Stomatitis	26.0%	2.9%	26.0%	26.5%	4.1%	26.5%	25.5%	1.8%	25.5 %
Myalgia (COSTART)	2.9%	0	2.9%	2.0%	0	2.0%	3.6%	0	3.6%
Hypotens.	7.7%	2.9%	7.7%	12.2%	6.1%	12.2%	3.6%	0	3.6%
Dehydrat. (COSTART)	9.6%	1.0%	9.6%	14.3%	2.1%	14.3%	5.5%	0	5.5%
Allergy	13.5% *	5.8%	13.5%	18.4%	4.1%	18.4%	9.1%	7.3%	9.1%

* Grade 3/4 refers to the treatment emergent column.

The overall percentages for these events in this population with previously treated lung cancer can be compared to the rates currently appearing in the label for previously treated patients with breast cancer and pooled all tumor types shown in the table below. The docetaxel dose administered in the pivotal trials for approval in breast cancer was 100 mg/m^2. Some of these rates of overall toxicity associated with the 100 mg/m^2 dose administered in TAX 317 were significantly higher than reported in the label for breast carcinoma. In particular all grades of infection – 38.8% vs. 22.5%, and grade 3/4 infection – 14.3% (treatment emergent) vs. 7.1% (all events). However, the percentages of overall stomatitis and neurosensory toxicity were higher in the breast cancer patients. Any stomatitis was reported in 53.3% of the breast cancer patients vs. 26.5% of the TAX 317 lung cancer patients treated with docetaxel 100 mg/m^2. Neurosensory toxicity of any grade was only slightly higher in the breast cancer patients – 56.8% vs. 51%.

Table 62 Adverse Events Currently Appearing in the Docetaxel Product Label

	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%
Stomatitis Any Severe	 53.3% 7.8%	 41.7% 5.5%
Diarrhea Any Severe	 42.2% 6.3%	 38.7% 4.7%
Acute Hypersensitivity Any Severe	 13.0% 1.2%	 21.0% 4.2%

Neurosensory Any Severe	 56.8% 5.8%	 49.3% 4.3%

In the following table treatment emergent adverse events (those that occurred for the first time after baseline assessment or worsened in severity from baseline), not limited to those attributed to therapy, are compared between best supportive care (combined dosing periods) and each docetaxel dose utilized on study. Overall events and those that were considered Grade ¾ are listed. NCI terms are used, except for the bolded COSTART terms. For the latter, the percentages falling in the Grade ¾ column are those rated "severe" under the COSTART system.

Table 63 TAX 317 Comparison of Treatment Emergent Adverse Events Between Docetaxel and Best Supportive Care

Treatment Emergent Adverse Events	**Best Supportive Care (N=100)**		**Docetaxel 100 mg (N=51)**		**Docetaxel 75 mg (N=49)**	
	Overall	Grade 3/4	Overall	Grade 3/4	Overall	Grade 3/4
Allergy	-	-	18.4%	2 (3.9%)	9.1%	4 (8.2%)
Asthenia	47.0%	28 (28%)	61.2%	11 (21.6%)	54.5%	10 (20.4%)
Anorexia	24.0%	3 (3%)	20.4%	1 (2%)	14.5%	2 (4.1%)
Cardiac Dysrhythmia	6.0%	0	14.3%	2 (3.9%)	7.3%	1 (2.0%)
Dehydration	4.0%	1 (1%)	14.3%	1 (2%)	5.5%	0
Diarrhea	5.0%	0	30.6%	2 (3.9%)	36.4%	1 (2.0%)
Fever in Absence of Infection	7.0%	0	36.7%	0	61.8%	0
Hypotension	2.0%	1 (1%)	12.2%	3 (5.9%)	3.6%	0
Infection	**21.0%**	**5 (5%)**	**36.7%**	**7 (13.7%)**	**30.9%**	**3 (6.1%)**
Motor Neuropathy	8.0%	3 (3%)	16.3%	2 (3.9%)	14.5%	1 (2.0%)
Sensory	10.0%	3	26.5%	1	20.0%	1

Treatment Emergent Adverse Events	Best Supportive Care (N=100)		Docetaxel 100 mg (N=51)		Docetaxel 75 mg (N=49)	
Neuropathy		(3%)		(2%)		(2.0%)
Nausea	21.0%	5 (5%)	34.7%	1 (2%)	36.4%	2 (4.1%)
Nail Disorder	0	0	16.3%	0	14.5%	1 (2.0%)
Peripheral Edema	12%	2 (2%)	26.5%	1 (2%)	23.6%	1 (2.0%)
Pulmonary	50.0%	30 (30%)	53.1%	18 (35.3%)	38.2%	11 (22.5%)
Skin	9.0%	1 (1%)	44.9%	3 (5.9%)	20.0%	0
Stomatitis	4.0%	0	26.5%	2 (3.9%)	25.5%	1 (2.0%)
Vomiting	22.0%	3 (3%)	26.5%	0	23.6%	2 (4.1%)

This comparison shows that for events like nausea, vomiting, pulmonary, infection and asthenia the "background noise" from the underlying disease itself is significant. Even peripheral edema, although higher in the docetaxel arms, has a significant presence in the disease itself. The treatment emergent neuropathies are also relatively common in the best supportive care group. Diarrhea, skin disorder, nail disorder, peripheral edema and fever in the absence of infection occur with considerably more frequency on the docetaxel arms. In terms of treatment emergent events, the comparison of the two docetaxel arms to each other shows only skin and pulmonary events appeared much higher on the docetaxel 100 mg arm than the 75 mg arm. The arms were similar in overall treatment emergent stomatitis, peripheral edema, and motor neuropathy. Sensory neuropathy was only slightly more common on the docetaxel 100 mg arm, as was infection. Diarrhea and fever in the absence of infection were higher on the docetaxel 75 mg arm than the 100 mg arm.

4.11.1.1 Hematologic Adverse Events

The following table summarized the overall distribution of worst grade cytopenias by patient for the entire docetaxel population in this study.

Table 64 TAX 317 Myelosuppression – By Patient. Derived from Sponsor Table 7.01 Hematological Toxicity – Frequencies of Worst NCI Grades p... Patient From Cycles with at Least One Blood Count between Day 2 and Next Cycle Appendix II F. Vol 68.6.

	Overall Docetaxel			Docetaxel 100 mg	Docetaxel 75 mg	BSC 100/75 (%)

	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 3/4	Grade 3/4	Grade ¾
Neutropenia	84.5%	16.5%	60.2%	87.5%	67.3%	0%/14.0%
Thrombocyt openia	5.9%	1.0%	0	2.1%	0%	0%
Anemia	91.3%	9.7%	1.0%	16.7%	5.5%	7.3%/13.7%

The median time to neutrophil nadir was 9 days, regardless of docetaxel dose, but the median neutrophil nadir value (by-cycle analysis) was lower on the docetaxel 100 mg dose level – 0.6 x $10^3/mm^2$ vs. docetaxel 75 mg/m^2 – 1.4 x $10^3/mm^2$.

Eleven of 12 docetaxel patients who developed febrile neutropenia, as defined by the protocol (grade 4 neutropenia + grade 2 or greater fever + IV antibiotics and/or hospitalization) were in the docetaxel 100 mg /m^2 treatment group. Onset was in cycle 001 in 8/12, and duration ranged 1-18 days. Half had their dose reduced in response. There were 5 additional patients who met the criteria for febrile neutropenia, but it was not deemed serious and no IV antibiotics were administered. Three were in the docetaxel 75 mg /m^2 group and the remaining 2 were treated with 100 mg /m^2. There were no treatment discontinuations for febrile neutropenia. In a "by-cycle" analysis, 6.8% of docetaxel 100 mg/m^2 cycles were complicated by febrile neutropenia, compared to only 0.8% of 75 mg/m^2 cycles.

Eleven patients treated at 100 mg /m^2 of docetaxel experienced 11 episodes of infection associated with neutropenia. At 75 mg/m^2, 8 patients experienced 9 episodes of infection associated with neutropenia. There were 2 additional episodes of infection not associated with neutropenia in that treatment group. One of the latter patients also had an infectious episode associated with neutropenia. There were 21 SAE reports for infections. Eleven were docetaxel 100 mg/m^2 patients, but the list of these patients only includes seven of the 11 tabulated as having had neutropenic infection. Three of the four docetaxel 100 mg/m^2 patients who appear on the neutropenic infection list as having had a grade 4 infection associated with grade 4 neutropenia AND appear on the infection SAE list of treatment related deaths. There were 10 patients with SAE infections in the docetaxel 75 mg/m^2 treatment group, and 5 best supportive care patients who developed serious infections.

Table 65 TAX 317 Infection as a Hematological Toxicity. Derived from Sponsor Tables 6.01 Number of Patients with Febrile Neutropenia, Infection Grade 3-4 and Death Due to AE by Treatment Group and Table 6.02 Number of Patients with NCI Grade ¾ Neutropenia Concomitant with grade 2 Fever By Treatment Group and Table 5.06A Number of Patients with NCI Classified Adverse Events - All AE Regardless of Relationship to Treatment of Infection with or without Neutropenia Possibly or Probably Related to the Treatment Appendix II F. Vol 68.6

	Overall Docetaxel N=104		Docetaxel 100 mg N=49	Docetaxel 75 mg N=55	Overall BSC N=100
	All Grades N (%)	Grade 3/4 N (%)	Grade 3/4	Grade 3/4	Grade 3/4
Infection	N=37 35.6%	N=10 9.6%	N=7 14.3%	N=3 5.5%	N=5 5.0%
Febrile Neutropenia*	11.5%		22.4% FDA =	1.8% FDA =	

	Overall Docetaxel N=104		Docetaxel 100 mg N=49	Docetaxel 75 mg N=55	Overall BSC N=100
	All Grades N (%)	Grade 3/4 N (%)	Grade 3/4	Grade 3/4	Grade 3/4
			14/49=28.6%[δ]	5/55=9.1%[δ]	
SAE's with Infection a Part of the Clinical Picture			N=10 20.4%	N=7 12.7%	

* Grade 2 fever + grade 4 neutropenia + hospitalization and/or IV antibiotics

[δ] *See Reviewer Comment Below for tabulation of these changes.*

The Grade ¾ infections in the above table were all associated with grade 3 or 4 neutropenia. There were 8 additional patients in the docetaxel 100 mg subgroup who developed grade 1-2 infections, and 5 were associated with grade 4 neutropenia. In the docetaxel 75 mg subgroup there were 10 additional patients with grade 1-2 infections, 6 of which were associated with grade ¾ neutropenia.

Reviewer Comment: The sponsor summarized the SAE's considered possibly or probably related to docetaxel in Table 101 of the study report, page 197. In that table, 12 patients had febrile neutropenia attributable (possibly or probably) to docetaxel – only one of those was a docetaxel 75 mg patient. In the FDA reviewer's review of the patient narratives, there were 3 additional patients treated at 100 mg/m^2 that the reviewer identified as having febrile neutropenia and four 75 mg/m^2 patients - bringing the total to 19 (docetaxel 100 mg/m^2=14 and docetaxel 75 mg/m^2= 5). Those patients added by the reviewer were:

Docetaxel 100 mg/m^2 = Pt's 05011, 05199, 05497 (3 + 11 = 14/49 = 28.6%)
Docetaxel 75 mg/m^2 = 05223, 05225, 05506, and 05514. (4 + 1 = 5/55 = 9.1%)

In addition, the reviewer found infection SAE's that were not considered possibly or probably related to docetaxel that she felt were at least possibly related to therapy. (The sponsor reported that there were 11 patients with infections related to therapy – 8 docetaxel 100 mg/m^2 and 3 docetaxel 75 mg/m^2 patients.) There were six such patients – four in the docetaxel 75 mg treatment group and 2 in the docetaxel 100 mg/m^2 group. Those patients added as having had infections possibly or probably related to therapy were:

Docetaxel 100 mg/m^2 = Pt's 05489 and 05170. (2+8 = 10/49 = 20.4%)
Docetaxel 75 mg/m^2 = 05275, 05276, 05269, and 05271. (4 + 3 = 7/55 = 12.7%)

4.11.1.2 Cardiac Dysrhythmias

Eleven (10.6%) of docetaxel patients - 7 in the 100 mg/m^2 group and 4 in the 75 mg/m^2 group - experienced treatment emergent cardiac dysrhythmia in the study, compared to six patients in the best supportive care arm. In only one docetaxel patient (100 mg/m^2) was the cardiac event attributed to study drug. That patient experienced tachycardia that necessitated hospitalization and administration of adenosine and verapamil the same day of administration of cycle 002. The episode took a month to resolve. An additional cycle was administered without recurrence.

4.11.1.3 Neurotoxicity

Treatment emergent neurosensory adverse events occurred with greater frequency in the docetaxel arms, as did neuromotor, although the differences were not quite as dramatic in the latter.

Table 66 TAX 317 Comparison of Treatment Emergent Neurotoxicity Across Treatment Arms and Docetaxel Doses

	Docetaxel 100mg N=49		Docetaxel 75 mg N=55		BSC N=119	
	Treatment emergent	Grade 3/4	Treatment emergent	Grade 3/4	Treatment emergent	Grade 3/4
Neuro-sensory	26.5%	1 (2.0%)	20.0%	1 (1.8%)	10 %	3 (2.5%)
Neuro-motor	16.3%	2 (4.1%)	14.5%	1 (1.8%)	8%	3 (2.5%)
Neuro-cortical	10.2%	5 (10.2%)	3.6%	2 (3.6%)	3 %	3 (2.5%)

The relative distribution of the grades of motor- and sensory neuropathy among treatment arms, including clinically pertinent grade 2 adverse events are summarized in the table below.

Table 67 TAX 317 Comparison of Distribution of Treatment Emergent Neurotoxicity Among Grades in the Treatment Arms and Docetaxel Doses

Treatment Emergent	**Docetaxel 100 mg N=49**		**Docetaxel 75 mg N=55**		**BSC N=119**	
	Motor	Sensory	Motor	Sensory	Motor	Sensory
Grade 2	2 (4.1%)	3 (6.1%)	3 (5.5%)	1 (1.8%)	5 (4.2%)	1 (0.8%)
Grade 3	2 (4.1%)	1 (2.0%)	1 (1.8%)	1 (1.8%)	3 (2.5%)	3 (2.5%)
Grade 4	0	0	0	0	0	0

There were two neurosensory SAE's – one in a docetaxel 75 mg/m^2 patient and one patient from the best supportive care arm. The docetaxel SAE, neurosensory toxicity prompted discontinuation of study treatment (grade 3 in cycle 004). In the best supportive care patient paresthesia in bilateral lower extremities accompanied epidural catheter placement for pain control in "cycle 005".

There were two neuromotor SAE's on the study – one in a docetaxel patient and one in the same best supportive care discussed above (epidural catheter placement for pain). The docetaxel 100 mg/m^2 patient was admitted to the hospital on Day 7 of cycle 002 with confusion and weakness, considered neuromotor toxicity

Serious neuro-cortical adverse events were reported in three docetaxel 100 mg patients and two best supportive care patients. One of those events, in a docetaxel 100 mg/m^2 patient, was complicated by death. That patient had a seizure in cycle 005 "that led to death". No autopsy was performed and the cause of death was attributed to disease. One of the best supportive care patients died the same day as admission for confusion, dehydration and hypercalcemia. The remaining docetaxel neurocortical SAE's were a patient treated with docetaxel 100 mg/m^2 who was hospitalized with seizures and confusion in cycle 4 – attributed to SIADH. The other patient (docetaxel 100 mg/m^2) was hospitalized with somnolence that responded to Narcan.

4.11.1.4 Gastrointestinal Adverse Events

Diarrhea occurred in greatest frequency in the docetaxel arms. No patient had study participation discontinued secondary to diarrhea, but there were two reports of grade 3 diarrhea leading to hospitalization in two docetaxel 100 mg/m^2 patients, and one such report in a docetaxel 75 mg/m^2 patient. One of the docetaxel 100 mg patients died due to sepsis the day following admission for grade 3 diarrhea and vomiting. The other docetaxel 100 mg patient was hospitalized for pseudomembranous enterocolitis. The docetaxel 75 mg patient was discharged in improved condition after an 8 day admission for grade 3 diarrhea on day 7 of cycle 001. There were no diarrhea SAE's in the best supportive care arm. The sponsor's table of SAE's considered possible or probably related to therapy includes only 3 diarrhea SAE's considered related to treatment. The FDA reviewer felt the SAE narratives reflected that that there were 3 additional patients – 2 in the docetaxel 75 mg/m^2 group – that were at least possibly related to underlying therapy. Those patients were Pt. 05231, 05503, and 05008. There was also one patient in the 100 mg/m^2 group whose treatment was complicated by pseudomembranous enterocolitis on day 13 of Cycle 002, Pt. 05487.

Table 68 TAX 317 Treatment Emergent Gastrointestinal Adverse Events Across Treatment Arms and Docetaxel Doses

	Docetaxel 100mg N=49		**Docetaxel 75 mg N=55**		**BSC N=119**	
	Treatment emergent	Grade 3/4	Treatment emergent	Grade 3/4	Treatment emergent	Grade 3/4
Diarrhea	30.6%	2 (4.1%)	36.4%	0	5.0%	0
Constipation	18.4%	0	14.5%	0	17.0%	2 (1.7%)
GI Hemorrhage	2.0%	0	0	0	1.0%	0
Intestinal Obstruction	0	0	0	0	2%	2 (1.7%)
Hyperbilirubinemia	**17.4%**	15.2% (7/46 evaluable)	**3.8%**	1.9% (1/53 evaluable)	**4.9%**	1.2% (1/82 evaluable)
Jaundice	2.0%	1 (2.0%)	0	0	1%	0
Nausea	34.7%	1 (2.0%)	36.4%	2 (3.6%)	21.0%	5 (5%)
Stomatitis	26.5%	2 (4.1%)	25.5%	1 (1.8%)	4%	0
Vomiting	26.5%	0	23.6%	2 (3.6%)	22%	3 (0.8%)

Serious vomiting occurred in 8 patients in TAX 317. Two were treated with docetaxel 100 mg/m^2, one with docetaxel 75 mg/m^2, and the remaining 5 were on the best supportive care arm. Pt. 05012 (Docetaxel 100 mg/m^2), discussed above with the diarrhea SAE's was admitted on day 9 of cycle 001 with diarrhea and vomiting and died of sepsis. One of the best supportive care

patients had abdominal films suggestive of ileus, and one other had a small bowel obstruction. Exploratory laparotomy revealed multiple abdominal metastases.

Stomatitis resulted in dose reduction in two patients, and hospitalization in 3 patients - two treated with docetaxel 100 mg/m^2 and one with 75 mg/m^2. One patient (100 mg/m^2) presented with febrile neutropenia and grade 3 stomatitis with proctitis on Day 9 of cycle 1. There was no recurrence after dose reduction in the next cycle. The other 100 mg/m^2 patient was hospitalized on Day 7 with neutropenic fever and grade 4 mucositis.

Hyperbilirubinemia Grade 3/4 elevations of bilirubin were reported in 4 docetaxel patients (docetaxel 100 mg/m^2 = 3 and docetaxel 75 mg/m^2 = 1) vs. 1 on the best supportive care arm. Two of the docetaxel 100 mg/m^2 patients had a history of liver metastases. Elevations of bilirubin were discovered during hospitalizations for febrile neutropenia in both of these patients. Pt 05175 had a bilirubin >3x ULN on Day 7 of Cycle 001, and he withdrew consent without receiving further therapy. No follow-up bilirubin levels were provided. The second patient, Pt. 05186, was discovered to have a bilirubin 2 x ULN on Day 9 after Cycle 001, but normalized the following day and further doses were reduced. The remaining docetaxel 100 mg patient, Pt. 05199, had a bilirubin 2 x ULN discovered during a hospitalization for neutropenic sepsis – on Day 10 of cycle 001. AST and ALT were also elevated (grade 3 and 2, respectively). This patient died a day after admission. The docetaxel 75 mg patient had a bilirubin 2 x ULN on day 22 of cycle 4 and discontinued therapy for PD. The best supportive care patient's elevated bilirubin, 2 x ULN, was discovered on Day 23 of cycle 002.

There was one bowel infarction SAE reported in a patient treated with docetaxel 100 mg/m^2. That patient, Pt. 05177, was admitted to the hospital on Day 10 of Cycle 001 for emergency laparotomy. The pathology read that there was acute peritonitis, acute inflammation of the appendix and mesenteric fatty tissue, and cecal ulceration "probably secondary to ischemia".

4.11.1.5 Fluid Retention

The following symptoms defined fluid retention – peripheral edema (localized or generalized) and/or effusion (pleural, pericardial, ascites) with or without weight gain. The sponsor presented fluid retention as those cases considered possibly or probably related to treatment. There were no patients reported to have had treatment discontinued secondary to fluid retention. A patient with both edema and pericardial effusion was hospitalized Day 25 of cycle 003 for a pericardial window. Cytology was negative for malignant cells. Docetaxel dose was reduced from 100 mg/m^2 for subsequent cycles. Another patient, treated with docetaxel 75 mg /m^2 had emergent drainage of a large pericardial effusion causing tamponade on day 23 of Cycle 006. That tap was also negative for malignant cells. The patient died during the hospitalization and his death was attributed to PD. There were two additional docetaxel patients (100 mg/m^2) whose death occurred shortly after presenting with some symptoms possibly related to fluid retention. Pt. 05182 was hospitalized on day 10 of Cycle 001 with a pleural effusion considered unrelated, and dyspnea. The patient had a cardiac arrest 2 days later. Death was attributed to PD. The other patient presented on day 6 of Cycle 001 with bilateral leg edema, wheezing, dyspnea, and pain. The patient's death 14 days later was attributed to carcinomatosis and baseline DVT with PE.

Table 69 TAX 317 Patients with Fluid Retention Attributed to Study Treatment. Derived from Sponsor Tables 6.07 and 6.08 Clinical Data Section of Vol 6.7.

	Docetaxel 100 mg N = 49	Docetaxel 75 mg N=55

	Docetaxel 100 mg N = 49	Docetaxel 75 mg N=55
Treatment Related		
Severity		
Mild	4 (8.2%)	4 (7.3%)
Moderate	1 (2.0%)	5 (9.1%)
Severe	0	0
Life-threatening	1 (2.0%)	0
Treatment Related		
Edema only	4 (8.2%)	7 (12.7%)
Pericardial Effusion Only	1 (2.0%)	0
Pericardial Effusion + Edema	1 (2.0%)	0
Weight Gain Only	0	2 (3.6%)
Treatment Discontinued Due to Fluid Retention		
	Docetaxel 100 mg	Docetaxel 75 mg
	0	0

The protocol defined grading of fluid retention was as follows:
Mild – Asymptomatic edema and/or effusion, no intervention required
Moderate – Symptomatic edema and/or requiring Diuretics. Effusion symptomatic, not requiring drainage
Severe – Edema symptomatic and resulting in Drug Discontinuation. Effusion symptomatic and requires drainage.

The following edema related COSTART term table was included to compare adverse events across arms (treatment emergent) that could be related to fluid retention. Because these are COSTART adverse event terms, the grade is expressed as "severe".

Table 70 Relative Distribution of COSTART "Edema" Adverse Events Across Treatment Groups, Treatment Emergent.

	Docetaxel 100mg N=49		**Docetaxel 75 mg N=55**		**BSC N=119**	
	Treatment emergent	**Severe**	**Treatment emergent**	**Severe**	**Treatment emergent**	**Severe**
Edema	0	0	3.6%	0	1.0%	0
Face Edema	4.1%	0	3.6%	0	1.0%	0
Generalized Edema					1.0%	1
Peripheral Edema	**26.5%**	1	**23.6%**	1	**12.0%**	2
Ascites					1.0%	0
Pericardial Effusion	2.0%	1	1.8%	1	1.0%	0

Pleural Effusion	2.0%	0	1.8%	0	1.0%	0

4.11.1.6 Skin

Skin was coded as an adverse event in 33.7% of the docetaxel group and 2.9% were grade 3 or 4. None led to dose reduction or treatment discontinuation.

4.11.1.6.1 Asthenia and Allergic Reactions

Asthenia was reported in 57.7% of patients in both docetaxel arms, and 47.0% of patients on the control arm. Asthenia was graded severe in 20.2% of the docetaxel treatment group and 28.0% of the best supportive care group. Asthenia was listed as a cause for discontinuation in 2 patients – one in the docetaxel 100 mg group (in cycle 7) and one in the docetaxel 75 mg group (cycle 001) There were 4 best supportive care patients who experienced serious asthenia.

Allergic reactions were reported in 12 if the docetaxel patients (7 treated with 100 mg/m^2). There were 2 allergy SAE's reported – one at each dose of docetaxel and both in cycle 002. One caused discontinuation from study and the other experienced no recurrence.

4.11.2 Treatment Discontinuation for Adverse Events

The sponsor reports that 8 patients on the docetaxel arm of TAX 317 discontinued therapy because of an adverse event. Three were treated in the docetaxel 100 mg/m^2 group and discontinued treatment in cycles 001, 002, and 007. Five were treated with docetaxel 75 mg/m^2 and discontinued therapy in cycle 001, 002, 004, 005, and 006. These patients are summarized in the table below. There was an additional patient who withdrew consent after an adverse event after cycle 001. That patient, 05175, is included in the table below.

Table 71 TAX 317 Summary of Discontinuation of Treatment for Adverse Event

Docetaxel 100 mg/m^2					
Pt. No.	**No. of Cycles**	**Event**	**NCI Grade**	**Severity**	**Serious**
05005	1	Allergy	2	-	No
05172	2	Pulmonary	2	-	No
05175	1	Mucositis, Fever			Yes
05183	7	Asthenia	-	Moderate	No
Docetaxel 75 mg/m^2					
Pt. No	**No. of Cycles**	**Event**	**NCI Grade**	**Severity**	**Serious**
05240	2	Allergy	3	-	Yes
05260	5	Neuromotor	3	-	No
05261	6	Nail disorder	-	Severe	No
053301	1	Asthenia	-	Severe	No
		Infection	2	-	Yes
05514	4	Neurosensory	3	-	Yes

4.11.3 Deaths on Study

There were 13/49 patients (27%) in the docetaxel 100 mg/m^2 treatment group who died within 30 days of the last infusion of docetaxel, and 4/55 patients (7.3%) who died within 30 days of the last infusion in the docetaxel 75 mg/m^2 treatment group. On the best supportive care arm, 15/51 patients (29%) in the BSC/100 group died within 30 days of a "cycle visit" (in cycles 001 = 6, 002 = 2, 003 = 2, 004 = 2, 005 = 2, and 006 = 1) and 19/49 (39%) in the BSC/75 group (in cycles 001 = 1, 003 = 5, 004 = 6, 005 = 1, 006 = 4, 007 = 1, and 008 = 1).

Reviewer Comment: On review of the SAE narratives the FDA reviewer found that Pt. 05507 on the docetaxel 75 mg/m^2 arm died on Day 30 of Cycle 002 and was not included in the sponsor's list of deaths within 30 days. If that patient is counted the percentage of such deaths in that treatment group comes to 5/55 = 9.1%.

It is interesting that the rate of deaths within 30 days of the last treatment cycle was essentially the same in the BSC/100 as the docetaxel 100 mg/m^2 group – the segment of the study that was not found to have a statistically significant survival advantage, and that the rate in the BSC/75 group was even higher. The rate of deaths within 30 days of "treatment" was higher in the best supportive care/75 group than in the BSC/100 group. . It was in the 75 mg dose period of the study that a significant survival difference was found between treatment arms. The rate of death within 30 days of "treatment" in the docetaxel 75 mg/m^2 group was lower than in the docetaxel 100 mg/m^2 group.

The comparison of the rate of death within 30 days of treatment/evaluation between docetaxel and the best supportive care arm must include an examination of the potential contribution of the treatment regimen to deaths. The reviewer examined the narratives of the patients who died within 30 days of the last cycle and the SAE narratives, and derived the deaths that could have been related to treatment. This is also of interest in examining the relative overall "early deaths" between the two docetaxel dose subgroups

In the **docetaxel 100 mg/m^2** treatment group, there were 13 patients identified who had died within 30 days after their last infusion. Of those 13 deaths, 8 were attributed to the underlying malignancy, 4 to toxicity, and one reported as unknown cause. The FDA reviewer considered the 4 deaths attributed to toxicity by the sponsor as deaths related to sepsis after reviewing the narratives. In addition, the reviewer believed that 4 additional early deaths could have been related to treatment – the patient with unknown cause attribution and 3 deaths attributed to underlying malignancy. Those patients whose attribution of death was changed by the reviewer are listed below.

Pt. 05004 – This patient was admitted to the hospital on Day 13 of Cycle 005 with diarrhea, vomiting, seizures, confusion, Kussmaul breathing, bradycardia, and apnea. The patient had been assigned a CR in the tumor assessment conducted in cycle 004. There was no history of seizure disorder or brain metastases. A CT head was not done and the patient was made a DNR and died within an hour of admission. No autopsy was done. and death was attributed to disease. Brain metastases could have been the etiology of the clinical picture, but given the presence of diarrhea the reviewer suggests toxicity from drug/infection cannot be excluded.

Pt. 05008 - was entered into the study at a docetaxel dose of 100 mg/m^2 (but all doses on study after cycle 001 were administered at 75 mg/m^2 because of an admission for febrile neutropenia, dehydration and diarrhea in cycle 001). On day 14 of Cycle 004 the patient was admitted with febrile neutropenia, hyponatremia, confusion, dyspnea, and lethargy. ANC was 130. Chest X-ray was read as carcinomatosis. The patient had a history of pulmonary fibrosis. Cultures were negative and he died 4 days after admission. Death was attributed to malignancy because of the

negative cultures, chest x-ray findings, and hyponatremia "thought to be due to SIADH". Given that the patient was neutropenic and had diarrhea significant enough to cause dehydration, the reviewer did not feel that contribution of drug toxicity to this patient's death could be excluded.

Pt. 05173 – This patient presented with a productive cough on Day 6 of Cycle 002 associated with a performance status that had deteriorated to 3. The patient was sent home on antibiotics and steroids and he died 3 days later in severe respiratory distress. Given the proximity of the onset of these symptoms to the time one would have expected this patient to be neutropenic, the reviewer believes contribution of treatment to the death cannot be excluded.

Pt. 05494 – This patient was found dead in the home by a family member on day 7 of Cycle 008. Because this is a time when the patient could have been neutropenic or recently neutropenic, the reviewer cannot exclude treatment as a contributing factor to his death.

The sponsor indicated in a fax dated December 1, 1999 that they concurred with the FDA's assessment of only one of these deaths, **Pt. 05173**. In a meeting between the sponsor and review team held December 3, 1999, the FDA reviewer agreed to accept that the death of **Pt. 05004** was not treatment related. The resulting three additional deaths and the 4 attributed by the sponsor to treatment result in 7/49 or **14.3% treatment related death rate in this group (100 mg/m^2)**. In the December 3 meeting, the FDA review team concurred that Pt. 05008 should be included with the 100 mg/m^2 dose group despite the fact that this patient received 3 cycles at 75 mg/m^2 prior to death.

In the **docetaxel 75 mg/m^2 group**, 3/4 early deaths were attributed to underlying malignancy. One was attributed to pneumonia (Pt. 05276) – not treatment related. On review of the serious adverse event narratives the reviewer thought that there were 2 deaths potentially related to treatment – one that occurred on Day 31 (Pt. 05234), and Pt. 05276 with pneumonia. A summary of these two patients follows:

Pt. 05276 – This patient was admitted on Day 9 of Cycle 2 with a 3-day history of increased dyspnea and purulent sputum. The patient was not reported to be neutropenic, but was started on antibiotics and G-CSF. Sputum culture grew *Klebsiella pneumoniae* and *Hafnia alvei*. Chest x-ray showed a LUL pneumonia that was considered unrelated to study therapy. The patient deteriorated and died 11 days later. Death was attributed to pneumonia and not study drug. The reviewer considers the pneumonia as possibly related to neutropenia secondary to treatment.

Pt. 05234 – This patient died on Day 31 of Cycle 006 after presenting on Day 23 for emergent drainage of a pericardial effusion. No malignant cells were identified in the tap. The patient reportedly worsened and expired. Death was attributed to underlying disease, but could have been related to fluid retention syndrome.

In a fax dated December 1, 1999, the sponsor disagreed with the FDA reviewer's assessment that these two deaths could have been treatment related. The December 3 meeting between the FDA review team and the sponsor, resulted in the FDA's agreement to consider only the death of **Pt. 05234** as treatment related. This one death resulted in a reviewer assigned treatment related death rate of 1.8% (1/55).

Table 72 TAX 317 Deaths Within 30 Days of Last Cycle and Proportion Attributable to Toxicity – RPR and FDA

	Docetaxel 100 mg	Docetaxel 75 mg	BSC/100	BSC/75

	RPR	FDA	RPR	FDA	RPR	RPR
Deaths Within 30 days of Last Infusion	27%	-	7.3% (4/55)	9.1% (5/55)	29%	39%
Deaths due to Drug-related Toxicity	6.1% (3/49)	14.3% (7/49)	0	1.8% (1/55)	NA	NA

5 Supportive Studies

The sponsor submitted 6 supportive phase 2 studies that enrolled patients who had a history of prior exposure to chemotherapy. The salient efficacy and safety data from these studies are summarized in the table below.

Table 73 Supportive Phase 2 Second Line Non-Small Cell Lung Carcinoma Studies – Summary of Relative Clinical Characteristics, Safety, and Efficacy.

	TAX 270 N=44	TAX 271 N=44	TAX 297 N=80	SI002A N=72	CHI-202* N=10	TAX241** N=22
IIIB	9.1%	22.7%	7.5%	18.1%	70%	31.8%
PS = 2	4.5%	22.7%	10.0%	37.5%	20.0%	36%
Response Rate (PR)	20.5%	13.6%	7.5%	11.1%	20.0%	13.6%
Drug Related Deaths	2.3%	2.3%	1.3%	2.8%	0	0
Discontinued for AE	13.6%	13.6%	13.8%	22.2%	0	13.6%
Withdrew Consent	4.5%	4.5%	10.0%	5.6%	20.0%	0
Median Cumulative Dose	467.5 mg/m^2	337.8 mg/m^2	318 mg/m^2	295 mg/m^2	224 mg/m^2	120 mg/m^2

* 75 mg/m^2
**60 $mg./m^2$

6 Summary of Efficacy and Safety

Two multi-center, open label phase 3 trials enrolling patients with prior platinum based chemotherapy were submitted by the sponsor in support of a proposed indication in advanced non-small cell lung carcinoma, specifically – **"for the treatment of patients with locally advanced or metastatic non-small cell lung carcinoma after failure of prior therapy."** TAX 317 compared docetaxel to best supportive care. Its interim analysis resulted in a docetaxel dose reduction (from 100 mg/m^2 to 75 mg/m^2) midway through the trial. In the second trial, TAX

320, there were two pre-specified docetaxel arms designed to examine two dose levels – 100 mg/m^2 and 75 mg/m^2 – vs. a control arm, investigator choice of vinorelbine or ifosfamide. The sponsor presented a number of unplanned efficacy analyses in this application. The motivation for doing so is understandable, and these analyses may be clinically meaningful, but they must be approached with caution as they are retrospective analyses. The Agency reviewed these exploratory analyses with interest as they appeared to signal clinical benefit in terms of survival, but the reviewer will ground the discussion that follows with the prospectively defined endpoints and the outcomes of their prospectively defined analyses. The exploratory retrospective analyses will then be examined in the context of those findings.

Both studies targeted the same patient population, and both stratified on the basis of performance status (ECOG PS 0, 1 vs. ECOG PS 2) and best response to prior platinum chemotherapy (PD vs. Non-PD). Stratification errors in both studies resulted in a slightly higher distribution of patients with PS<2 + Non-PD response to prior platinum on TAX 320's docetaxel 75 mg arm, and a higher distribution of poorer prognosis patients (PS = 2 + PD as best response to prior platinum) on the TAX 317 control arm prior to the interim analysis relative to after. Despite the stratification errors, the patient populations were similar across studies (see table below), except for a somewhat higher percentage of patients with non-PD prior platinum response in the docetaxel 75 mg arm of TAX320 compared to the control arm and a higher percentage of patients having IIIB disease in the docetaxel 75 mg subgroup compared to the best supportive care arm during the same randomization period in TAX 317. The best supportive care arm of that trial also had a higher percentage of elevated LDH, but a higher percentage of favorable performance status patients. Overall, there was a higher percentage of IIIB disease in TAX 317 compared to TAX 320 -particularly in the second portion of the study.

In general, the patient sub-populations remained similar across arms and across studies (see Table 73 below). For patients treated with docetaxel 75 mg and the respective control (see gray-shaded columns), there were more patients on TAX 317 with Stage IIIB disease and with only one organ involved, as compared to patients on TAX 320.

Table 74 Comparison of Favorable Patient Characteristics Across Randomized Study Arms in TAX 317 and TAX 320

Demo-graphic Variable	TAX 317				TAX 320		
	Docetaxel 100 mg N=49	BSC/100 N=51	Docetax 75mg N=55	BSC/75 N=49	Docetaxel 100 mg N=125	Docetaxel 75 mg N=125	V/I Control N=123
PS = 0, 1	78%	71%	74%	80%	83%	82%	85%
Non-PD Platinum Response	82%	78%	82%	82%	67%	76%	68%
Stage IIIB	18%	18%	27%	20%	14%	10%	9%
Female	25%	29%	36%	41%	34%	34%	35%
No. of Organs Involved =1	20%	28%	46%	39%	26%	30%	29%

Demo-graphic Variable	TAX 317				TAX 320		
	Docetaxel 100 mg N=49	BSC/100 N=51	Docetax 75mg N=55	BSC/75 N=49	Docetaxel 100 mg N=125	Docetaxel 75 mg N=125	V/I Control N=123
No. Prior Chemo Regimen =1	67%	75%	80%	78%	65%	74%	72%
LDH WNL	71%	60%	75%	61%	74%	78%	71%
Weight Loss < 10%	90%	82%	93%	92%	89%	93%	90%

The primary endpoint in both studies was overall survival. The prospective analysis plan was a Kaplan-Meier time to event analysis, tested with log rank. The survival censoring plan differed between the studies. Censoring in TAX 320 was limited to those patients not known to have died, while the TAX 317 statistical analysis plan censored for further therapy including chemotherapy, surgery, and radiotherapy. TAX 320 prespecified that the comparison of the docetaxel 75 mg/m^2 arm would not be performed if the comparison of docetaxel 100 mg/m^2 to control detected no statistically significant difference.

The prospectively defined secondary endpoints in both trials were response rate, time to progression, duration of response, and QoL evaluations that included analyses of QoL subscales from the LCSS in both trials (in TAX 317, a small subset would also use an EORTC QoL instrument), evaluation of analgesic use, change of performance status, and change of weight. The analyses of performance status and weight were pre-specified as evaluations of interval change from baseline to last assessment on study. Time to progression censoring in both studies included further therapy.

The following table summarizes the results of these prespecified intent to treat analyses.

Table 75 Summary Comparison of Prespecified Efficacy Analyses in TAX 317 and TAX 320

	TAX 317		TAX 320		
	Docetaxel 100 + 75mg N=104	Best Supportive Care N=100	Docetaxel 100 mg N=125	Docetaxel 75 mg N=125	V/I Control N=123
Survival	7.2 mo	4.7 mo	5.5 mo	5.7 mo	5.6 mo
95% CI	(5.5 , 9.2)	(3.7 ,6.0)	(4.6, 6.6)	(5.1, 7.9)	(4.3, 7.9)
Log Rank	P = 0.14		P=0.93 (vs. Control)	P=0.14 (vs. Control)	
November 5 Survival Update	7.0 mo (5.5, 9.0) p=0.047 Log Rank	4.6 (3.7, 6.0)	5.5 mo (4.6, 7.2) p=0.577	5.7 mo (5.1, 7.1) p=0.131	5.6 mo (4.4, 7.9)
TTP - RPR	10.6 weeks	6.7 weeks	8.4 weeks	8.5 weeks	7.9 weeks
95% CI	(7.6, 12.1)	(6.0, 7.3)	(6.7, 11.0)	(6.7, 11.0)	(6.9, 11.0)
Log Rank	P<0.001		P=0.04	P=0.09	

	TAX 317		TAX 320		
	Docetaxel 100 + 75mg N=104	**Best Supportive Care N=100**	**Docetaxel 100 mg N=125**	**Docetaxel 75 mg N=125**	**V/I Control N=123**
TTP - FDA	10.1 weeks	6.8 weeks	8.4 weeks	8.3 weeks	7.6 weeks
95% CI	(7.6, 12.1)	(6.0, 8.0)	(7.0, 10.1)	(7.0, 11.7)	(6.7, 10.1)
Log Rank	0.008		P=0.06	P=0.07	
Response Rate - RPR	5.8%		10.5%	6.5%	0.8%
95% CI	(2.4, 12.8)		(5.9, 17.6)	(3.0, 12.7)	(0.0, 5.2)
Fisher's Exact			P=0.001 (vs. Control)	P=0.036 (vs. Control)	
Response Rate – FDA	No Change		9.7%	5.7%	0.8%
95% CI			(5.1, 16.3)	(2.3, 11.3)	(0.0, 4.5)
Fisher's Exact			P=0.001	P=0.04	
Duration of Response			32.1 weeks	39.3 weeks	25.6 weeks
Log Rank			P=0.30	P=0.28	
QoL LCSS – RPR Longitudinal Analysis with Pattern Mixture	Patient Pain Scale favors docetaxel p<0.10		NS <u>Observer</u> total score = 0.048	NS Patient Lung Cancer QoL Today = p=0.058	
QoL LCSS - FDA Longitudinal Analysis with Pattern Mixture			NS	NS	
Performance Status	42% = proportion worse Mean Change = 0.56 ANCOVA p=0.11	46% = proportion worse Mean Change = 0.80	38.5% = proportion worse 5.8% = proportion better Mean Change = 0.39 SE = 0.07 p=0.20	33.0% = proportion worse 5.5% = proportion better Mean change = 0.34 SE = 0.07 p= 0.07	42.5%= proportion worse 3.8% = proportion better Mean change = 0.53 SE = 0.08
Analgesic Use	Not presented			Favored control arm	

	TAX 317		TAX 320		
	Docetaxel 100 + 75mg N=104	**Best Supportive Care N=100**	**Docetaxel 100 mg N=125**	**Docetaxel 75 mg N=125**	**V/I Control N=123**
Weight Loss ≥ 10%	7% p=0.07	15%		5% p=NS	8%

In TAX 320 the docetaxel 75 mg/m^2 arm appears to yield a higher, though meager, response rate compared to ifosfamide or vinorelbine, and did not significantly change time to progression compared to vinorelbine/ifosfamide. When pooled, the two docetaxel arms from TAX 320 (an unplanned analysis) and TAX 317 (planned analysis) do prolong time to progression compared to the control, p=0.05 and p<0.001, respectively. The difference in median time to progression between the docetaxel arms and control, however, is fairly small.

The QoL endpoints were in general not found to be statistically significantly different, except in ANCOVA analyses, which the Agency does not consider valid QoL analysis methodology because it ignores data collected between the two time points analyzed. The longitudinal pattern mixture analysis of the patient pain scale data from TAX 317, however, did suggest a trend favoring the docetaxel arm, which the Agency could not confirm as a robust finding when the same data was re-tested. (See the FDA Statistical Review.) The Agency could not demonstrate that in the specific subscales it examined, patient pain scale and QoL Today patient subscale, that treatment with docetaxel caused deterioration of QoL compared to the control arms in these studies.

In the original NDA submission, the prospectively defined survival analyses from both trials failed to demonstrate a significant difference favoring docetaxel. The updated (October 1999) survival analysis log rank comparison of the overall docetaxel arm of TAX 317 vs. best supportive care yielded a p=0.047, the minimum alpha pre-specified to define significance in the survival analysis of the data from the April 1999 cut-off. The p value determined in the updated survival analysis from October is viewed with caution by the Agency because the p-value at the planned final analysis for this study prior to filing was not statistically significant.

The unplanned pooling of the TAX 320 time to progression data from the 100 mg and 75 mg docetaxel arms, discussed above in the context of comparing the results of the two trials, leads to the sponsor's exploratory analyses that were performed in an effort to demonstrate that clinical benefit beyond a low, but significant, response rate and a brief prolongation of time to progression was associated with docetaxel in this setting. There were two different retrospective approaches taken by the sponsor to the survival data from these trials that were based on clinical issues in TAX 317, and examination of the survival curves in TAX 320.

<u>TAX 317 Docetaxel vs. Best Supportive Care</u> In TAX 317 the planned interim analysis yielded safety information (toxic deaths) that suggested the docetaxel dose should be reduced from 100 mg/m^2 to 75 mg/m^2. Though rates of death within 30 days of treatment/assessment rates are similar between the best supportive care/100 and the docetaxel 100 mg/m^2 arms (29% vs. 27%, Table 75), those early deaths were frequently attributable to treatment on the docetaxel arm. Comparison of these death rates (within 30 days of a cycle/evaluation) to TAX 320 reveals a much higher death rate associated with docetaxel 100 mg in TAX 317, compared with the 100 mg dose arm in TAX 320 (27% vs. 14.1%, see Table 75). Was this related to patient demographic factors, or did the fewer early deaths in TAX 320 reflect more aggressive supportive care relative to TAX 317? Comparison of the two docetaxel 100 mg arms

from these separate studies reveals no dramatic patient characteristic differences between the two study groups, except that there are more PS = 2 patients, fewer females, and fewer patients with one organ site of disease in the TAX 317 docetaxel 100 mg group. The United States sites entered 56/100 patients accrued to the first half of TAX 317 (100 mg/m^2 docetaxel dosing period) and TAX 320 was conducted in the US. It is possible that the disparity in the sizes of the two studies' docetaxel 100 mg treatment groups could contribute to the differences in these safety observations between trials – the TAX 317 docetaxel 100 mg subgroup is half the size of the same group in TAX 320. Although the absolute difference in percentage of patients with PS = 2 between the two studies' docetaxel 100 mg arms is not large – 22% in TAX 317 vs. 17% in TAX320, it should be acknowledged. At the May 1999 ASCO Meeting Johnson, Zhu, Schiller, et al, reported that in a phase III study of stage IIIB and IV NSCLC, accrual of patients with PS=2 had to be stopped due to unexpected toxicity. One of the four treatment arms was a docetaxel 75 mg/m^2 + cisplatin combination regimen. It was associated with 56% Grade 4 toxicity and 17% grade 5 toxicity in the PS 2 population.[i]

Table 76 Comparison of Deaths Within 30 Days of Study Treatment Among Study Arms and Between Studies – TAX 317 and TAX 320.

TAX 317	Docetaxel 100 mg		Docetaxel 75 mg		BSC/100	BSC/75
	RPR	FDA	RPR	FDA	RPR	RPR
Deaths Within 30 days of Last Infusion	27%	-	7.3%	9.1%	29%	39%
Deaths due to Drug-related Toxicity	6.1% (3/49)	14.3% (7/49)	0	1.8% 1/55	NA	NA

TAX 320	Docetaxel 100mg		Docetaxel 75 mg		V/I	
	RPR	FDA	RPR	FDA	RPR	FDA
Deaths Within 30 days of Last Infusion	14.1% (17/121)		10.7% (13/121)		9.2% (11/119)	
Deaths due to Drug-related Toxicity	2.5% (3/121)	5.0% (+4=7/121)	0	3.3% (+4/121)	1.7% (2/119)	3.4% (+2=4/119)

Given the high toxic death rate in the docetaxel 100 mg arm of TAX 317, the sponsor proposed unplanned separate analyses of the two docetaxel dose levels. The best supportive care patients in this analysis would be divided into two groups based on which docetaxel dose level they were concurrently randomized against. Referral to the earlier demographic table shows that such splitting of the BSC population results in what appears to be a more favorable prognosis BSC population in the second half of the trial compared to the first. The BSC patients accrued during the second portion of the study had a slightly lower percentage of poor performance status patients compared to the docetaxel 75 mg group, a higher percentage of females, and higher

proportion of adenocarcinoma. There were more patients, however, in this best-supportive care group that had elevated baseline LDH. Despite these favorable prognostic factors in the second best supportive care group, this subgroup had a higher percentage of deaths "within 30 days of an evaluation"(39% vs. 29%; 20 vs. 14 deaths), and the percentage of one year survivors was higher in the BSC/100 patients.

Splitting TAX 317 into study periods based on the docetaxel dose at the time of randomization, alters the clinical benefit perspective. The trial now suggests docetaxel 75 mg/m^2 prolongs survival compared to best supportive care. The median survival in the docetaxel 75 mg/m^2 group was 9.0 months (95% CI = 5.5, 13.1) vs. 4.6 months (95% CI = 3.7, 6.1) in the best supportive care patients randomized during the same study period (Table 76). The BSC confidence intervals remain essentially unchanged from the pooled BSC population. The time to event comparison with the log rank test is statistically significant at p=0.016. These results must be juxtaposed against the lower median survival on the TAX 320 docetaxel 75 mg arm (pre-specified arm) – 5.7 months (95% CI = 5.1, 7.9), which might be explained by the lower percentage of IIIB disease in that study – 10% vs. 27% in TAX 317. The updated survival analysis of TAX 317 submitted by the sponsor revealed the median survival had decreased on the docetaxel 75 mg arm – 7.5 months (95% CI = 5.5, 12.8). (That analysis was submitted in November and has not been evaluated by the FDA statistical reviewer at the time this review was completed in draft form.) Retrospective subsetting of the survival data appears to have been clinically relevant, given the interim analysis prompted the dose change based on safety.

Troubled by the fact that these findings came from a retrospective analysis and the disparity in median survivals at that dose level between the two pivotal trials, the review team conducted additional exploratory analyses. The sponsor's TAX 317 survival analysis was performed with pre-specified censoring for further therapy. The FDA review team performed its own exploratory analysis of the sponsor's 75 mg dosing period subgroup data, eliminating censoring for further therapy, and found the median survivals were 9.0 months vs. 4.7 months for the docetaxel 75 mg and BSC/75 subgroups (Table 76), log rank p = 0.041. The FDA statistical reviewer performed a Cox Regression utilizing the factors prespecified in the sponsor's analysis plan and confirmed that a statistically significant difference remained between 75 mg subgroups of that trial. (See Statistical Review for a detailed discussion.) A further exploratory analysis was conducted pooling the survival data from the two 75 mg groups from TAX 317 and TAX 320 and comparing them to the combined survival data from the vinorelbine/ifosfamide control arm in TAX 320 and the best supportive care/75 subgroup from TAX 317. There was no censoring performed for further therapy in any of the patients of this combined, exploratory analysis. The log rank comparison of the pooled groups' survival in this exploratory analysis revealed a p=0.019. Cox Hazard Regression identified disease stage, performance status, and weight loss at study entry as significant factors, and when those were incorporated into the analysis, the difference was associated with a p=0.053.

Did splitting the study into two treatment period subgroups impact on the secondary endpoints of TAX 317? The prospectively defined TTP endpoint was already found to be significantly different in the planned pooled analysis. In the sponsor's analysis of the dose defined subgroups, docetaxel was found to have a longer time to progression than the best supportive care arm, regardless of dose (9.1 weeks for docetaxel 100 mg, 12.3 weeks for docetaxel 75 mg vs. 5.9 and 7.0 weeks for the respective best supportive care subgroups). Those results are summarized in the table below, where the medians can be compared to the same dose levels in TAX 320 (8.4 weeks for docetaxel 100 mg, 8.5 weeks for docetaxel 75 mg, vs. 7.9 weeks for the vinorelbine/ifosfamide control). Although the pre-specified docetaxel 75 mg arm of TAX 320 was not found to significantly prolong TTP compared to vinorelbine/ifosfamide, that dose in

TAX 317 did appear to significantly prolong TTP against best supportive care, in an unplanned subgroup analysis.

Regarding TAX 317's secondary quality of life endpoints, the time period subgroup analyses found only the docetaxel 100 mg subgroup significantly different in the LCSS longitudinal analysis of patient pain scale changes. Observer scale longitudinal analyses were positive in the fatigue, appetite and total scores. The ANCOVA analyses are not considered valid assessments of QoL data by the Agency. In the 75 mg study period, the sponsor found the proportion of patients starting additional "morphinic" analgesics (15% vs. 45%), and initiating morphinic analgesic on study (7% vs. 35%) was significantly less in the docetaxel subgroup compared to the BSC/75 subgroup, $p<0.01$. The clinical meaning of the sponsor's analyses may be limited by the apparent lack of standardization of pain control prior to study entry and the lack of analysis of dose changes. The sponsor found that there were significantly fewer patients who lost ≥10% weight in the TAX317 docetaxel 75 mg subgroup (2% vs. 22%, $p\leq0.001$). This may be meaningful, although the fluid retention syndrome could confound the weight change comparison. This analysis was not prospectively defined with the subsetting of weight change at a cutoff of 10%. The median dose delivered to the TAX 317 docetaxel 75 mg group was 299 mg/m^2, and moderate "treatment related" fluid retention was reported in 12% of the patients. (Moderate fluid retention was defined in the protocol as symptomatic edema or edema requiring diuretics; or symptomatic effusion not requiring drainage.) The pre-specified performance status evaluation was to be a comparison of change from baseline. The sponsor presented a number of performance status analyses, including a non-significant comparison of proportion of patients in each group whose performance status worsened on study between baseline and last assessment (48% in the docetaxel 75 mg group vs. 60% in the BSC/75 group), and comparison of mean changes in ECOG PS in the first 3 cycles and mean changes from baseline to last assessment. The latter comparison was reportedly significant, p=0.039. Approximately 2/3 of the docetaxel 75 mg subgroup and ¾ of the BSC/75 subgroup had a PS recorded in the electronic dataset at cycle 003.

TAX 320 Docetaxel 100 mg/m^2 and 75 mg/m^2 vs. Vinorelbine/Ifosfamide In TAX 320, the unplanned analyses were driven by the lack of a demonstrable survival difference among the treatment arms with the log rank analysis of the survival curves, in the face of a late separation of the curves that suggested potential late survival benefit on the docetaxel 75 mg/m^2 arm. The sponsor explored this issue by comparing rates of survival at one year utilizing the Chi-Square test, and found the 1-year survival rate was significantly different favoring docetaxel 75 mg, p=0.025. The rates of one year survival reported with this comparison are those derived from the K-M curves – 32% (95% CI = 23, 40) for docetaxel 75 mg/m^2 vs. 19% (95% CI = 12, 26) on the control. The sponsor's similar retrospective comparison of the TAX 320 docetaxel 100 mg/m^2 arm to vinorelbine/ifosfamide control found no difference between arms.

Retrospective analyses of 1 year survival were also performed in TAX 317 and are presented for comparison in the table below – both as the overall study patient population and the retrospectively defined two study period subgroups. Like TAX 320, the sponsor utilized a Chi-Square to compare rates of survival at one year between the TAX 317 docetaxel 75 mg subgroup and the best supportive care control - 40% (95% CI = 26,54) vs. 16% (95% CI = 3,30), p=0.016.

Table 77 Comparison of Retrospective Exploratory Efficacy Analyses – TAX 317 and TAX 320

	TAX 317				TAX 320		
	Docetax. 100 mg N=49	BSC/100 N=51	Docetax. 75mg N=55	BSC/75 N=49	Docetaxel 100 mg N=125	Docetaxel 75 mg N=125	V/I Control N=123

	TAX 317				TAX 320		
	Docetax. 100 mg N=49	**BSC/100 N=51**	**Docetax. 75mg N=55**	**BSC/75 N=49**	**Docetaxel 100 mg N=125**	**Docetaxel 75 mg N=125**	**V/I Control N=123**
Survival % 1-year	19%	28%	**40%**	16%	21%	**32%**	19%
95% CI	(7,30)	(14, 41)	**(26, 54)**	(3, 30)	(14, 28)	**(23, 40)**	(12,26)
			P=0.016 **Chi Square**		P=NS **Chi - Square** (vs. Control)	P=0.025 **Chi Square** (vs. Control)	
Nov.1999 Survival Update	19% (7,30)	26% (13,39)	37% (24,50) p=0.010 **Chi square**	12% (2, 23)	23% (15,30) **p=NS Chi-Square**	30% (22,39) p=0.05 **Chi-Square**	20% (13,27)
Median Survival	5.9 mo	4.9 mo	9.0 mo	4.6 mo	5.5 mo	5.7 mo	5.6 mo
95% CI	(4.5, 8.0)	(3.5, 8.0)	(5.5, 13.1)	(3.7, 6.1)	(4.6, 6.6)	(5.1, 7.9)	(4.3, 7.9)
Log Rank	P=0.871		**P=0.016**		P=0.93	P=0.14	
Nov. 1999 Survival Update	5.9 (4.5, 8.0) p=0.78	4.9 (3.5, 8.0)	7.5 (5.5,12.8) p=0.010	4.6 (3.7,6.1)			
Median Survival **FDA – No Censored Further Therapy**			9.0 mo	4.7 mo			
Log Rank			P=0.041				
TTP – RPR	9.1 weeks	5.9 week	**12.3 weeks**	7.0 weeks	8.4 weeks	**8.5 weeks**	7.9 weeks
95% CI	(6.1, 10.7)	(4.0, 7.3)	**(9.0, 18.3)**	(6.0, 9.3)	(6.7, 11.0)	**(6.7, 11.0)**	(6.9, 11.0)
Log Rank	P=0.037		P=0.004		P=0.04	P=0.09	
TTP – FDA					8.4 weeks	8.3 weeks	7.6 weeks
95% CI					(7.0, 10.1)	(7.0, 11.7)	(6.7, 10.1)
Log Rank					P=0.06	P=0.07	
Pooled** TTP Log Rank	10.6 weeks (7.6, 12.1) p<0.001				P=0.05		

	TAX 317				TAX 320		
	Docetax. 100 mg N=49	**BSC/100 N=51**	**Docetax. 75mg N=55**	**BSC/75 N=49**	**Docetaxel 100 mg N=125**	**Docetaxel 75 mg N=125**	**V/I Control N=123**
Response Rate – RPR	6.3%		5.5%		10.5%	6.5%	0.8%
95% CI	(1.6, 18.2)		(1.4, 16.1)		(5.9, 17.6)	(3.0, 12.7)	(0.0, 5.2)
Fisher's Exact					P=0.001 (vs. Control)	P=0.036 (vs. Control)	
Response Rate – FDA					9.7%	5.7%	0.8%
95% CI					(5.1, 16.3)	(2.3, 11.3)	(0.0,4.5)
Fisher's Exact					P=0.001	P=0.04	
Duration of Response	26.1 weeks		23.9 weeks		32.1 weeks	39.3 weeks	25.6 weeks
95% CI					(25.7, 41.9)	(19.1, 51.0)	Non-Est
QoL LCSS – RPR Longitudinal Analysis with Pattern Mixture	Patient Pain Scale NS p=0.008		Patient Pain Scale favors docetaxel NS p<0.10 <u>Observer</u> Scales p<0.10		NS	NS	
QoL LCSS – FDA Longitudinal Analysis with Pattern Mixture	NS		NS		NS	NS	

	TAX 317				TAX 320		
	Docetax. 100 mg N=49	**BSC/100 N=51**	**Docetax. 75mg N=55**	**BSC/75 N=49**	**Docetaxel 100 mg N=125**	**Docetaxel 75 mg N=125**	**V/I Control N=123**
Perf. Status	39% = proportion worse Mean Change = 0.45 SE=0.14 ANCOVA p=NS	33% worse; p=NS Mean Change= 0.50 SE=0.13	45% worse; P = NS Mean Change = 0.65 SE= 0.13 p<0.05	59% worse Mean Change = 0.09 SE=0.16	38.5% = proportion worse 5.8% = proportion better Mean Change = 0.39 SE = 0.07 p=0.20	33.0% = proportion worse 5.5% = proportion better Mean change = 0.34 SE = 0.07 p= 0.07	42.5%= proportion worse 3.8% = proportion better Mean change = 0.53 SE = 0.08
Analgesic Use	NS		"Less Analgesic Use" p<0.01			NS	
Weight Loss ≥ 10%	12% p=0.07	8%	2% p<0.01	22%		5% p=NS	8%

Upon closer examination, the 40% probability of survival at one year in the docetaxel 75 mg subgroup of TAX 317 is the upper limit of the confidence interval of the 75 mg arm of TAX 320. The TAX 317 updated probability of 1-year survival (October 1999) was 37%, which is again close to the upper limit of the confidence interval for the 75 mg arm of TAX 320. In either case, (original or the updated analysis) the probability of 1-year survival for the docetaxel 75 mg group on TAX 317 exceeds the upper limit of the confidence interval for the BSC/75 group in TAX 317 and the control arm from TAX 320. The updated median survival of the TAX 317 docetaxel 75 mg/m^2 subgroup (7.5 months) is longer than that of the 75 mg/m^2 arm of TAX 320 (5.7 months), but falls within the confidence interval of both the docetaxel 75 mg arm and the vinorelbine/ifosfamide control arm of that trial.

The sponsor presented additional retrospective analyses of TAX 320 utilizing survival censoring for further therapy. These were retrospective analyses and of unclear clinical merit. They will not be discussed further here.

The quality of life comparisons between the docetaxel 75 mg arm and the control arm were not found to be statistically signficant, except in an exploratory analysis of change of performance status in the first 3 cycles. Less than a half of the patients participating in those arms had a PS recorded in the electronic database at cycle 003.

Survival Summary

The findings in the prospectively defined and pertinent retrospectively defined survival analyses of the comparisons involving the docetaxel 75 mg/m^2 dose level are summarized in the table below.

Table 78 Summary of Docetaxel 75 mg/m^2 Survival Analyses

	TAX 317		TAX 320	
	Docetaxel 75 mg	**BSC/75**	**Docetaxel 75 mg**	**Vinorelbine/ Ifosfamide**
Median Survival	9.0 mo (5.5 , 13.1)	4.6 mo (3.7, 6.1)	5.7 mo (5.1, 7.9)	5.6 mo (4.3, 7.9)
Survival Update October 1999	7.5 mo (5.5 , 12.8)	4.6 (3.7, 6.1)	5.7 (5.1,7.1)	5.6 mo (4.4, 7.9)
% 1-year survival	40% (26, 54)	16% (3 , 30)	32% (23 , 40)	19% (12, 26)
Update October 1999	37% (24, 50)	12% (2, 23)	30% (22, 39)	20% (13, 27)
Deaths Within 30 Days of Treatment	7.3% (RPR) 9.1% (FDA)	39%	10.7%	9.2%
Treatment Related Death	1.8% (FDA)	-	3.3% (FDA)	3.4% (FDA)

Conclusions:

- The probability of one-year survival for docetaxel 75 mg/m^2 is consistent across both studies and is appears higher than that associated with the control arms in both studies.
- Median survival for docetaxel 75 mg/m^2 is consistent across both studies, and similar to the control arm of TAX 320 and longer than the best supportive care/75 subgroup in TAX 317.
- Deaths within 30 days of treatment with docetaxel 75 mg/m^2 were consistent across studies, and similar to that of the vinorelbine/ifosfamide arm.
- Treatment related deaths associated with docetaxel 75 mg/m^2 are consistent across studies, and similar to that associated with the vinorelbine/ifosfamide control arm of TAX 320.

Safety. Given that the only prospectively defined analyses showing clinical benefit in these two pivotal phase 3 trials were a significantly different, but low, response rate and a brief prolongation in time to progression (and quality of life in a patient pain subset), and that the apparent survival benefit was defined from retrospective analyses, it is important to put these endpoints in perspective with an examination of safety. The following table compares the observed toxicity of the two docetaxel dose levels in TAX 317 and TAX 320 to that labeled for breast cancer patients (100 mg/m^2) and all tumor types (60, 75, and 100 mg/m^2). The toxicity rates for 75 mg/m^2 are similar to those labeled, except for infections and treatment related death. In those categories the grade ¾ infections at the 75 mg dose level in TAX317 occur at a rate similar to that currently labeled. The rate in TAX 320, however, is nearly doubled (12.4%). Treatment related deaths associated with docetaxel 75 mg/m^2 in one study (TAX 317) occurred at a rate similar to that already labeled for 100 mg/m^2, but in TAX 320 these deaths appeared to

occur at a somewhat higher rate at docetaxel 75 mg/m^2 (utilizing the FDA reviewer's analysis of treatment related mortality in that study). Higher rates of grade 3/4 infection and treatment related death could be related to a higher risk of obstructive pneumonitis in a lung cancer population, a higher risk for respiratory infection in a population with underlying COPD, and perhaps the use of chronic prednisone in some members of this population. (In TAX 320 the reviewer identified 6-9% of patients in the study were on baseline prednisone.) Otherwise, the docetaxel 75 mg arm had a generally lower rate of grade ¾ toxicity than what appears in the label in the adverse events listed below.

Table 79 Comparison of the Safety Analyses of TAX 317 and TAX 320 with Selected Adverse Events from the Current Docetaxel Product Label.

	Breast Cancer Label N=730	All Tumor Types Label N=2045	TAX 317		TAX 320	
	100 mg	60, 75 and 100mg	100mg N=49	75 mg N=55	100 mg N=121	75 mg N=121
Febrile neutropenia*	11.8%	11.0%	22.4%RPR	1.8% RPR	11.4% RPR	8.3% RPR
Infection Any Grade ¾ or Severe	22.5% 7.1%	21.6% 6.1%	36.7% 14.3%	30.9% 5.5%	41.3% 14.9%	35.5% 12.4%
Septic Death or Treatment Related Death	1.5%	1.6%	6.0% RPR 14.3% FDA	0% RPR 1.8% FDA	2.5% RPR 5.0% FDA	0% RPR 3.3% FDA
Diarrhea Any Severe or Grade ¾	42.2% 6.3%	38.7% 4.7%	30.6% 3.9%	36.4% 2.0%	34.7% 3.3%	11.8% 1.7%
Stomatitis Any Severe Grade 3/4	53.3% 7.8%	41.7% 5.5%	26.5% 3.9%	25.5% 2.0%	31.4% 2.3%	27.3% 1.7%
Neuro-Sensory Any Severe	56.8% 5.8%	49.3% 4.3%	51.0% 2%	38.2% 2%	52.8% 5.8%	54.5% 0.8%
Neuromotor Severe or Grade 3/4	4.4%	-	3.9%	2%	2.5%	2.5%

	Breast Cancer Label N=730	All Tumor Types Label N=2045	TAX 317		TAX 320	
Fluid Retention	-					
Any		64.1%	(12.2%)*	(16.4%)*	50.2% (27.3)*	41.3% (24.8%)*
Severe		6.5%	(0%)*	(0%)*	5.0% (4.1%)*	3.3% (0%)*

* Numbers in parentheses are rates attributed to study drug.

Historical Perspective.. The retrospective survival data presented in this application might be a flickering signal of clinical benefit, but it clearly is not a beacon. We are challenged to examine the retrospective analyses for evidence that they are believable on statistically valid grounds. In both studies it was the 75 mg/m^2 dose level that was associated with potential survival benefit, and it is this lower dose that demonstrated a toxicity profile akin to what is already described for this agent in the product label. The higher dose studied in this population was associated with higher treatment related morbidity and mortality and was not found in prespecified or exploratory analyses to be associated with survival benefit, though it was associated with a somewhat higher response rate. The FDA statistical review team tested these retrospective survival analyses at the 75 mg dose level for robustness by pooling of the survival data from the patients treated with 75 mg/m^2 in both studies and comparing survival against the pooled control arm data in an effort to unmask inconsistency and seek signs these findings were not robust. The results of this retrospective, exploratory analysis were discussed above. They cannot exclude the possibility that the suggested survival benefit observed for docetaxel 75 mg/m^2 did not occur secondary to chance.

The population in this trial is not one normally targeted for phase 3 studies of lung cancer – they had already been exposed to prior therapy. This is a population generally accepted to a have a poor median survival. Chang, DeVore, and Johnson have stated that the expected median survival in refractory metastatic non-small cell lung carcinoma is 3 months.[ii] It is impossible to put the data presented in this application in a historical perspective by comparing the results to other phase 3 trials in similar populations (second treatment of advanced disease) because of the lack of such published trials. The reviewer was able to find some data on the expected survival in this population, but they are limited by the fact that they are from phase 2 trials or retrospective evaluations of institutional datasets. The pivotal trials presented in this study are unique in that they evaluated therapy in a randomized fashion in a poor prognosis population generally excluded from clinical trials. The studies from the medical literature in the discussion that follows are summarized relative to the same endpoints and patient characteristics found in TAX 317 and TAX 320 to facilitate comparisons in the table below.

Table 80 Literature Review Second Line and First Line Treatment of Non-Small Cell Lung Carcinoma

Study		Arm (n)	Stage - %IIIB	%PS = 2	Median Survival	% 1-year Survival	2 year Surv.%	TRM
Second Line								
TAX 317	**Prior Platinum**	**Docetaxel 75 mg (49)** **Docetaxel 100 mg (55)** **BSC/75 (51)** **BSC/100 (49)**	**27%** **18%** **20%** **18%**	**26%** **22%** **20%** **29%**	**9.0 mo** **5.9 mo** **4.6 mo** **4.9 mo**	**40%** **19%** **16%** **28%**	**NA**	**5.5%** **14.3%**
TAX 320	**Prior Platinum**	**Docetaxel 75 mg (125)** **Docetaxel 100 mg (125)** **Vinorelbine/Ifos (123)**	**10%** **14%**	**18%** **17%**	**5.7 mo** **5.5 mo** **5.6 mo**	**32%** **21%** **19%**	**NA**	**1.8%** **5.8%** **3.4%**
MDACC Fosella (Sem. Onc. 1997)	Failed Platinum	Historic Phase 1 cohort N= 36	≈ 16%	19%	16 weeks	16%		
MDACC Phase 2 (Sem. Onc. 1997)	Failed Platinum	Paclitaxel N=40		33%	17.5 weeks	16%		
ECOG (Bonomi. JCO, 1989)	Failed carboplatin	MVP = 43 Non-MVP = 36 **Non-Randomized** Crossover in a phase 3 trial	IIIB/IV	?20%	36.4 weeks 29.3 weeks			2.4%
First Line								
MIC 2 (Cullen, et al. JCO 1999)	No prior rx Phase 3	MIC = 175 BSC = 176	IV+IIIB with pleural effus. Or cannot be encompassed in XRT port	31% 26%	6.7 mo (8.0, 11.4) 4.8 mo (4.0, 5.7)	25% (18, 32) 17% (12.23)	5% 4%	0%
NCI of Canada (Rapp, JCO, 1988)	No prior rx	CAP = 48 VP = 49 BSC = 53	IIIB/IV IIIB = 14% IIIB = 18.2% IIIB = 10%	41.9% 43.2% 40.0%	24.7 weeks 32.6 weeks 17 weeks	22% 22% 10%		

Cartei, et al(JNCI, 1993)	No prior rx	Cisplat+Mito+CTX=52 BSC = 50	IV	KPS=50-60 52% 50%	8.5 mo 4.0 mo	38.5% 12%	9.6% 0%	0%
SWOG ASCO 1999 (Abstract#1777: Kelly)	No prior rx	Paclitaxel+Carbo = 184 Cisplat+Vinorelb = 181	12% 11%	0% 0%	8 mo 8 mo	36% 33%		
SWOG Wozniak, JCO1998	No prior rx	 Cisplatin = 209 Cisplatin+vinorelb=206	IV + IIIB with effusion or multiple ispilat. nodules 8% 8%	 0% 0%	 6 mo 8 mo	 20% 36%		(0.5%) 2.5%
SWOG Gandara, JCO 1993	No prior rx	Cisplat. Std. Dose=105 HiDose Cisplat = 108 HiDose Cis+Mito= 110	(IV – M1)	21% 19% 22%	5.3 mo 6.9 mo 7.2 mo			1.0% 1.0% 1.9%
Crawford JCO 1996	No prior rx	5-FU + LV = 68 Vinorelbine = 143	(IV) 0% 0%	KPS 70 = 41.1% KPS 70 = 14.7%	22 weeks 30 weeks	16% 25%		1.5%

In a review of the management strategies for second-line treatment of non-small cell lung carcinoma, Fossella, Lee and Hong reported they had retrospectively identified a 36 patient cohort from the MD Anderson cancer Center (MCACC) protocol data management base with advanced non-small cell lung carcinoma and had failed first-line platinum based therapy - in all but one patient – for comparison to a phase 2 evaluation of docetaxel.[iii] This historical control group had been enrolled in various phase 1 trials and 19% had a PS = 2. The distribution of IIIB and IV disease was not specifically stated, but was reportedly similar to the phase 2 docetaxel study cohort, of which 16% had IIIB disease. The historical control cohort had a median survival of 16 weeks and a 1–year survival of 16%. The TAX 317 best supportive care/75 subgroup (20% IIIB and 20% PS = 2) had a median survival of 4.6 months and a 1-year survival of 16%, while the control arm of TAX 320 (9% IIIB and 15% PS = 2) had a 5.6 months median survival (95% CI = 4.3, 7.9) and a 1-year survival of 19%. A phase 2 study evaluating paclitaxel conducted at MDACC in 40 patients who had failed one prior platinum based regimen (33% with PS = 2) yielded similar survival data – 16% one year survival and 17.5 week median survival. The remainder of the phase 2 data reported in the review by Fossella, et al, either had no associated survival data or were from study populations of less than twenty. Three of these studies examined vinorelbine in the second line setting and in 2/3 of those studies there were no responders. In the third study (n=10; 100% PS=1) there were 2 PR's to vinorelbine dosed 30 mg/m^2/week in the second-line setting.

A phase 3 ECOG study of first-line treatment reported by Bonomi, et al, specified that patients who failed treatment on two of the single agent arms of the trial (carboplatin and iproplatin) would cross over to second line treatment with one of the combination arms, MVP (mitomycin+cisplatin+vinblastine).[iv] Not all such patients went on to MVP treatment, and a non-randomized comparison of those that crossed over vs. those who did not after initial treatment with carboplatin (43 = MVP vs. 36 = non-MVP) demonstrated a 36.4 week median survival with second line MVP vs. 29.3 weeks in the non-MVP group, p=NS. These patients' clinical characteristics are not reported. PS of ≤2 (20% of the carboplatin randomized arm) and IIIB or IV disease were eligibility requirements for study entry. The cross-over treatment group's survival is similar to that of the docetaxel 75 mg subgroup of TAX 317. The cross-over group that remained untreated had a median survival that appeared longer than the control arm of TAX 317.

It is of some interest to compare the survival data from TAX 317 and TAX 320 to that from phase 3 studies published regarding first-line treatment of NSCLC. The recently published MIC trials[v] reported survival benefit for patients with non-small cell lung carcinoma associated with chemotherapy. These studies enrolled previously untreated patients with advanced non-small cell lung cancer and PS of 0-2 and excluded intracranial metastases. MIC1 enrolled IIIB patients with no pleural effusion and tumors encompassible by a radical RT volume. These patients were randomized between RT + best supportive care vs. RT + chemotherapy (cisplatin + mitomycin + ifosfamide). MIC 2 enrolled patients with Stage IV disease or IIIB disease that did not meet the eligibility criteria of MIC1, and randomized between best supportive care vs. chemotherapy (cisplatin + mitomycin + ifosfamide) + BSC. The objective response rate was 54% in MIC 1 and 32% in MIC 2. The median survival on MIC1 was 11.6 months (95% CI= 9.5, 14.0) on chemotherapy + XRT vs. 9.7 months (95% CI = 8.0, 11.4) on RT. The MIC2 trial median survival was 6.7 months (95% CI = 8.0, 11.4) on the chemotherapy + BSC arm vs. 4.8 months (95% CI = 4.0, 5.7). The one year survival in the MIC2 trial was 25% (CI = 18, 32) on the treatment arm vs. 17% (95% CI = 12,23) on the best supportive care arm. The median follow-up at the time of the analysis was 26 months. The 2-year survival probability in MIC 2 was 5% on

the active treatment arm and 4% on the best supportive care arm. This first line chemotherapy data appears similar to the docetaxel 75 mg/m^2 second line data, and in fact, the probability of 1-year survival appears less in the first line trial. Though the proportion of IIIB disease in the MIC study was similar to that of the second half of TAX 317, the type of IIIB disease was specifically defined to be limited to a poorer prognosis subgroup in that trial (associated pleural effusion). In addition, the best supportive care arm of TAX 317 appears to have a similar prognosis to the first line best supportive care arm in MIC 2. This too may reflect differences in IIIB patients between the trials.

A similar first line NSCLC phase 3 trial reported in the JNCI by Cartei, et al, in 1993 enrolled only stage IV disease.[vi] Patients with KPS as low as 50% were eligible for participation. (Approximately half of the patients in both arms had a KPS = 50-60%.) The median survival and probability of one year survival of the best supportive care and treatment arms (cisplatin+mitomycin+cyclophosphamide) were similar to those reported for the two post-interim analysis subgroups of TAX 317.

An older and frequently referenced study that examined chemotherapy vs. best supportive care in NSCLC is the NCI of Canada trial reported by Rapp, et al in 1988.[vii] Patients with Stage IIIB and IV disease were randomized among 3 arms – best supportive care, cisplatin + doxorubicin + cyclophosphamide, and cisplatin + vindesine. Forty per cent of patients in this study group had an ECOG PS = 2 and the distribution of stage IIIB disease varied slightly among arms – BSC = 10%, CAP = 14%, and VP = 18.2%. Patients entered the study between 1983 and 1986. The median survival on the BSC arm was 17 weeks (approximately 4 months) and the actuarial survival at one-year was 10%. The median survival in the patients randomized to treatment with CAP was 24.7 weeks, 1 year survival was 22%. On the cisplatin/vindesine arm the median survival was 32.6 weeks and one year survival probability was 22%. Comparison of the best supportive care arms from this first line study and TAX 317 reveals the median survivals are similar and the probability of 1-year survival appeared somewhat lower in the first line setting. Again there were differences in patient characteristics between the trials that might account for this. There were slightly fewer patients with IIIB disease in this first line study's BSC arm, and a higher percentage of PS=2 patients compared to the BSC arm of TAX 317.

The phase 3 data from the SWOG trial randomizing patients with IIIB and IV NSCLC between first-line treatment with paclitaxel +carboplatin vs. cisplatin + vinorelbine were presented at the May 1999 ASCO Meeting.[viii] Patients with a performance status of 2 were not eligible for participation, and there were approximately 12% IIIB patients in each arm. Accrual occurred between 4/96 and 1/98. The median survival on both arms was 8 months and the percentage of one –year survival was 36% on the paclitaxel arm and 33% on the vinorelbine arm. These survival statistics in the first line setting are similar to those reported for the docetaxel 75 mg/m^2 subgroup of TAX 317. The proportion of IIIB disease was higher in TAX 317, but contrary to the SWOG trial, TAX 317 included PS=2 patients.

An earlier SWOG phase 3 study comparing cisplatin vs. cisplatin + vinorelbine in the first-line setting, enrolled patients with stage IV disease and stage IIIB with pleural effusion or multiple ipsilateral lung nodules (8% on both arms), and PS<2.[ix] Median survival was 8 months on the cisplatin + vinorelbine arm and 6 months on the cisplatin arm. The probability of survival at one year was 36% for the combination arm and 20% for single agent cisplatin. The two year survival probability was 12% in the combination arm and 6% in the single agent arm. The survival analysis was based on 187/209 possible events on the single agent arm, and 170/206 possible events on the combination arm. These survival statistics appear similar, if not slightly inferior, to the second line survival data associated with docetaxel 75 mg/m^2 in TAX 317. Again this might

be explained on the basis of differences in patient characteristics, since the first line trial enrolled a lower percentage of IIIB disease and that disease stage had to have certain characteristics that likely made this a worse prognosis IIIB population than that participating in TAX 317.

Yet another SWOG trial publish in JCO in 1993 by Gandara, et al, randomized Stage IV-M1 patients with no prior treatment and PS=0-2, to one of 3 arms – standard-dose cisplatin, high-dose cisplatin, and high-dose cisplatin +mitomycin.[x] Approximately 20% of patients on this study had a PS = 2. The median survival on each of the 3 arms was 5.3 months, 6.9 months, and 7.2 months, respectively. These medians are similar to the median survival for the docetaxel 75 mg/m^2 group of TAX 317, but this might be explained by the SWOG study's population having been limited to stage IV disease. A phase 3 study reported by Crawford, et al in JCO, 1996 also limited accrual to patients with stage IV disease.[xi] Eligible patients had to have a KPS ≥70% and no prior treatment. Patients were randomized between 5-FU + leucovorin vs. vinorelbine. The probability of one year survival on the vinorelbine arm was 25% vs. 16% on the 5-FU arm. Median survivals were 30 weeks and 22 weeks, respectively.

These comparisons to historical data are flawed, but the first-line comparisons are interesting because the survival reported is similar to that seen in a second line setting in TAX 317. It is clear that patient selection could account for these similarities. The survival statistics for the best supportive care arms in both the first and second line settings were similar, reinforcing the impact of patient characteristics. The critical impact of the variability of patient characteristics on outcomes of NSCLS clinical trials and their interpretability in attempting comparisons across trials is well-recognized. The higher proportion of IIIB patients in TAX 317 compared to TAX 320 might explain why the difference in survival outcome was improved for docetaxel 75 mg/m^2 in TAX 317 and not in TAX 320. An appraisal of what new information TAX 317 and TAX 320 bring to the second line setting of NSCLC treatment must factor in the following major issues of this review:

- Survival benefit was "established" with retrospectively defined exploratory analyses
- The %1-year survival benefit appears to be associated with the same dose level in both pivotal trials (75 mg/m^2).
- There is no known effective therapy for second line treatment of NSCLC and this patient population is normally excluded from phase 3 studies in lung cancer. The Kaplan-Meier curve for the 75 mg subgroup analysis of TAX 317 strongly suggests clinical benefit in this population, but must be interpreted with great caution because of the issues outlined previously.
- The safety profile for the 75 mg/m^2 dose in this population appears similar to that currently labeled for 100 mg/m^2.

Adherence to statistical doctrines designed to prevent us from accepting an outcome that may well have merely been a result of chance, appear to dictate that one must conclude no definitive survival benefit has been demonstrated in these trials. At 75 mg/m^2, a dose that yields a toxicity profile akin to what is already labeled for 100 mg/m^2, the response rate associated with docetaxel in this disease is extremely low. Clinical benefit in terms of quality of life was not definitively established, although there were trends favoring docetaxel in some analyses. There was no evidence that docetaxel caused deterioration in quality of life relative to the control arms. The clinical issues discussed in the bullets above, lead us to wrestle with whether we are ignoring

clinically meaningful benefit in this population by holding to important statistical rules. The docetaxel 75 mg subgroup of TAX317 seems a clinically relevant group for subset analysis because the interim analysis of that trial necessitated dose reduction for patient safety.

This is a patient population in need of an effective therapeutic option. Whether the statistical issues can be set aside because the clinical data are sufficiently persuasive is an issue pending the ODAC's input.

7 Oncologic Drugs Advisory Committee Meeting Summary

This application was considered at the December 13, 1999 meeting of the ODAC. The following background information and accompanying questions were presented to the Committee for discussion and vote after the presentations of the sponsor and the FDA. The ODAC vote is recorded with each question.

In this supplemental NDA, the sponsor proposes a new docetaxel indication, "for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy," with a labeled dose of 60-75 mg/m^2 intravenously over 1 hour every 3 weeks.

The principal efficacy and safety data are derived from two multi-center, randomized, controlled trials that enrolled patients with NSCLC whose disease had progressed on or after treatment with one platinum based chemotherapy regimen. In TAX 317, patients were randomized to treatment with docetaxel or best supportive care. Upon review of safety in TAX 317, the docetaxel dose was reduced from 100 mg/m^2 to 75 mg/m^2 because of unacceptable toxicity at the higher dose. In TAX 320, patients were randomized to one of 3 arms – docetaxel 100 mg/m^2, docetaxel 75 mg/m^2, and investigator's choice of vinorelbine or ifosfamide.

Efficacy

- **Pre-specified Analyses of Survival**

Original analyses. The following table summarizes the pre-specified survival analyses from the two principal trials in the original supplemental application. In TAX317, data for docetaxel 100 and 75 mg/m^2 have been pooled. Note that the 100mg/m^2 dose is not being considered for approval due to unacceptable toxicity.

Original Analyses	TAX317		TAX 320		
	Docetaxel 100 + 75 mg/m^2 N = 104	Best Supportive Care N = 100	Docetaxel 100 mg/m^2 N=125	Docetaxel 75 mg/m^2 N=125	Control (V/I) N= 123
Median Survival	7.2 months	4.7 months	5.5 months	5.7 months	5.6 months
95% CI	(5.5, 9.2)	(3.7, 6.0)	(4.6, 6.6)	(5.1, 7.9)	(4.3, 7.9)

	log rank p=0.14	Doc 75 vs. V/I: log rank p = 0.14 Doc 100 vs. V/I: log rank p = 0.93

Updated Analyses. In TAX 317, the updated analysis of survival conducted in September 1999 favored the docetaxel arm (data for 100 and 75 mg/m^2 pooled), with p = 0.047, as shown below.

Updated Pre-specified Analyses	TAX317		TAX 320		
	Docetaxel 100 + 75 mg/m^2 N = 104	**Best Supportive Care N = 100**	**Docetaxel 100 mg/m^2 N=125**	**Docetaxel 75 mg/m^2 N=125**	**Control (V/I) N= 123**
Median Survival	7.0 months	4.6 months	5.5 months	5.7 months	5.6 months
95% CI	(5.5, 9.0)	(3.7, 6.0)	(4.6, 7.2)	(5.1, 7.1)	(4.4, 7.9)
	log rank p=0.047		Doc 75 vs. V/I: log rank p = 0.13 Doc 100 vs. V/I: log rank p = 0.58		

- **Survival Analyses (Docetaxel 75 mg/m^2 dose only), Not Pre-specified**

Original Analyses. The following table summarizes the median survival and % 1-year survival data for the docetaxel 75 mg/m^2 dose level only for each phase 3 study submitted in the original supplemental application. The shading in the table designates a comparison that was prospectively defined. The median survival favors the docetaxel 75 mg/m^2 arm in TAX 317. The % 1-year survival favors the docetaxel 75 mg/m^2 arm in both studies.

Original Analyses	TAX317		TAX 320	
	Docetaxel 75 mg/m^2 N = 55	**Best Supportive Care/75 N = 49**	**Docetaxel 75 mg/m^2 N=125**	**Control (V/I) N= 123**
Median Survival	9.0 months*	4.6 months	5.7 months	5.6 months
95% CI	(5.5, 13.1)	(3.7, 6.1)	(5.1, 7.9)	(4.3, 7.9)
			log rank p = 0.14	
% 1-year Survival	40%*	16%	32%*	19%
95% CI	(26, 54)	(3, 30)	(23, 40)	(12, 26)

*Unadjusted p < 0.05, per FDA

Updated Analyses. The following table summarizes the updated analyses (September 1999) of median survival and % 1-year survival for the docetaxel 75 mg/m^2 dose level only. The

comparison shown in the shaded portion of the table represents a prospectively defined analysis. The median survival and % 1-year survival favors the docetaxel 75 mg/m^2 arm in TAX 317 only.

Updated Analyses	TAX317		TAX 320	
	Docetaxel 75 mg/m^2 N = 55	Best Supportive Care/75 N = 49	Docetaxel 75 mg/m^2 N=125	Control (V/I) N= 123
Median Survival	7.5 months*	4.6 months	5.7 months	5.6 months
95% CI	(5.5, 12.8)	(3.7, 6.1)	(5.1, 7.1)	(4.4, 7.9)
			log rank p = 0.13	
% 1-year Survival	37%*	12%	30%	20%
95% CI	(24, 50)	(2, 23)	(22, 39)	(13, 27)

*Unadjusted $p < 0.05$, per FDA

1. **Are the median and %1-year survival data presented for docetaxel 75 mg/m^2 adequate to demonstrate a survival benefit associated with this docetaxel dose in the second-line treatment of NSCLC?**

YES = 10
NO = 2
ABSTAIN = 1

- **Other Efficacy Outcomes**

Additional efficacy outcomes are tabulated below (per FDA). The comparisons shown in the shaded portion of the table represent prospectively defined analyses. The remaining comparisons were not pre-specified.

Original Analyses	TAX317		TAX 320	
	Docetaxel 75 mg/m^2 N = 55	Best Supportive Care/75 N = 49	Docetaxel 75 mg/m^2 N=124	Control (V/I) N= 122
Time to Progression	12.3 weeks*	7.0 weeks	8.3 weeks	7.6 weeks
95% CI	(9.0, 18.3)	(6.0, 9.3)	(7.0, 11.7)	(6.7, 10.1)
			log rank p = 0.07	
Response Rate	5.5%	NA	4.8%**	0.8%
95% CI	(1.1,15.1)	-	(1.8, 10.2)	(0.0, 4.5)

			Fisher's Exact p = 0.12

*Unadjusted $p < 0.05$, per FDA; $p < 0.001$ for the pre-specified comparison of docetaxel 100 and 75 mg/m^2 pooled vs. best supportive care

**This percentage was the FDA response rate prior to agreeing to addition of one additional PR to the 75 mg/m^2 dose arm of this study which resulted in a 5.7% response rate (95% CI = 2.3, 11.3; p=0.04)

APPEARS THIS WAY
ON ORIGINAL