Completers								

Docetaxel 100 mg	*Range of # assessments	QoL Today			Additional Two Global Questions			
		≥30	≥40	≥50	≥20	≥30	≥40	≥50
Docetaxel 75 mg								
PR (N=3; **50%**) Completer: 3/3	1-17 #1-25	1/3	1/3	0	2/3	2/3	1/3	1/3
NC (N=14; **33%**) Completer: 12/14	1-9 #1-12	12/14	8/14	4/14	6/14	4/14	3/14	3/14
PD (N=9; **15%**) Completer: 4/9	1-4 #1-4	8/9	5/9	3/9	9/9	9/9	5/9	3/9
IMP (N=2; **100%**) Completer: 2/2	1-32	1/2	1/2	0	0	0	0	0
Control								
PR (N=0)								
NC (N=6; **15%**) Completer: 4/6	1-3 #1-9	3/6	3/6	0	4/6	4/6	2/6	2/6
PD (N=5; **8%**) Completer: 2/8	1-2 #1-5	5/5	2/5	0	3/5	3/5	2/5	2/5
IMP (N=0/1) Completer								

* The first range in the cells of this column is the range of number of cycles a single atient had meeting this minimum change . The second range (with "#" preceding the numbers) is the range of numbered cycle with the specified minimum change, eg. #1 = Cycle 001.

This analysis of tumor response/QoL relationship is a responder analysis, and thus tenuous at best. It is also limited by the small number of patients in each response category that completed QoL assessments. It does show, however, that some patients reported fairly large improvements on global scores, regardless of their best tumor response on study.

3.10.5 Performance Status

There was a prospective plan to compare performance status in this study, but no analysis was submitted in the study report. The prespecified plan was that this would be a comparison of

change between baseline and last assessment on study. In response to an inquiry by the reviewer, the sponsor submitted a summary of this analysis, which they stated was not submitted with the application earlier because it was incomplete at the time of initial submission.

In this analysis the sponsor found that most patients did not experience a change in ECOG PS from baseline. One hundred four docetaxel 100 mg patients, 109 docetaxel 75 mg patients, and 106 control arm patients who had both a baseline and at least one subsequent PS assessment were available for these analyses. There were 6 patients identified in each docetaxel treatment arm who experienced improvement in PS on study, and 4 on the control arm. There were six patients at each docetaxel dose level who worsened by 2 or more performance status levels, and 12 who did so on the control arm. In the comparison of average change –baseline to last assessment – inclusive of all possible evaluation periods on study, there appeared to be a possible trend favoring docetaxel 75 mg over the control arm in having less of a decrement between first and last assessments – 0.34 vs. 0.53 (means), p=0.07. In an exploratory retrospective analysis limiting this same comparison to the first 3 cycles on study, the sponsor was able to show a significant reduction in decrement of performance status from baseline to cycle 3 in the docetaxel 75 mg group compared to the control – 0.05 vs. 0.36, p=0.03. Based on the data presented in the sponsor's November 5, 1999 correspondence it appears that the total number of patients in these two arms having a cycle 3 assessment was 50 in each of the control and docetaxel 75 mg/m^2 arms (less than half the patients in each treatment arm) and the number of patients from each of those arms utilized in the averaging of performance status across Cycles 1-3 were control = 43 and docetaxel 75 mg/m^2 = 48.

3.10.6 Tumor Related Analgesics

A comparison of analgesic usage between control and docetaxel was prospectively planned in the protocol. There was no apparent effort to optimize pain medications at baseline in a standard fashion across treatment arms, and the analysis conducted by the sponsor does not appear to take into account changes in either starting/stopping pain medication or change in doses. Because of this, the analgesic analysis submitted in the sponsor's November 5, 1999 correspondence does not appear to be meaningful.

Reviewer Comment: The sponsor "submitted" an analyis of change from baseline use of morphine analgesics in its ODAC briefing document (submitted November 16, 1999).. That data suggested that more patients on docetaxel 75 mg started additional opoids or started de novo opoids while on study than the control arm, although the difference was not found to be statistically significant.

3.11 Safety

3.11.1 Adverse Events

The sponsor presented tables of the 15 – 16 most commonly reported adverse events in a number of different formats in its study report – most frequent adverse events (n=15), most frequent treatment-related adverse events (n=16), new onset adverse events (n=15), new onset treatment-related adverse events (n=16). These tables were collapsed into one table below, to facilitate comparisons, but treatment related new onset analyses are not included (because the reviewer did not believe that those analyses added useful information given the treatment emergent analyses and the presence of a control arm). The data presented below is for adverse events classified by the NCI system. Those adverse events reported by the sponsor in COSTART terms only, which utilizes a "Severe" category rather than Grade 3/4, are shown with the adverse event term bolded.

Table 30 TAX 320 Adverse Events Including Overall, Grade 3 and 4, and Treatment Emergent

	Docetaxel 100 mg N=121			Docetaxel 75 mg N=121			Control N=119		
	All Events	Grade 3/4	New Onset	All Events	Grade 3/4	New Onset	All Events	Grade 3/4	New Onset
Pain (COSTART)	92.6% **#1**	1.7%	41.3%	85.1% **#1**	2.5%	32.2%	84.9% **#1**	0.8%	37.8% **#3**
Asthenia (COSTART)	83.5% **#2**	17.4% **#1**	62.8% **#1**	82.6% **#2**	12.4% **#1**	52.1% **#1**	76.5% **#3**	10.9% **#1**	53.8 **#1**
Pulmonary	77.7%	8.3% **#3**	44.6% **#3**	72.7% **#3**	2.5%	42.1% **#2**	80.7% **#2**	1.7%	45.4% **#2**
Cough Increased (COSTART)	71.9%		29.8%	66.9%		28.1%	49.6%		31.9%
Alopecia	65.3%	0	45.5% **#2**	66.9%	0	35.5%	49.6% **#3**	0	15.1%
Neuro-sensory	52.9%	5.8%	31.4%	54.5%	0.8%	24.8%	51.3%	3.4% **#3**	28.6%
Neuro-motor	26.4%	2.5%	23.1%	22.3%	2.5%	16.5%	16.8%	0.0	10.1%
Nausea	47.9%	7.4%	40.5%	40.5%	3.3% **#3**	32.2%	40.3%	4.2% **#2**	31.1%
Vomiting	30.6%	6.6%	29.8%	24.0%	0.8%	20.7%	23.5%	4.2% **#2**	21.8%
Fever (infx Absent)	45.5%	0.8%	43.8%	42.1%	5.0%	37.2% **#3**	33.6%	0.8%	28.6%
Anorexia (COSTART)	42.1%	3.3%	28.9%	43.8%	1.7%	28.1%	42.0%	1.7%	28.6%
Infection	41.3%	12.4% **#2**	39.7%	35.5%	5.0% **#2**	34.7%	31.9%	2.5%	30.3%
Peripheral Edema (COSTART)	39.7%	3.3%	33.1%	32.2%	0.0	26.4%	14.3%	0.8%	8.4%
Diarrhea	34.7%	3.3%	33.1%	19.0%	1.7%	16.5%	11.8%	1.7%	11.8%

	Docetaxel 100 mg N=121			Docetaxel 75 mg N=121			Control N=119		
	All Events	Grade 3/4	New Onset	All Events	Grade 3/4	New Onset	All Events	Grade 3/4	New Onset
Constip. (COSTART)	33.9%			24.8%			33.6%		
Skin	33.1%		31.4%	23.1%		19.8%	21.0%		16.8 %
Stomatitis	31.4%	2.5%	29.8%	26.4%	1.7%	26.4%	9.2%	0.8%	7.6%
Myalgia (COSTART)		2.5%			0.0%			0.0%	
Hypotens.	7.4%	1.7%	7.4%	6.6%	0.0	6.6%	4.2%	0.8%	4.2%
Dehydrat. (COSTART)		1.7%			2.5%			0.0%	
Allergy	7.4%*	0	7.4%	4.1%	1	4.1%	0.8%		0.8%

3.11.1.2` Hematologic/Infection

The following table summarizes the hematologic toxicities, broken into all grades, grade 3, and grade 4 categories. This analysis is by patient, not by cycle.

Table 31 TAX 320 Hematological Toxicity

Toxicity	Docetaxel 100 mg N=121			Docetaxel 75 mg N=121			Control N=119		
	All Grade	Gr.3	Gr. 4	All Grade	Gr. 3	Gr. 4	All Grade	Gr 3	Gr. 4
Neutropenia	94.2	11.7	77.5	89.4	11.9	54.2	85.1	**27.6**	**31.0**
Thrombocytopenia	8.3	1.7	0.8	10.0	2.5	1.7	7.7	1.7	0.0
Anemia	95.1	14.9	0.8	93.3	10.8	0.0	92.2	12.8	1.7
Febrile Neutropenia* (ANC=Gr. 4)	**11.6 %**= Sponsor 14.9% = FDA (18/121)			**8.3%** = Sponsor 11.6% = FDA (14/121)			1.1		
Infection All grades	**41.3%** 50/121			**35.5%** 43/121			**31.9%** 38/119		

	Docetaxel 100 mg N=121	Docetaxel 75 mg N=121	Control N=119
SAE's with Infection Listed as Part of the Clinical Picture	28.1% 34/121	18.1% 22/121	13.5% 16/119
Infection Grade ¾	**14.8%** (n=18)	**12.4%** (n=15)	**9.2%**

*Febrile Neutropenia was defined as concomitant Grade 4 neutropenia, Grade 2 fever, and hospitalization and/or IV antibiotics.
**The Numbers in the Infection SAE's column were derived from the reviewer's examination of the narratives associated with SAE's in the Study Report. In SAE CRF Patient Tabulations, Table 17, Volume 44 there are 31 "infection" SAE's (25.6%) and 3 "pneumonia" SAE's (28.1%) on the docetaxel 100 mg/m^2 arm; 20 "infection" SAE's and 2 "pneumonia" SAE's on the docetaxel 75 mg/m^2 arm.

Reviewer Comment:
The FDA numbers in the above table were derived from the SAE narratives, in which there were patients reported to have been hospitalized with febrile neutropenia, but did not appear in the sponsor's lists of neutropenic infection or febrile neutropenia, submitted in correspondence November 15, 1999. The docetaxel patients counted by the reviewer as SAE's Infection and Neutropenic fever are listed below. Those bolded appear in sponsor's lists of febrile neutropenia and neutropenic infection submitted in correspondence November 15, 1999. Those in parentheses are in sponsor's list for that category (column). Those not bolded and not in parentheses are additional patients that were reported to have febrile neutropenia in the SAE narratives, but appear in neither list.

Table 32 Reviewer Tabulation of Infection SAE's and Neutropenic Fever References Derived from the SAE Narratives

Docetaxel 100 mg Infection SAE	Docetaxel 100 mg Neutropenic Fever SAE	Docetaxel 75 mg Infection SAE	Docetaxel 75 mg Neutropenic Fever SAE
10007	**10007**	10006	(10006)
10011	10011	10018	10018
10016	**10021**	10026	10029
10021	10054	10035	10079
10045	(10062)	10042	10100
10062	10064	10044	(10346)
10078	**10166**	10079	(10364)
10083	**10188**	10099	(10379)
10102	(10327)	10331	**10395**
10103	**(10353)**	10339	(10475)
10166	(10385)	10395	(10490)
10169	10391	**(10410)**	(10658)
10177	(10423)	10415	(10689)
10178	**10443**	10416	
10188	**10458**	(10419)	
10335	(10474)	10438	
10344	(10484)	10472	
10353	(10486)	10499	

10366 10372 **10409** **10417** **10443** 10444 **10458** **10466** **10468** 10477 **10491** **10495** **10655** **10661** **10670** **10675** 10682	**10491** **10495** (10659) **(10661)** (10662) **(10680)** (10686)	10501 10514 10520 **10668**	

Four additional febrile neutropenia patients were derived in each docetaxel treatment arm. In most of these patients febrile neutropenia was reported in the narrative, but the patient was not coded as having had a fever adverse event or the ANC was not found in the electronic dataset.

In correspondence dated November 15, 1999, the sponsor explained that the tabulation of febrile neutropenia was based on criteria that defined febrile neutropenia in the protocol. The patients that were reported in narratives to have febrile neutropenia by investigators and were not so tabulated, did not meet the protocol's definition of febrile neutropenia. The FDA reviewer accepted the sponsor's tabulation of febrile neutropenia on the basis of this explanation at a meeting with the sponsor December 3, 1999.

The percentages in Table 32 TAX 320 Hematological Toxicity for overall infection are higher than that reported in the current label for both previously treated breast cancer patients and all tumor types. Those previously reported values are shown below. The rate of grade 3/4 infections in TAX 320 (Table 31 above) associated with the 100 mg dose was higher than currently labeled, while the rate at the 75 mg dose level was similar to that labeled for 100 mg.

	Breast Cancer with Previous Treatment with Chemotx (n=730)	All Tumor Types (n=2045)
Febrile neutropenia (Grade 4 with fever and antibiotics and/or hospitalization)	**11.8%**	**11.0%**
Infection Any GRADE 3/4	 22.5% **7.1%**	 21.6% Severe = **6.1%**
Septic Death	1.5%	1.6%

None of the patients who developed febrile neutropenia had a second occurrence, and all episodes occurred in patients with PS <2. Its incidence was greatest in Cycle 1. The median day to neutrophil nadir was Day 7 in both docetaxel treatment groups, and Day 14 on the control arm. The median time to recovery on all arms was 7 days. The median time to platelet nadir was Day 13 on the docetaxel 100 mg arm and the control arm, and Day 9 on the docetaxel 75 mg arm.

On the docetaxel 100 mg arm, 2/18 treatment discontinuations for adverse events were attributed to infection (**1.7% of the 121** patients on this arm that received any treatment on study), while 1/11 (0.8% of 121 treated) on the docetaxel 75 mg arm and 1/11 (0.8% of 119 treated) on the control arm had treatment discontinued for this reason. The docetaxel 75 mg patient was hospitalized on Day 13 of Cycle 5 with pneumocystis carinii.

Reviewer Comment: The list of patients discontinued from study due to adverse event appears on page 148 of the Study Report. In that list the reviewer found two patients on the docetaxel 100 mg arm who were discontinued for "infection" and an additional patient discontinued for "pneumonia". That patient, Pt. 10083, was admitted on day 15 of cycle 2 with fever, hypoxia, and bilateral pulmonary infiltrates, and was treated with antibiotics. The reviewer considers this an infection as well, bringing the percentage up to 3/121 (2.5%). An additional patient on this arm, Pt. 10016, withdrew consent 2 days after discharge from the hospital where he had been hospitalized on Day 21 of Cycle 1 for four days with bilateral pneumonia treated with IV antibiotics. Due to the proximity of this event the reviewer counted that as a discontinuation for adverse event=infection, bringing the total to 4/121 ***(3.3%) discontinuations for infection on the docetaxel 100 mg arm.***

On the docetaxel 75 mg arm there was an additional patient, Pt. 10028, who was hospitalized on day 10 of cycle 1 with respiratory distress and neutropenia, grade 2. She was treated with IV antibiotics and "infection resolved after 22 days". On Day 20 of Cycle 3 she was admitted with dyspnea and treated with IV antibiotics. She was discharged with a diagnosis of pneumonia, not related and removed from study at her request. She died 2 weeks later. Her death was attributed to malignancy. Her last hospitalization and study removal were likely secondary to her malignancy, so was not counted as infection by the reviewer. Pt. 10044 on this arm was removed from study for "poor tolerance of chemotherapy" after each of 3 cycles of docetaxel 75 mg was complicated by fever. She received IV antibiotics in cycle 1 and 3, and in the last cycle was diagnosed with an upper respiratory infection after presenting with a fever on day 13. This patient brings the percentage on the ***docetaxel 75 mg arm who were discontinued due to an AE related to infection to 2/121 (1.7%).***

The review of the infection SAE's revealed that many were not coded as related to the study drug, although some narratives indicated that the patient was neutropenic at the time. There were cases of diarrhea that were "culture positive", "responded to Flagyl", or positive for C. difficile that were not considered study drug related, but would likely not have occurred if the patient had not been on antibiotics for neutropenia or prophylactic antibiotics. The reviewer did not take causality into account for the infections she tabulated. There were patients who had no documentation of neutropenia in the electronic dataset on the date of admission with fever, and it was possible for patients to be admitted complaining of fever after having been neutropenic a few days earlier, but were not neutropenic at the time of admission.

The reviewer identified more cases of neutropenic fever on review of the infection SAE narratives than reported in the study report, which is reflected in the above table. The sponsor was sent a request on 10/21/99 for a list of patients counted as infection and neutropenic fever to resolve this issue. In correspondence dated November 15, 1999, the sponsor explained that the tabulation of febrile neutropenia was based on criteria that defined febrile neutropenia in the protocol. The patients that were reported in narratives to have febrile neutropenia by investigators and were not so tabulated, did not meet the protocol's definition of febrile neutropenia. The FDA reviewer accepted the sponsor's tabulation of febrile neutropenia on the basis of this explanation at a meeting with the sponsor December 3, 1999.

3.11.1.2 Neurologic Toxicity

Docetaxel has recognized neurological toxicity – both neurosensory and neuromotor. Neurocortical toxicity, though less common, has been reported. The sponsor notes that this analysis was potentially confounded by the fact that patients had a history of prior treatment with cisplatin, and possibly, prior taxane therapy. The sponsor presented the grades regardless of treatment relatedness as follows.

Table 33 Tax 320 Motor and Sensory Neuropathy by Grade Regardless of Relationship to Treatment Among the Treatment Arms. Derived from Sponsor Table 5.01A Number of Patients with NCI Classified Adverse Events Volume 6 of Clinical Data Section.

	Docetaxel 100 mg		Docetaxel 75 mg		Control	
	Motor	Sensory	Motor	Sensory	Motor	Sensory
Grade 2	9.1%	11.6%	5.0%	11.6%	5.9%	9.2%
Grade 3	4.1%	6.6%	5.8%	1.7%	3.4%	5.0%
Grade 4	0	0	0	0	0.8%	0

There was one patient on each of the docetaxel arms and the control arm with neuro-vision as a reported toxicity related to study treatment, and in no patient was it grade 3/4.

There was 1 ifosfamide patients who went off study for neurocortical toxicity and 1 vinorelbine patient who went off study in cycle 5 for grade 3 neurosensory toxicity. There were no docetaxel 75 mg patients who went off study for neurotoxicity. This was not the case on the docetaxel 100 mg arm. On review of the serious adverse event narratives for docetaxel 100 mg, there were 3 neurological SAE's that could be explained by intracranial metastases - 6 on the docetaxel 75 mg arm and 3 on the control arm. The remaining patients with a neurological SAE included 5 docetaxel 100 mg and 2 docetaxel 75 mg patients. Their brief narratives can be found in the Appendix.

There were 6 patients who were removed from study for neurotoxicity They were:

Pt. 10389 (docetaxel 100 mg) who was treated with 8 cycles and discontinued study due to grade 2 neurosensory toxicity (and fatigue and moderate edema);

Pt. 10477 (docetaxel 100 mg) who discontinued therapy for severe paresthesia in cycle 2;

Pt. 10504 (docetaxel 100 mg) who went of study in cycle 5 for increasing neurosensory toxicity (grade 3).;

Pt. 10657 (docetaxel 100 mg) who went off study in cycle 10 for grade 3 neurosensory toxicity;

Pt. 10680 (docetaxel 100 mg) who went off study in cycle 3 for grade 3 neurosensory toxicity;

Pt. 10682 (docetaxel 100 mg) who went off study in cycle 4 for grade 3 neurosensory toxicity.

3.11.1.3 Gastrointestinal Toxicity

The following table summarizes the most common gastrointestinal adverse events or most pertinent. The percentages by arm are shown first regardless of assigned relationship to treatment, followed by the percentage of those attributed "probably or possibly" to study treatment. The bold percentage in that category is the percentage of grade ¾ attributed to study drug.

Table 34 TAX 320 Summary of Gastrointestinal Adverse Events. Derived from Sponsor Tables 56 and 57. Volume 8, page 122.

	Docetaxel 100 mg N=121		Docetaxel 75 mg N=		Control N=	
	Regardless Relationship	Tx Related (Gr¾) *	Regardless Relationship	Tx Related (Gr ¾)	Regardless Relationship	Tx Related (Gr ¾)
Stomatitis	31.4%	26.4% **(2.3%)**	26.4%	24.8% **(1.7%)**	9.2%	7.6% **(0.8%)**
Diarrhea	34.7%	22.3% **(3.3%)**	19.0%	11.6% **(1.7%)**	11.8%	5.9% **(4.2%)**
Constipation	33.9%	11.6% (0%)	24.8%	6.6% **(0.8%)**	33.6%	10.1% **(0.8%)**
Vomiting	30.6%	22.3% **(6.6%)**	24.0%	16.5% **(0.8%)**	23.5%	18.5% **(4.2%)**
GI Hemorrhage	5.0%	1.7% (0.0%)	4.1%	0%	0.8%	0%
Jaundice	0.8%	0%	3.3%	0%	1.7%	0%
Intestinal Obstruction	1.7%	0%	0.0%	0%	1.7%	0%

* The (Gr ¾) refers to grade 3 + grade 4 events – regardless of whether considered treatment related.

The docetaxel 100 mg arm had the highest percentage across all these categories of adverse events, except for the uncommon events: intestinal obstruction and jaundice. The incidence of gastrointestinal hemorrhage was similar on the two docetaxel arms, and higher than the control arm.

<u>Stomatitis</u> The docetaxel 100 mg treatment arm was the only arm on which stomatitis was reported as an SAE. There was one patient on docetaxel 75 mg who was admitted on Day 10 of cycle 1 with dysphagia secondary to candida esophagitis and was coded dysphagia and infection. No patient was reported to discontinue therapy for stomatitis. The stomatitis SAE narratives may be found in the Appendix.

Diarrhea There were 5 docetaxel 100 mg patients and 3 docetaxel 75 mg patients whose SAE narratives included diarrhea. Those narratives can be found in the Appendix. No patient was reported to have been removed from study for diarrhea.

Bowel Obstruction The SAE's that included bowel obstruction in the list of events were as follows

Docetaxel 100 mg (n=4)

1. Pt. 10062 was admitted on Day 19 of Cycle 3 with small bowel obstruction and UTI, preceded by severe vomiting x 5 days. She was hospitalized in Cycle 1 with vomiting, diarrhea, fever and neutropenia.

2. Pt. 10372 was admitted on Day 9 of Cycle 10 with small bowel obstruction (attributed to adhesions). Endoscopy revealed pseudomembranous colitis.

3. Pt. 10413 was admitted on Day 4 of Cycle 1 with bowel obstruction and intestinal perforation. Sigmoid colon resection performed.

Ifosfamide (n=1)

1. Pt. 10328 was admitted on Cycle 1 Day 7 with vomiting. He was readmitted on Day 21 with vomiting, abdominal pain, and cramping. A small bowel obstruction was diagnosed

Vinorelbine (n=1)

1. Pt. 10653 was admitted on Day 8 of Cycle 1 with a bowel infarction and severe constipation.

Vomiting There were 8 docetaxel 100 mg patients, 3 docetaxel 75 mg patients, and 1 control arm patient whose SAE narratives included vomiting. Their SAE narratives can be found in the Appendix. There were patients from the Docetaxel 75 mg and Control arm who were **removed from study** because of vomiting. They are listed below:

Docetaxel 75 mg (n=2)

Pt.10664 developed grade 4 vomiting in cycle 1 and continued to experience this with each infusion. The patient discontinued therapy after Cycle 3 for vomiting and asthenia.

Pt. 10669 discontinued therapy after cycle 8 for vomiting, asthenia and dehydration.

Vinorelbine (n=1)
Pt. 10459 discontinued therapy after Cycle 1 for nausea and vomiting.

Jaundice The SAE's that included jaundice in the list of events were as follows

Docetaxel 100 mg

1. Pt. 10424 was admitted on Day 27 of Cycle 1 with elevated bilirubin and transaminases. PD was diagnosed.

Vinorelbine

1. Pt. 10390 was admitted on Day 14 of Cycle 1 with respiratory distress and was neutropenic. He gradually became jaundiced and unresponsive and died 1 week later, attributed to PD.

Ifosfamide

1. Pt. 10328 was admitted on Cycle 1 Day 7 with vomiting. He was readmitted on Day 21 with vomiting, abdominal pain, and cramping. A mall bowel obstruction was diagnosed.

One patient was removed from the study for elevated bilirubin - Pt. 10042 on the docetaxel 75 mg arm, who developed grade 3 hyperbilirubinemia causing a >3 week delay in cycle 1. The protocol directed study removal. Grade 3/4 liver function test elevations were seen uncommonly on study. No patient developed grade 3-4 elevation in alkaline phosphatase or ALT. Two patients on the docetaxel 100 mg arm developed grade 3 elevation in AST. Two patients on that arm also developed grade 3 elevation in bilirubin and 1 patient developed grade 4 elevation. There were 2 patients on the docetaxel 75 mg arm that developed grade 3 elevation of the bilirubin, and one patient on the control arm.

The gastrointestinal events that prompted study removal were jaundice and vomiting. SAE's were most common in each category on the docetaxel 100 mg arm, except jaundice and gastrointestinal hemorrhage.

3.11.1.4 Fluid Retention

Fluid retention was reported in 50.4 % (61/121) of the docetaxel 100 mg patients, 41.3 % (50/121) of the docetaxel 75 mg patients, and 19.5% of the control patients. Fluid retention was considered severe in 6/61 docetaxel patients, 4/50 docetaxel 75 mg patients, and 3/17 control arm patients. It was considered moderate in 24/61 docetaxel 100 mg patients, 15/50 75 mg patients and 7/17 control patients. In those patients in each arm that the fluid retention was attributed to treatment, the presence of edema as the only defining clinical finding was most common - 23/33 on the docetaxel 100 mg arm, 24/30 on the docetaxel 75 mg arm, and 2/4 on the control arm. These are summarized for the docetaxel arms in the table below:

Table 35 TAX 320 Summary of Fluid Retention Derived from Sponsor Table 69 Summary of patients with Fluid Retention Vol 8; page 132.

	Docetaxel 100 mg N = 121	Docetaxel 75 mg N=121
Regardless of Relatedness		
Overall	61 (50.2%)	50 (41.3%)
Mild	30 (24.8%)	30 (24.8%)
Moderate	24 (19.8%)	15 (12.4%)
Severe	6 (5.0%)	4 (3.3%)
Life-threatening	1 (0.8%)	1 (0.8%)
Treatment Related		

Overall	33 (27.3%)	30 (24.8%)
Mild	15 (12.4%)	18 (14.9%)
Moderate	13 (10.7%)	11 (9.1%)
Severe	5 (4.1%)	0
Life-threatening	0	1 (0.8%)
Treatment Related	33 (27.3%)	30 (24.8%)
Edema only	23 (19.0%)	24 (19.8%)
Pleural Effusion Only	1 (0.8%)	4 (3.3%)
Pleural Effusion + Edema	2 (1.7%)	0
Pericardial Effusion Only	1 (0.8%)	0
Treatment Discontinued Due to Fluid Retention		
	Docetaxel 100 mg	Docetaxel 75 mg
Regardless of Relationship to Study Tx	7 (5.8%)	2 (1.7%)
Treatment Related	6 (5.0%)	2 (1.7%)

The median dose to onset of fluid retention was greater on the docetaxel 75 mg arm than it was on the 100 mg arm – 446 mg vs. 300 mg (in the analysis disregarding treatment relationship) – or approximately 6 doses vs. 3 doses. The median number of doses delivered in each docetaxel arm was 3. The fluid retention findings from this study are consistent with data in labeling, eg. the median dose delivered until onset was 399 mg on the 3 day dexamethasone premedication regimen (the regimen used in this study) and 479 mg on the 5 day regimen. In previous reports, overall fluid retention developed in 64.1% of patients treated with the 3-day regimen and it was severe in 6.5%.

Peripheral edema was listed in the reasons for discontinuation in five patients on the docetaxel 100 mg arm (the only reason listed in 3) and in one patient on the docetaxel 75 mg arm. Pleural effusion was the reason for discontinuation in two docetaxel 100 mg patients and one docetaxel 75 mg patient. Neither was listed as a cause for discontinuation on the control arm. The maximum cycles delivered in those patients discontinued on the docetaxel 100 mg arm for peripheral edema were 009, 008, 005 x 2, and 001 for peripheral edema. For pleural effusion the cycles of discontinuation on the docetaxel 100 mg arm were 001 and 006. On the docetaxel 75 mg arm the cycles of discontinuation were 005 for edema and 001 for pleural effusion.

There were 117 docetaxel 100 mg patients, 110 docetaxel 75 mg patients, and 102 control patients that had both a baseline and one additional weight documented on study. Of those, 48.7% of the docetaxel 100 mg patients, 40.9% of the docetaxel 75 mg patients, and 42.2% of the control patients experienced a >5% weight gain.

100 mg (N= 117) = 16.2% gained weight
(32.5% lost weight). One patient gained and lost >5%.

75 mg (N= 110) = 19.1% gained
(24.6% lost weight)

Control (N= 102)= 8.8% gained
(33.3% lost weight)

One of the manifestations of the docetaxel fluid retention syndrome is pleural effusion. The incidence of pleural effusion on the docetaxel 100 mg and 75 mg arms was 12.4% and 13.2%, respectively, compared to 7.6% on the control arm. Six of the 15 pleural effusions on the 100 mg arm were considered treatment related and 5 were severe. Four of the 16 patients with pleural effusions on the docetaxel 75 mg arm were considered treatment related and one was considered severe. See further discussion of pleural effusion AE's in the next section, 3.11.1.5 Pulmonary.

3.11.1.5 Pulmonary

The signs and symptoms falling under this category of adverse events would be expected to present at baseline in this study's disease population. Therefore, the sponsor included a treatment emergent analysis – new onset or worsening from baseline – in its summary of these data.

Table 36 TAX320 Summary of Pulmonary Adverse Events; Derived from Sponsor Tables 66 and 68; Volume 8, pages 129 and 131.

	Docetaxel 100 mg N=121	Docetaxel 75 mg N=121	Control
	Pulmonary		
Regardless of Relationship	77.7%	72.7%	81%
Treatment Emergent	45%	42%	45%
Treatment Related (Grade ¾)	13.2% (8.9%)	9.9% (2.5%)	
	Cough Increased		
Regardless of Relationship	71.9%	66.9%	77%
Treatment Emergent	30%	28%	32%
Treatment Related (Grade ¾)	5.0% (0)	6.6% (0)	
	Hemoptysis		
Regardless of Relationship	19.8%	17.4%	8%
Treatment Emergent			
Treatment Related (Grade ¾)	1.7% (0)	1.7% (0)	
	Pleural Effusion		
Regardless of Relationship	12.4%	13.2%	7.6%
Treatment Emergent	8%	7%	3%
Treatment Related (Grade ¾)	5.0% (0.8%)	3.3% (0.8%)	
	Pneumonia		
Regardless of Relationship	5.0%	2.5%	
Treatment Emergent			

Treatment Related (Grade ¾)	0.8% (0.8%)	0.8% (0.8%)	-

Reviewer Comment: There were 4 patients on the control arm, 4 patients on the docetaxel 100 mg arm , and 7 patients on the docetaxel 75 mg arm who had pleural effusions coded as unrelated to study therapy. Of those patients, review of the Tumor electronic dataset revealed that only 2 of the docetaxel 100 mg patients had abnormal pleural findings at baseline (Pt. 10181 had pleural based nodularity and Pt. 10436 had pleural thickening) and one 75 mg patient had a baseline pleural effusion. In those patients whose effusions were coded as AE's unrelated to therapy, excluding the 3 patients with the abnormalities listed above, the AE of pleural effusion was first noted in Cycle 001 in 2 docetaxel 75 mg patients; Cycle 002 in one docetaxel 100 mg patient, 2 docetaxel 75 mg patients, and one control patient; Cycle 4 in 2 control patients; Cycle 005 in 1 control patient; Cycle 006 in 2 docetaxel 75 mg patients, and follow-up 061 in one docetaxel 100 mg patient (Pt. 10486). (There were 4 additional patients with pericardial effusions coded as unrelated to study treatment – 2 on each of the control and docetaxel 100 mg arms. These effusions occurred in cycle 1 and 003 on the docetaxel 100 mg arm and cycles 003 and 005 on the control arm).

Those patients whose AE of pleural effusion was coded remotely related to study treatment included one patient on each of the control arm and the docetaxel 75 mg arm, Cycle 006 and cycle 002, respectively. Remotely related pericardial effusion was coded in one patient on the docetaxel 100 mg arm , cycle 002.

Lung cancer is one of the most common malignancies to have pleural effusions as part of its clinical manifestations. The incidence of malignant pleural effusion in lung cancer as a general category is 10-24% (Malignant Pleural Effusions Recent Advances in Diagnosis and Management Editor: John Ruckdeschel, MD 1992, Bristol-Meyers Squibb Company. Page 8.)

The percentage of pneumonia considered related to underlying treatment in this study was quite low. The reviewer found in the narratives of serious adverse events there were 14 docetaxel 100 mg patients whose pneumonia was likely related to neutropenia secondary to chemotherapy: A list of these patients can be found in the Appendix.

Reviewer Comment: 14/121 treated =11.6% This is higher than the overall percentage reported in the table above, and much higher than the treatment related percentage above.

The following cases of pneumonia were considered of "Questionable relationship" to treatment by the FDA reviewer on review of the narratives of docetaxel 100 mg SAE's:

1. *Pt. 10016 was admitted on Cycle 1 Day 21 with bilateral pneumonia. (not related)*
2. *Pt. 10028 was admitted on Day 20 Cycle 3 with dyspnea. She was discharged to Hospice with a diagnosis of pneumonia (not related).*
3. *Pt. 10340 was admitted on Day 17 of Cycle 3 with pneumonia (not related) and respiratory arrest. He died 5 days later, death attributed to malignant disease.*

If these 3 patients' pneumonia are counted, then the total percentage of treatment related pneumonia SAE's = 3+14 = 17/121 = 14.1%

Other Respiratory Infections:
Pt. 10188 admitted on Day 10 of Cycle 1 with fever and neutropenia and positive sputum culture.
Pt. 10179 admitted on day 7 Cycle 1 with bronchitis.

Pt. 10366 was admitted on Day 3 of Cycle 1 with dyspnea and sputum cultures were positive (not related).
Pt. 10655 was admitted on Day 4 of Cycle 2 for hyperglycemia, became neutropenic and developed a positive sputum culture.

There were 9 docetaxel 75 mg patients whose SAE narratives included pneumonia that could have been related to neutropenia. The list of these patients can be found in the Appendix.

Reviewer Comment: 9/121=7.4% This is higher than the overall percentage for this arm in the table above, 2.5%, and higher than the treatment related percentage attributed to this arm of 0.8%.

The following case of pneumonia was considered by the reviewer of questionable relationship to treatment on FDA review of the narratives for the docetaxel 75 mg SAE's:

1. *Pt. 10055 was admitted Day 2 of Cycle 3 with hypotension, weakness, and pneumonia (not related.) Radiotherapy palliatively was planned in response.*

If this patient's pneumonia is counted, the total percentage of treatment related pneumonia SAE's = 1+9 = 10/121 = 8.3%

On the control arm there were 5 patients whose pneumonia appeared to be treatment related in the SAE Narrative.

The following cases of pneumonia were considered of questionable relationship to treatment on review of the narratives for the control arm SAE's:

1. *Pt. 10175 was admitted on Day 2 of Cycle 2 with fever and lung infection (not related). The serious adverse events that did not appear related to an underlying infectious process or tumor progression upon review of the narratives are listed below.*
2. *Pt. 10452 was admitted on Day 13 of Cycle 4 with post obstructive pneumonia (not related).*

Other
Pt. 10671 was admitted Day 25 of Cycle 1 for respiratory infection with cough, but unchanged chest X-ray

The following are tabulations of pulmonary events that did not appear to be related to underlying infection and were listed in the SAE narratives as "pulmonary".

Docetaxel 100 mg (N=11)

1. Pt. 10004 was admitted on Day 5 of Cycle with grade 4 dyspnea that had its onset one day after the first infusion of docetaxel. The patient's condition deteriorated and his death on Day 20 was considered secondary to toxicity.

2. Pt. 10083 was admitted on Day 15 of Cycle 2 with bilateral interstitial infiltrates, fever, and hypoxia. He was treated with antibiotics, diuretics, and mechanical ventilation, but he deteriorated and died.

3. Pt. 10169 was admitted on Day 1 of Cycle 1 with dyspnea and wheezing. She was treated with inhalation therapy, antihistamine and diuretic and was discharged the following day. She was readmitted on Day 15 with progressive dyspnea, cough and "pneumonia" and was treated with inhalation therapy, diuretics, steroids, and oxygen. antibiotics are not listed. She was discharged after 11 days, only to be readmitted on Day 33 with ARDS. Her death 2 days later was attributed to PD.

4. Pt. 10340 – Had no pericardial effusion reported at baseline. It is first reported in the electronic dataset at Cycle 002. He was admitted in Cycle 3, Day 17 with cardiac dysrhythmias, pneumonia, and respiratory arrest, necessitating intubation. Treatment does not include antibiotics and his death 5 days later was attributed to malignant disease.

5. Pt. 10391 was admitted on Day 22 of Cycle 4 with dyspnea, pleural effusion, and peripheral edema. There was no evidence of DVT and he was treated with diuretics.

6. Pt. 10406 developed dyspnea, cyanosis and chest tightness one minute into the infusion of Cycle 2. This was considered an allergic reaction and prompted this patient's removal from study.

7. Pt. 10454 was admitted on Day 18 of Cycle 4 with dyspnea increasing over 5 days, rash and fever. He was treated with steroids and benadryl and was discharged on oral steroids, but removed form study secondary to these toxicities.

8. Pt. 10465 had a right pleural effusion at baseline. He was admitted on Day 5 of Cycle 1 with severe dyspnea, myalgia, and lower extremity weakness. X-ray revealed the right lung was completely opaque for pulmonary fluid and consolidation. His death 4 days later was attributed to malignant disease.

9. Pt. 10488 was admitted on Day 23 of Cycle 6 with increase in pleural effusion and was removed from study for this event.

10. Pt. 10517 was admitted on Day 24 of Cycle 1 with increasing dyspnea and loss of consciousness. She deteriorated rapidly and died the same day.

11. Pt. 10519 – This 76 year old male was admitted on Day 4 of Cycle 1 with dyspnea and mild CHF. He was treated with steroids and antibiotics. Diuresis is not mentioned in the narrative.

Docetaxel 75 mg (N=3)

1. Pt. 10080 was admitted on Day 19 of Cycle 1 with severe dyspnea and pleuritic pain in the posterior chest. PE workup was negative by angiogram. He was treated with inhalers, analgesics and steroids and discharged in "stable condition" 4 days later, after which he refused further treatment.

2. Pt. 10339 was admitted on Day 21 of Cycle 4 with ARDS. He had been removed from study earlier in the cycle for PD.

3. Pt. 10499 was removed from study for a pleural effusion in Cycle 1, after having been admitted for septic shock, effusion, and pneumonia.

Control (N=1)

1. Pt. 10348 was admitted on Day 18 of Cycle 4 (vinorelbine) with persistent cough, chills and sore throat. His condition was called pneumonitis most likely secondary to radiation therapy or chemotherapy.

There were 2 docetaxel 75 mg patients, 6 docetaxel 100 mg, and 3 control patients whose reasons for discontinuing therapy on study included some type of pulmonary event.

3.11.1.6 Skin

Skin was coded as an adverse event in 33.1% of the docetaxel 100 mg patients and 23.1 % of the 75 mg patients. When considering only those events attributed to therapy, the percentage decreased to 20.7% on the 100 mg arm and 15.7% on the 75 mg arm. Of those events considered related to treatment, only 0.8% were graded 3 or 4. Rash was coded in 1.7% of the docetaxel 100 mg arm and 2.5% of the 75 mg arm. Nail disorders were reported in 17.4% of the 100 mg group and 10.7% of the 75 mg group. None were grade 3-4 when considering only those attributed to therapy.

3.11.1.7 Asthenia, Allergic Reaction, Lacrimation

Asthenia was reported in 83% of patients in both docetaxel arms, and 76% of patients on the control arm. Asthenia was listed as a cause for discontinuation in 3 patients on the docetaxel 100 mg arm (along with another toxicity in all 3), in 4 patients on the docetaxel 75 mg arm (the only toxicity listed in the cause in two), and 2 patients on the control arm (the only cause listed in both).

Allergic reactions were reported in 7% of the docetaxel 100 mg patients and 4% of the 75 mg treatment arm patients. It was cause for discontinuation of therapy in one patient on each of the docetaxel arms. It was reported as an SAE in Pt. 10170 who developed flushing, diaphoresis, dyspnea, seizure-like activity and altered consciousness less than 5 minutes into the infusion. CT head was negative. A docetaxel 75 mg patient, Pt. 10406, developed cyanosis, dyspnea, chest tightness, and elevated BP one minute after initiation of Cycle 2, which had been given at a reduced dose due to a mild allergic reaction observed in Cycle 1. The patient was removed from study for this event. Pt. 10519 on the docetaxel 100 mg arm had an allergic reaction in Cycle 1 – 30 seconds into the infusion – with flushing, dyspnea, and seizure like activity. This was not considered an SAE.

Lacrimation disorder was reported in 6.6% of the docetaxel 100 mg arm patients and 2.5% of the 75 mg arm .

3.11.2 Discontinuations from Study Treatment for Adverse Events

The sponsor presents a tabulation of those patients who were removed from study for adverse events in Table 81 of the Study Report, page 148. In that table there are 18 docetaxel 100 mg arm patients (18/121 = 14.9%), 11 docetaxel 75 mg patients (8.3%), and 10 control patients (10/119 =

8.4%) removed for adverse event. In her review of the narratives of SAE's on study, the reviewer found 3 additional patients on the docetaxel 100 mg arm who appear to have been removed from study treatment for SAE, bringing the total percentage withdrawn for adverse event to **17.4%.** Those 3 additional patients were:

1. Pt. 10072 who was reportedly removed from study for hematological toxicities.

2. Pt 10178 withdrew consent after repeated hospitalization during 4 cycles of docetaxel therapy, one admission per cycle and two admissions in cycle 4. Three of the admissions involved infections and two nausea/vomiting. The last admission was for nausea and vomiting and dehydration. The reason for the patient's request for withdrawal was "declining performance status".

2. Pt. 10165 was removed at the patient's request after an admission on Day 12 of Cycle 1 for persistent nausea and vomiting, requiring IV fluids and antiemetics.

Review of the narratives for deaths within 30 days of study treatment, Pt. 10492, on the docetaxel 75 mg arm was found to have withdrawn consent on Day 12 of Cycle 1, which was complicated by moderate stomatitis, severe neuro-motor, and grade 2 infection. This brings the total discontinuations for toxicity on that arm, docetaxel 75 mg, to 12/121 **(9.9%).**

Neurotoxicity (primarily neurosensory) and fluid retention (primarily fluid retention) were the most common AE's causing treatment discontinuation on the docetaxel 100 mg arm – 7 patients for each toxicity. No patient on the docetaxel 75 mg arm discontinued therapy for neurotoxicity and only 2 for fluid retention. Two patients on the control arm discontinued therapy for neurotoxicity. The next most common reason for discontinuation on the docetaxel 100 mg arm was asthenia (n=3) and pulmonary (n=3). On the docetaxel 75 mg arm there were 5 patients discontinued for asthenia and 2 patients for vomiting. Asthenia (n=2) and pulmonary (n=2) equaled neurotoxicity on the control arm in cause of discontinuation.

3.11.3 Deaths on Study

Deaths within 30 days of last infusion were more common on the docetaxel arms. The sponsor found that deaths due to drug-related toxicity were quite low and equal on the docetaxel 100 mg and control arms – 1.6%. The sponsor attributed no deaths to toxicity on the docetaxel 75 mg arm. These data are summarized in the table below with the changes made in treatment related deaths by the FDA reviewer based on review of the narratives submitted on patients who had died within 30 days of infusion. *Percentages are given based on using the intent to treat population (125/125/123) vs. the actually treated population (121/121/119) as denominators.*

Table 37Tax 320 Summary of Patient Deaths – RPR and FDA. Derived from Sponsor Table 77; Volume 8, page 142.

	Docetaxel 100 mg ITT = 125 Treated = 121		**Docetaxel 75 mg ITT = 125 Treated = 121**		**Control ITT = 123 Treated = 119**	
	RPR	FDA	RPR	FDA	RPR	FDA