	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
Deaths due to Drug-related Toxicity	3/125 2.4% 3/121 = 2.5%	+3=6/121 = 5.0%*	0	+4/121 = 3.3%	2/123 1.6% 2/119 = 1.7%	+2=4/119 = 3.4%
Deaths Within 30 days of Last Infusion, All Causes	17/125 13.6% 17/121 = 14.1%		13/125 10.4% 13/121 = 10.7%		11/123 8.9% 11/119 9.2%	

***There was an additional death on the docetaxel 100 mg/m^2 arm that occurred on Day 36 after the last infusion attributed by the investigator to toxicity (Pt. 10083). This brings the toxicity related death total to 7/121 = 5.9%.**

The reviewer had the following disagreements with the sponsor's assignments of causality of death relationship with drug toxicity:

Docetaxel 100 mg

1. Pt. 10021 was admitted to the hospital in cycle 2 Day 4 with acute respiratory distress and pneumonia. (He had been admitted in cycle 1 with neutropenia and pneumonia.) Chest X-ray on the second admission revealed RLL and LLL infiltrates with progression of pneumonia. He expired on day 7. No autopsy. No ANC documented in dataset beyond a high WBC on day of treatment in Cycle 2.

2. Pt. 10372 was admitted Cycle 10 Day 9 with a diagnosis of small bowel obstruction. A pseudomembranous colitis was diagnosed and abdominal films suggested ileus. She expired during a central venous catheter insertion on Day 23 from a PE, possibly related to her immobilization from side effects of treatment.

4. Pt. 10465 was admitted on Day 5 of cycle 1 with dyspnea, myalgia, and lower extremity weakness. Chest X-ray was read as complete consolidation of the right lung and pulmonary fluid. Treatment included G-CSF and antibiotics. The patient died on Day 9. ANC that day was 250.

5. Pt. 10491 was admitted on Day 8 of Cycle 2 with neutropenia, fever, and pneumonia. ANC was 80. Chest X-ray revealed ARDS and he was intubated despite recovery of neutropenia. He developed ventricular tachycardia and cardiac arrest and expired 10 days after admission, attributed to PD. The timing and neutropenia make it difficult to exclude a relationship with treatment.

Docetaxel 75 mg

1. Pt 10084 treated as an outpatient at the hospital on Day 9 of Cycle 1 for dyspnea with IV antibiotics. ANC was 120. He expired at home the same day – attributed to grade 4 pulmonary.

2. Pt 10180 was admitted on Day 15 of Cycle 3 with hypotension and bradycardia, and dyspnea. Death was the same day as admission, attributed to PD.

3. Pt. 10461 neurocortical event death on Day 13 of Cycle 3.

4. Pt. 10492 developed moderate stomatitis, severe neuro-motor toxicity and grade 2 infection in the first cycle of therapy. She withdrew consent on Day 12 and expired 4 days later. Death was attributed to malignant disease.

5. Pt. 10520 was admitted to the hospital on Day 5 of Cycle 1 with neutropenia, fever and pneumonia. Sputum culture was positive. He developed cardiac dysrhythmias, confusion, stomatitis, severe edema and died 6 days after admissions after becoming hypotensive when complaining of back pain.

Control

1. Pt. 10173 was admitted on Day 1 of Cycle 1 with dyspnea. He developed myocardial ischemia and expired the following day after treatment with ifosfamide.

2. Pt. 10002 was treated with vinorelbine and was admitted on Day 13 of Cycle 2 with small bowel obstruction and SVC syndrome. He developed dyspnea, jaundice, and agitation and expired on Day 26 while still in the hospital. PD had been diagnosed on bone scan.

The sponsor responded in a fax dated December 1, 1999 that it agreed with the FDA assessments of death causality in all patients listed above at docetaxel 100 mg/m^2, except **Pt. 10372**. At a meeting between the FDA review team and the sponsor on December 3, 1999, the FDA reviewer agreed to accept that the death of **Pt. 10372** was not toxicity related. With regard to the docetaxel 75 mg/m^2 dose level deaths questioned by the FDA reviewer, the sponsor concurred with the FDA assessment in all but **Pt. 10461**. In the December 3, 1999 meeting between the sponsor and the FDA review team, the FDA reviewer agreed to accept that the death of **Pt. 10461** was not toxicity related. The sponsor concurred with the FDA reviewer's assessment of causality for the control patients listed above.

3.12 Summary

Please refer to the review summary, which correlates the efficacy and safety data from TAX 320 with those data from the second pivotal trial in this application, TAX 317.

4 Pivotal Study – TAX 317 : A Multicenter, Randomized Phase 3 Study of Docetaxel Versus Best Supportive Care in Patients with Non-Small Cell Lung Cancer Previously Treated with Platinum-based Chemotherapy

Trial Accrual Start Date: **November 23, 1994**

Data Cutoff Date: **January 31, 1999 for all analyses except survival**
April 12, 1999 for survival analyses

4.1 Rationale

When this study was designed, first-line chemotherapy for advanced non-small cell carcinoma of the lung generally consisted of a cisplatin-based regimen, and effective "salvage therapy" after first-line therapy had not been defined. Phase 2 studies of docetaxel in this setting justified phase 3 investigation of docetaxel in this disease, and a best supportive care comparator arm was selected because there had been no convincing evidence that there was existing therapy superior to best supportive care in the setting of disease that had progressed despite prior platinum-based chemotherapy (second-line setting). Disease eligibility was based on progression during or after treatment with one platinum-based regimen that could have been administered in the adjuvant or neoadjuvant setting for Stage III disease. Prior taxane exposure was excluded.

4.2 Objectives of the Study

- The primary objective was to evaluate survival in patients with non-small cell lung cancer previously treated with platinum-containing chemotherapy who were treated with either docetaxel or best supportive care
- Comparison of the quality of life of patients in each treatment arm was a secondary objective
- Evaluation of safety, response rate, and duration of response associated with docetaxel treatment in this disease setting was another secondary objective.

4.3 Study Design

This study was an open label, randomized, multi-center phase 3 trial with 36 participating centers located in Europe, Canada, and the United States. One hundred four patients were randomized to the docetaxel arm during the course of this study, and 100 to best supportive care. A protocol amendment after a planned interim analysis resulted in a dose reduction of docetaxel from 100 mg/m^2 to 75 mg/m^2 mid-way through the study. This resulted in 49 patients treated with docetaxel 100 mg/m^2 and 55 treated at the lower dose. Fifty-one patients were randomized to the best supportive care arm during the docetaxel 100 mg/m^2 dosing period of the study. Subsequent to the dose reduction protocol amendment, 49 patients were randomized to best supportive care. Patients were stratified by best response to prior platinum-based therapy (progressive disease vs. other response) and ECOG performance status (0-1 vs. 2). Four possible strata were defined:

Table 38 TAX 317 Patient Stratification

Strata	ECOG Performance Status	Best Response to Prior

		Platinum-Based Therapy
1	0-1	PD
2	0-1	NC, PR, CR
3	2	PD
4	2	NC, PR, CR

A computer generated randomization schedule was used to allocate treatment assignments to the investigator at the time each patient was registered. The information required for stratification was obtained prior to assignment of treatment during the registration process, which was conducted via an automated telephone call.

Reviewer Comment: The sponsor reported in correspondence with the FDA dated 9/10/99 that there were stratification errors made based on both reporting the best response to prior platinum therapy (n=13) and baseline performance status (n=11). Among the 13 stratification errors based on reported best response to prior platinum therapy, 12 were randomized incorrectly on the basis of having PD as a best response to prior therapy, when in fact, the CRF indicated that the response was a non-PD, and only one was randomized in error as a non- PD when, in fact, the patient had had PD as a best response. The 12 participants with an actual more favorable response to prior platinum were distributed among treatment arms as follows: Best supportive care = 4 (three randomized during the period of dosing docetaxel at 100 mg and 1 during the 75 mg docetaxel study period) and docetaxel = 8 (docetaxel 100 mg = 4 and docetaxel 75 mg = 4). Two of the participants also had mis-stratification errors based on performance status (Pt. 05013 randomized to docetaxel 100 mg and Pt. 05509 randomized to docetaxel 75 mg). One (Pt. 05013) was mis-stratified on the docetaxel treatment arm (100 mg) as having had a best response of PD to prior platinum (in contrast to the PR reported on the CRF) and as having a performance status of 0-1, rather than the PS = 2 on the CRF. Pt. 05509 was mis-stratified on the docetaxel treatment arm (75 mg) as having had a non-PD response to prior platinum and a performance status of 2 (CRF = PD was best response and PS = 1).

Six of the performance status errors were mis-stratified as an ECOG performance status of 2, contrary to each having an ECOG PS=1 on the CRF. Those six participants were distributed among the treatment arms as follows: Best supportive care = 2 (both treated during the docetaxel 100 mg dosing study period) and docetaxel = 4 (three docetaxel 100 mg patients and 1 docetaxel 75 mg patient, Pt. 05509 mentioned above). The remaining five were mis-stratified as a performance status ≤ 1, when the PS = 2 on the CRF in 4 of the patients (two best supportive care patients treated during the docetaxel 100 mg study period and two docetaxel patients – one 100 mg and one 75 mg) and PS = 3 in one patient, a best supportive care patient treated during the docetaxel 75 mg dosing period of the study.

The distribution of the stratification factors among treatment arms arising from these errors is summarized below. The control patients are divided into the study period under which they were randomized – before or after the change in docetaxel dose with the interim analysis. During the initial docetaxel 100 mg dose period there were more patients in the favorable category (PS <2 + Non-PD response to prior platinum) on the docetaxel arm compared to the control, whereas there were similar numbers of such patients enrolled in both arms during the 75 mg period.

Note: The differences between some of these groups in Tables 39-40 involve 1-2 patients only.

Table 39 TAX 317 Distribution of Stratification Factor Prognostic Factors Between Arms Pre- and Post Protocol Change Modifying Docetaxel Dose

	Docetaxel					
	100 mg			75 mg		
	PS = 0,1	PS = 2	Total	PS = 0,1	PS = 2	Total
Best Response to Prior Platinum = Non-PD	31 (63%)	9 (18%)	40 (82%)	36 (65%)	9 (16%)	45 (82%)
Best Response to Prior Platinum = PD	7 (14%)	2 (4%)	9 (18%)	5 (9%)	5 (9%)	10 (18%)
Total	38 (78%)	11 (22%)	49	41 (75%)	14 (26%)	55
	Control/100			Control/75		
	PS=0,1	PS = 2	Total	PS=0,1	PS=2	Total
Best Response to Prior Platinum = Non-PD	28 (55%)	12 (24%)	40 (78%)	32 (67%)	7 (15%)	39 (81%)
Best Response to Prior Platinum = PD	8 (16%)	3 (6%)	11 (22%)	7 (15%)	2 (4%)	9 (19%)
Total	36 (71%)	15 (29%)	51	39 (81%)	9 (19%)	48

The distribution of the stratification factor response to prior platinum therapy over disease stage groups within the treatment arms is summarized in the table below, again dividing the best supportive care arm into those randomized before or after the change in docetaxel dose on study. In the second portion of the study there were more patients randomized with locally advanced disease compared to the earlier part of the study, particularly in the docetaxel arm. The proportion of patients with Stage IV disease was highest on the control arm. The distribution of the disease stages by response to prior therapy was similar between the docetaxel 75 mg and the control/75 groups

Table 40 TAX 317 Distribution of Response to Prior Platinum Therapy Between Disease Stages by Treatment Group

	Docetaxel					
	100 mg			75 mg		
	IIIB	IV	Total	IIIB	IV	Total
Best Response to Prior Platinum = Non-PD	7 (14%)	33 (67%)	40 (82%)	15 (27%)	30 (55%)	45 (82%)

Best Response to Prior Platinum = PD	2 (4%)	7 (14%)	9 (18%)	0	10 (18%)	10 (18%)
Total	9 (18%)	40 (82%)	49	15 (27%)	40 (73%)	55
	Control/100			**Control/75**		
	IIIB	IV	Total	IIIB	IV	Total
Best Response to Prior Platinum = Non-PD	8 (16%)	32 (63%)	40 (78%)	10 (21%)	30 (63%)	39 (81%)
Best Response to Prior Platinum = PD	1 (2%)	10 (20%)	11 (22%)	0	9 (19%)	9 (19%)
Total	9 (18%)	42 (82%)	51	10 (21%)	39 (81%)	48

Those patients randomized to the best supportive care arm would have full assessments at 3-week intervals for 18 weeks, the equivalent of 6 cycles, after which they would be considered to have completed treatment on study. Follow-up would then revert to an every 2 month basis.

The study design included a prospectively planned interim analysis when half of the patients had completed 6 cycles or had been discontinued from the study. It was that interim analysis that led to the alteration of the docetaxel dose from 100 mg /m^2 to 75 mg/m^2.

4.3.1 Treatment Plan

The treatment arms in this study were:

ARM #1: **Docetaxel 100 mg/m^2**, one hour infusion, cycled every 21 days (revised to 75 mg/m^2 after the interim analysis). Premedication = Dexamethasone 8 mg per os q 12 hours starting 24 hour before the docetaxel infusion and continuing for a total of 5 doses. Patients in this arm were to receive best supportive care in addition to docetaxel. The protocol specified that if palliative radiotherapy was deemed necessary, progressive disease would be designated at the time of radiotherapy. Patients would be treated with 6 cycles. If they stopped docetaxel treatment before the planned 6 cycles, like the best supportive care arm patients, they would continue the planned q 3 week assessments until the 18 week initial treatment period had ended.

ARM #2: **Best Supportive Care** – as judged by the treating physician, and according to institutional standards. Best supportive care could include analgesics, transfusion, antibiotic, and symptomatic therapy. Radiotherapy that was localized and delivered to alleviate symptoms of pain, cough, dyspnea, hemoptysis was considered best supportive care as long as the total dose was in

the range considered palliative. Best supportive care did not include chemotherapy or other systemic anticancer therapy.

4.3.2 Dose Modifications

On the docetaxel arm grade 4 neutropenia of >7 days duration or associated with fever or parenteral antibiotics prompted either a 25% dose reduction, or initiation of prophylactic G-CSF in subsequent cycles as a first measure, instead of dose reduction. However, if despite G-CSF, grade 4 neutropenia associated with fever or parenteral antibiotic administration recurred, a 25% dose reduction would then have to be applied. Grade 4 thrombocytopenia required 25% dose reduction. A maximum of two dose reductions was permitted.

In terms of non-hematological toxicities, the protocol specified that doses be reduced by 25% for grade 4 vomiting that occurred despite prophylactic antiemetics, grade ≥ 3 diarrhea that occurred despite antidiarrheal treatment, and non-hematological toxicities of grade ≥ 3. Toxicities of grade ≥ 3 prompted holding therapy until resolution to at least grade 1, then reinstitution at a 25% dose reduction "if medically appropriate". Discontinuation from the study was required for grade ≥ 3 peripheral neuropathy. Symptomatic fluid retention prompted administration of diuretics (furosemide, followed by spironolactone if ineffective).

Dose adjustments for abnormal liver function tests follow (a maximum of 2 dose reductions were permitted):

Docetaxel (100mg and 75mg) and Ifosfamide:

Bilirubin		Alkaline phosphatase		SGOT/SGPT	Action
>ULN	or	>5 x ULN	or	>5 x ULN	Wait ≤ 3 weeks. If recovers, dose reduce by 25%. No recovery, then off study
≤ ULN	and	≤5 x ULN	and	1.6 – 5 x ULN	Dose reduce by 25%

Anaphylactic reactions required removal of the patient from study treatment. The protocol specified interventions for hypersensitivity reactions not considered anaphylactic that included administration of diphenhydramine and/or dexamethasone and/or epinephrine as needed. Docetaxel infusions complicated by hypersensitivity reactions would be interrupted and resumed within 3 hours after recovery. If a severe reaction recurred despite additional premedication, the patient was to be removed from study therapy.

4.3.3 Concomitant Therapy

The protocol specified that prophylactic G-CSF administration was optional in lieu of dose reduction in cases of grade 4 neutropenia of >7 days duration or associated with fever or parenteral antibiotics.

Reviewer Comment: Query of the electronic dataset identified 6 patients treated with G-CSF – 3 during the docetaxel 100 mg dose period on study and 3 during the 75 mg docetaxel period. The indication for use in the docetaxel 100 mg patients was "4" adverse event (all but one in cycle 001, the remaining one was in cycle 002), and in two docetaxel 75 mg patients it was coded "5" for prophylaxis (cycle 002 was the first use in both). There were 2 patients identified treated with erythropoietin – one docetaxel 100 mg patient (in cycles 004 and 008, coded "4" adverse event) and one best supportive care arm patient entered during the docetaxel 100 mg dosing period on study - in cycle 001 (coded "6" other).

4.3.4 Evaluation on Study

Monitoring included a baseline history and physical examination (including a complete neurological examination); blood work including hematology, chemistry, and HCG in patients of childbearing potential; 12 lead ECG; ECOG performance status assessment and a quality of life assessment using the LCSS or EORTC Quality of Life Questionnaire for Lung Cancer. Baseline radiographic imaging included a chest X-ray, and, if clinically indicated, CT of the brain, chest and upper abdomen, and radionuclide bone scan.

At the end of each cycle (or on the first day of the next cycle, just prior to infusion) the history and physical examination (including neurological examination, assessment of performance status, and assessment of toxicity), chemistries, and clinical tumor measurements were to be repeated on the docetaxel arm. The best supportive care arm was to have the physical examination, weight, ECOG performance status and neurological examination repeated every 3 weeks. The quality of life assessment with LCSS or EORTC Quality of Life Questionnaire for Lung Cancer was to be completed prior to administration of dexamethasone in each cycle on the docetaxel arm, and every 3 weeks on the best supportive care arm. CBC's were to be repeated during the course of a cycle "as clinically indicated". Hematology was to be checked every 6 weeks on the best supportive care arm, along with the serum chemistries. Chest X-ray and other radiographic tumor assessments were to be repeated (using the same methodology as baseline) every 2 cycles "as required" on both arms.

Participants treated with docetaxel were to be given a thermometer at the time of first treatment and instructed how to use it. They were to record their temperature twice a day in a log book that was to be reviewed with the participant prior to each cycle of treatment. Mandatory monitoring of all participants treated with docetaxel was outlined in the protocol, and it was 'recommended" that similar guidelines be followed on the best supportive care arm. That monitoring included telephone contact a minimum of twice during the treatment cycle (at least one contact between Day 5 and 7 of the cycle). The telephone contact within a week of treatment was to include a review of the temperature for that day, a review of measures to prevent infection, a review of symptoms of infection, and a reminder that docetaxel patients were at high risk for infection. The remaining telephone contact was to check on the well-being of the patient and reinforce risks of infection and the importance of seeking immediate attention for symptoms of infection.

At completion of study therapy, all the baseline assessments were to be repeated 30 days after the last drug administration, with the exception of the height, HCG, and ECG. The latter would be checked only if clinically indicated. Subsequently, every 2 months radiographic and clinical tumor assessments would be performed until disease progression had been documented in patients who had responded "on docetaxel therapy". Lab work would be done only as clinically indicated. Weight and assessments of performance status, LCSS, and toxicity would be performed every 2 months after completing the initial 18 week active study period.

All participants were to be followed the first 18 weeks on study as if they were being treated with docetaxel, even if the docetaxel treatment was terminated before reaching cycle 6. If a best supportive care arm patient could not meet the every 3 week schedule, or received a systemic anticancer therapy during the initial 18 week study period, they were to continue follow-up every 3 weeks until the 18 week period was completed.

4.3.5 Efficacy Evaluation Requirements

Patients were required to have measurable or evaluable lesions to be eligible for the study. Evaluable disease included disease in which *only one dimension could be defined*, which included palpable soft tissue or abdominal masses and lung lesions not completely surrounded by aerated lung, but with one definable dimension. Such unidimensional lesions were required to be ≥1 cm on physical exam or chest X-ray, and ≥ 2 cm by CT or MRI. Non-measurable but evaluable disease was defined in the protocol as including confluent multinodular lung metastases, confluent skin metastases, lymphangitic pulmonary metastases, osteolytic bone metastases, and bi- and uni-dimensional lesions that did not meet the minimum size requirements set forth in the protocol. The minimal bidimensional measurement on CT was 2 cm in one dimension, and on chest X-ray and clinical exam the minimum in both dimensions was 1 cm. Lesions considered non-evaluable included osteoblastic bone lesions, any lesion in a field of prior irradiation that had not progressed, malignant effusions, palpable masses not measurable in at least one dimension, carcinomatous lymphangitis of the skin and lung, and diffuse hepatomegaly without radiographically measurable lesion.

Baseline radiographic imaging on this study included a chest X-ray, and, if clinically indicated, CT of the brain, chest and upper abdomen, and radionuclide bone scan. At the end of each cycle (or on the first day of the next cycle, just prior to infusion) the history and physical examination (including assessment of performance status), clinical tumor measurements, and quality of life assessment were to be repeated on the docetaxel arm. On the best supportive care arm these were to be repeated every 3 weeks. The LCSS or EORTC Quality of Life assessment was to be completed prior to administration of dexamethasone in each cycle on the docetaxel arm, and every 3 weeks on the best supportive care arm. Radiographic tumor assessments were to be repeated (using the same methodology as baseline) every 2 cycles (or 6 weeks on the best supportive care arm) "as required".

At completion of study therapy, the baseline assessments were to be repeated 30 days after the last drug administration. Subsequently, radiographic and clinical tumor assessments would be performed every 2 months until disease progression had been documented in patients who had responded "on docetaxel therapy". Weight, assessments of performance status, and completion of the LCSS or EORTC Quality of Life assessment would be performed every 2 months after completing therapy.

4.4 Inclusion/Exclusion Criteria

4.4.1 Inclusion Criteria

- Age ≥ 18 years
- Histologically or cytologically confirmed non-small cell lung carcinoma
- Unresectable locally advanced or metastatic non-small cell lung carcinoma.
- Disease must have progressed while on or after treatment with one platinum based regimen, which could have been administered adjuvantly, neoadjuvantly, or as part of combined modality therapy.
- ECOG performance status 0-2
- Measurable and/or evaluable lesion(s).
- Signed informed consent
- WBC count ≥ 3500/mm^3, ANC ≥2000/mm^3, platelet count≥ 100,000/mm^3, creatinine ≤ 2.0 mg/dL or creatinine clearance ≥60 ml/min, total bilirubin ≤ ULN, SGOT and/or SGPT ≤ 1.5 x ULN, alkaline phosphatase ≤5 x ULN.
- No evidence of myelodysplastic syndrome or abnormal bone marrow reserve by history or routine hematologic testing.

4.4.2 Exclusion Criteria

- Pregnant or lactating women or women of childbearing potential not using effective contraception
- History of other malignancies likely to relapse within study period
- Symptomatic or uncontrolled brain metastases
- Radiation therapy to >10% of bone marrow or to a target lesion within 30 days prior to entry. Total radiation therapy > 25% of bone marrow.
- Peripheral neuropathy of grade ≥3
- Chemotherapy, immunotherapy or biological systemic anti-neoplastic therapy within 21 days prior to entry (42 days for mitomycin and nitrosoureas).
- Prior docetaxel or paclitaxel
- Serious intercurrent illness
- Participation in a clinical trial or one or more experimental agents within 30 days of entry

4.5 Protocol Amendments

The content and dates of a six protocol amendments are summarized below. Enrollment on the study started November 23, 1994.

4.5.1 Amendment #1 – April 14, 1995

- Eligibility criteria were reworded from "Stage III or IV disease" to "locally advanced and/or metastatic NSCLC".
- LDH was added to the pretreatment laboratory evaluations. Electrolytes and magnesium were deleted from on-study laboratory evaluations.

- Patients with peripheral neuropathy of NCI grade 2 were deemed eligible.
- Appendix III, Neurologic Examination, was removed to allow investigators to use examination methods they deemed appropriate for neurological examination.
- Dose reductions for grade 3 neutropenia with fever were removed.
- Provisions were made for docetaxel arm patients to be followed every 3 weeks for the first 18 weeks on study , regardless of whether they received drug.
- Provisions were made for best supportive care participants no longer able to meet the every 3 week examination schedule during the first 18 weeks on study to be followed every 3 weeks by telephone or fax for that period, after which they could be followed at 2-month intervals.
- The Partial Response category was changed to include bidimensionally measurable disease only. A response category of "improvement" was added to cover unidimensional and non-measurable disease.
- Additions were made to accommodate the addition of Canadian study centers.
- A comment was added indicating that for chest X-ray's, posteroanterior and lateral views were preferred.
- Abnormal values no longer required a comment on the laboratory report.
- Requirement for non-polyvinyl chloride infusion bag and infusion tubing was added.

4.5.2 Amendment #2 – July 19, 1995

- Inclusion/exclusion criteria involving liver function test requirements and dose reduction for abnormal liver function testes were redefined to reflect current available information.
- Provision that patients with Grade 4 neutropenia lasting > 7 days with fever requiring parenteral antibiotics could be treated in subsequent cycles with G-CSF x10 days in lieu of the first dose reduction.
- Provision that either AST of ALT could be part of the pre-study and on-study chemistry evaluations.
- The "improvement" response category was added to the table for determining overall response.
- Administrative change to make the required chemistry tests consistent throughout the protocol.

4.5.3 Amendment #3 – August 8, 1995

A protocol modification to meet drug preparation and delivery regulations in Canada.

4.5.4 Amendment #4 – June 27, 1996

- The protocol was opened to additional sites worldwide.
- The dose of dexamethasone premedication was changed from 8 mg PO BID x 5 days to 8 mg PO BID x 5 doses starting the day before docetaxel infusion.
- The requirement that continuous ECG monitoring be established in the event of bradycardia was eliminated.
- The protocol section describing follow-up tests was changed to reflect the CRF.
- A clarification was added to utilization of a table to determine overall response at each cycle of treatment.

4.5.5 Amendment #5 – July 3, 1996

- The protocol was modified so that the European sites would use the EORTC Quality of Life Questionnaire for Lung Cancer.

4.5.6 Amendment #6 – January 31, 1997

- **The dose of docetaxel was reduced from 100 mg to 75 mg/m^2 because of higher than expected toxic death rate.**
- The required Day 10 CBC/DIFF with platelet count was dropped for each cycle. The protocol now required that these be performed as clinically indicated throughout the balance of the treatment cycle.
- The Educational Pamphlet was added to the appendix (labeling).
- New monitoring guidelines were added.
- A Canadian version of the protocol was created, which contained the international drug preparation and labeling instructions.

4.6 Enrollment, Protocol Violations, Removal From Study

Sites in five countries accrued patients to TAX 317. The countries with highest accrual were Canada (90/204 total participants), USA (60/204 total participants), and Poland (16/204). One Canadian one investigator was responsible for accruing 58/90 patients, and in the US the highest single accruing site enrolled 11/60 patients. **The bulk of US study accrual occurred in the first portion of the study, when docetaxel was administered at 100 mg/m^2 – 56/60 entered at US sites were entered in the first portion of the study.** (The US accrual accounted for over half of the patients entered in the first dosing period of the study.) In Canada, 53/90 patients were entered in the docetaxel 75 mg treatment phase of the trial. All of the patients enrolled in the European sites, except for 4 patients entered in Finland, were randomized in the second portion of the study.

All randomized patients were "treated". Three participants on the docetaxel arm (one randomized during the initial 100 mg phase, and the remaining two during the 75 mg phase) and 7 participants on the best supportive care arm (three during the 100 mg phase of the study and 4 during the docetaxel 75 mg phase) were found to be ineligible. One, a participant on the best supportive care (100 mg phase) arm was ineligible on the basis of histology (breast carcinoma), and another, a docetaxel 100 mg patient had inadequate confirmation of cancer diagnosis. One participant on the best supportive care arm (100 mg phase) was ineligible on the basis of an AST that was >1.7 x ULN. Elevated creatinine levels excluded 2 participants – one docetaxel 75 mg patients and one best supportive care (100 mg phase) patient. The remaining five patients (one on the docetaxel 75 mg arm and four on best supportive care – 75 mg phase) were ineligible on the basis of missing baseline laboratory values. One of those patients, Pt. 05236 in the best supportive care (75 mg) group also had an ECOG PS too poor for eligibility – 3.

The patients ineligible for study participation were considered inevaluable for efficacy. There were two additional participants considered inevaluable for efficacy (both on the docetaxel 100 mg arm) because they were treated with radiotherapy on the same day as their cycle 001 infusion. Participants were also considered inevaluable for response if they were ineligible, had missing

tumor assessments, incomplete tumor assessments beyond baseline, or received only one cycle of docetaxel. A total of 25 docetaxel patients met one of these criteria for inevaluability for response – 14 in the docetaxel 100 mg treatment phase of the trial and 11 in the 75 mg phase. Seven of the docetaxel 100 mg patients had no tumor assessments after baseline or cycle 001, or had no tumor assessments in Cycles 1 and 2. Three docetaxel 100 mg received only one cycle of treatment. Five of the docetaxel 75 mg patients were inevaluable on the basis of no tumor assessments after baseline or cycle 1, and three for receiving only one cycle of therapy.

4.7 Patient demographics and baseline characteristics; tumor characteristics

Randomization was stratified for performance status (0-1 vs. 2) and best response to prior cisplatin chemotherapy. There were 13 stratification errors on the basis of best response to prior cisplatin chemotherapy in this study, and 11 were mis-stratified on the basis of performance status. Please refer to **Section 4.3 Study Design** of this review for a detailed discussion of the impact these stratification errors had on the distribution of prognostic factors across treatment arms. That discussion pointed out that there were differences in patient characteristics between the two phases of the study – the early docetaxel 100 mg dosing period and the later docetaxel 75 mg dosing period. Because of these differences, the sponsor has pointed out that pooling of the groups for comparisons could be misleading. The pooled data shows that the overall study populations between arms were relatively well-balanced, although slightly more females were enrolled on the best supportive care arm. This slight imbalance in distribution of genders across study arms held up over both study periods. The balance between arms in distribution of ECOG performance status = 2 patients seen in the pooled study population, unravels slightly when looking at each of the study periods individually. In the early portion of the trial, there were somewhat more patients with PS = 2 on the best supportive care arm, and the opposite relative distribution occurs in the second portion of the trial, with more PS=2 patients appearing on the docetaxel 75 mg arm. These relationships are summarized in the table below.

Table 41 TAX 317 Comparison of Patient Demographics by Enrollment Period; Derived from Sponsor Tables 21 and 22 in Study Report; Volume 68.2, pages 85 and 86.

	Overall Docetaxel	Overall BSC	Docetaxel 100 mg	BSC/100	Docetaxel 75 mg	BSC/75mg
Median Age	61 y	61 y	61 y	63 y	61 y	56 y
Female	30.8%	35.0%	24.5%	29.4%	36.4%	40.8%
Male	69.2%	65.0%	75.5%	70.6%	63.6%	59.2%
PS = 0	16.3%	22.0%	8.2%	15.7%	23.6%	28.6%
PS = 1	59.6%	53.0%	69.4%	54.9%	50.9%	51.0%
PS = 2	24.0%	25.0%	22.4%	29.4%	25.5%	20.4%

Collapsing the two treatment arms and comparing the same demographics between the two study periods demonstrates that there was a higher percentage of females enrolled in the second portion

of the study, that patients were somewhat younger, and that the proportion with PS = 0 was higher in the second study period. This is summarized in the table below.

Table 42 TAX 317 Comparison of Patient Demographics Across Study Periods; Derived from Sponsor Table 23 Patient Demographics by Enrollment Period in Vol. 68.2, page 87.

	First Study Period (100 mg)	Second Study Period (75 mg)
Median Age	62	58
Female	27%	38.5%
Male	73%	61.5%
PS = 0	12.0%	26.0%
PS = 1	59.6%	53.0%
PS = 2	26.0%	23.0%

Similarly, there were differences across study periods for categories of tumor characteristics and prior treatment (summarized in the table below).

Table 43 TAX 317 Comparison of Tumor Characteristics and Treatment History Across Enrollment Periods. Derived from Sponsor Tables 27, 28, 30 and 31 in Volume 68.2, pages 89, 90, 92 and 93.

	Overall Docetaxel	Overall BSC	Docetaxel 100 mg	BSC/100	Docetaxel 75 mg	BSC/75mg
	Disease Extent					
Locally advanced	23.1%	19.0%	18.4%	17.6%	27.3%	20.4%
Metastatic	76.9%	81.0%	81.6%	82.4%	72.7%	79.6%
	Number of Organs Involved					
1	33.7%	33.0%	20.4%	27.5%	45.5%	38.8%
2	37.5%	34.0%	46.9%	31.4%	29.1%	36.7%
≥3	28.8%	33.0%	32.7%%	41.2%	25.5%	24.5%
	Measurability					
Bidimens.	81.7%	70.0%	87.8%	76.5%	76.4%	63.3%
Unidimens.	12.5%	8.0%	12.2%	3.9%	12.7%	12.2%
Evaluable Only	5.8%	22.0%	0	19.6%	10.9%	24.5%

	Number of Prior Chemotherapy Regimens					
1	74.0%	76.0%	67.3%	74.5%	80.0%	77.6%
2	14.4%	15.0%	16.3%	17.6%	12.7%	12.2%
≥3	11.5%	9.0%	16.3%	7.8%	7.3%	10.2%
Median Time – Last Chemotx to Randomization	3.0 mo	3.4 mo	2.8 mo	3.7 mo	3.5 mo	2.8 mo
	Response to Prior Platinum					
Non-PD	81.7%	80.0%	81.6%	78.4%	81.9%	81.6%
PD	18.3%	20.0%	18.4%	21.6%	18.2%	18.4%
	Other Therapy					
Prior XRT	41.3%	43.0%	38.8%	49.0%	43.6%	36.7%
Prior Surgery	13.5%	9.0%	12.2%	11.8%	14.5%	6.1%

Collapsing the two treatment arms and comparing the same tumor characteristics and prior treatment histories between the two study periods reveals a higher percentage of IIIB disease enrolled in the second portion of the study, as did fewer patients with ≥3 organs involved, and a somewhat higher percentage of evaluable only disease. There were fewer prior treatment regimens in patients enrolled in the second portion of the study, but the distribution of non-PD to PD as best response to prior platinum was similar. The reviewer examined the relative distribution of number of prior regimens in those patients with IIIB disease patients among treatment arms, and found they were very similar - 78-80% were treated with only one prior regimen. The maximum number of prior regimens in the IIIB subgroup was 3: 11% of the docetaxel 100 mg IIIB patients, 13% of the docetaxel 75 mg IIIB patients, 0% of the best supportive care/100 mg patients, and 10% of the best supportive care/75 mg patients. There were 7 patients in this study who had IIIB disease and a pleural or pericardial effusion (n=1). Two were treated with docetaxel 100 mg/m^2, 3 with docetaxel 75 mg/m^2 and there was one patient in each of the best supportive care study periods. These issues are summarized in the table below.

Table 44 TAX 317Comparison of Tumor Characteristics and Treatment History Across Study Periods; Derived from Sponsor Tables 29 and 32; Volume 68.2, pages 91 and 94.

	First Study Period (100 mg)	Second Study Period (75 mg)

	First Study Period (100 mg)	Second Study Period (75 mg)
Disease Extent		
IIIB	**18%**	**24%**
IV	82%	76%
Number of Organs Involved		
1	**24.0%**	**42.3%**
2	39.0%	32.7%
≥3	**37.0%**	**25.0%**
Measurability		
Bidimensional	82%	70.2%
Unidimensional	8.0%	12.5%
Evaluable Only	10.0%	**17.3%**
No. of Prior Chemotx Reg's		
1	**71.0%**	**78.8%**
2	17.0%	12.5%
≥3	**12.0%**	**8.7%**
Response to Prior Platinum		
Non-PD	80.0%	81.7%
PD	20.0%	18.3%
Median Time from last Chemotx to Randomiz.	3.2 mo	3.1 mo
Prior Radiation	44.0%	40.4%
Prior Surgery	12.0%	10.6%

Reviewer Comment: The reviewer also examined the electronic dataset for differences between treatment arms in baseline LDH and relative distribution of patients with ≥10% weight loss at study entry. A higher percentage of participants on the best supportive care arm in both the first and second study periods had a baseline LDH ≥ ULN. A higher percentage of the best supportive care patients in the early study period had experienced ≥10% weight loss at study entry compared to the docetaxel 100 mg arm, but in the second portion of the study distribution between arms was more even.. These findings are summarized in the table below.

Table 45 TAX 317 Comparison of Baseline LDH and Extent of Weight Loss Across Treatment Groups and Study Periods

	Overall Docetaxel	Overall BSC	Docetaxel 100 mg	BSC/100	Docetaxel 75 mg	BSC/75mg
LDH ≥ ULN	27%	**39%**	29%	**40%**	25%	**39%**
≥10% Weight loss	9%	13%	10%	**18%**	7%	8%

The reviewer also examined the electronic dataset to compare the distribution of patients who were on supplemental oxygen at baseline. She identified 7 on the docetaxel arm (docetaxel 100 mg = 3 and docetaxel 75 mg = 4), and 7 on the best supportive care arm (best supportive care/100 = 5 and best supportive care/75 = 2).

4.8 On-study Treatment

All of the patients on the docetaxel arm were administered at least one cycle of chemotherapy on study. The median number of cycles delivered in the 100 mg/m^2 treatment group was 2, and 67.9% of cycles were administered at full dose. The median number of cycles delivered in the 75 mg/m^2 group was 4, and 68.9% were administered at full dose. The maximum number of cycles delivered to one patient was 22.

Doses were reduced in 22/187 (11.8%) cycles of docetaxel 100 mg/m^2 and in **40.8%** of patients. Delays occurred in 28/187 (15.0%) cycles. 4.3% of docetaxel 100 mg/m^2 cycles were delayed longer than 7 days. The total number of patients who experienced delays longer than 3 days was 21/49 (42.8%). The most common reason given for treatment delay by cycle and patient was "other" (22.4% by patient), followed by hematological toxicity (2.7% of cycles; 10.2% of patients). "Other" reasons found in the CRF's included holidays, storm, scheduling conflicts, and WBC elevation. Non-hematological toxicity followed - 6.1% by patient and 1.6% by cycle.

Doses were reduced in 18/264 (6.8%) cycles of docetaxel 75 mg/m^2 and in **29.1%** of patients. Delays occurred in 23/264 (8.7%) cycles. 2.3% of cycles were delayed longer than 7 days. The total number of patients who experienced delays longer than 3 days was 18/55 (30.9%). The most common reason given for treatment delay by cycle and patient was "other" (10.9% by patient), followed by "non-drug related" (12.7% of patients; 3.0% of cycles). Hematological toxicity and non-hematologic toxicity followed at 1.8% each by patient, and 0.4% each by cycle. Reason for delay was missing in one patient. The relative modifications and delays between the two docetaxel dose levels on TAX 317 are summarized in the table below.

Table 46 TAX 317 Dose Reductions and Dose Delays by Docetaxel Dose – 100 mg or 75 mg/m^2. Derived from Sponsor Tables 56, 58, and 60. Volume 68.2 ; pages 132, 133, and135.

	By-Patient		By-Cycle	
	Docetaxel 100 mg/m^2	**Docetaxel 75 mg/m^2**	**Docetaxel 100 mg/m^2**	**Docetaxel 75 mg/m^2**
Dose Reduction	**40.8%**	**29.1%**	**11.8%**	**6.8%**
Reduced for:				
Heme Toxicity	26.5%	16.4%	7.0%	3.4%
Non-Heme Tox.	4.1%	1.8%	1.1%	0.4%
Heme & Non-Heme Tox	1.8%	0	0.5%	0
Other	8.2%	0	2.1%	0
Dose Delay	**34.7%**	**25.5%**	**15.0%**	**8.7%**
Delay 3-7 days	30.6%	20.0%	10.7%	6.4%
Delay >7 days	12.2%	10.9%	4.3%	2.3%
Delayed for:				
Heme toxicity Non-	10.2%	1.8%	2.7%	0.4%
Heme Tox	6.1%	1.8%	1.6%	0.4%
Heme & Non-heme Tox	1.8%	0	0.5%	0
Non-drug related	4.1%	12.7%	1.1%	3.0%
Other	22.4%	10.9%	9.1%	4.5%

Unlike the other pivotal trial in this application, TAX 320, in which the two docetaxel treatment arms (100 mg and 75 mg) were similar in the percentage of cycles and patients impacted by treatment delays, but not dose reduction, both dose reductions and dose delays were more common at docetaxel 100 mg/m^2 in TAX 317. The smaller percentage of by-cycle dose reductions on the docetaxel 100 mg arm in TAX 320 likely reflected that protocol's specified practice of administering G-CSF in lieu of the dose reductions performed in the other treatment arms. The TAX 320 study report did not discuss absolute numbers of patients who were administered doses at a **reduced dose**. The reviewer determined through her examination of the DoseEval electronic dataset that there were **25/121 (21%) treated patients** on the TAX 320 docetaxel 75 mg arm that underwent planned dose reduction (code = 2) – a higher percentage than the docetaxel 100 mg arm.

The sponsor compared dose delivery on study among treatment groups using Relative Dose Intensity, the ratio of the actual dose intensity, expressed as mg/m^2/ week, to the planned dose intensity. The following formula expresses this ratio:

$$\frac{\text{[Total Actual Dosed received (mg/m}^2\text{)/Actual number of weeks on study]}}{\text{[Total Planned Dose (mg/m}^2\text{)/ Total number of cycles x 3 weeks]}}$$

The sponsor determined that the docetaxel 100 mg/m^2 treatment group dose intensity was 0.92. It was 0.99 in the docetaxel 75 mg/m^2 treatment group. The median cumulative dose was 211 mg/m^2 in those patients treated with 100 mg /m^2, and 299 mg/m^2 in those treated with 75 mg/m^2. In TAX 320 the sponsor determined that the docetaxel 100 mg/m^2 arm dose intensity was 0.99, while that of the docetaxel 75 mg/m^2 arm was 0.98.

4.9 Endpoints/Statistical Considerations

The primary endpoint in this study was survival - measured from the date of randomization to date of death. The study's sample size estimation was based on the assumption that the median survival for docetaxel (100 mg) and best supportive care would be 7 months and 4 months, respectively, that the patient accrual time would be 10 months, and that the follow-up after the last patient enrollment would be 5 months. It was estimated a sample size of 100 patients per arm would yield 90% power and a Type I error rate of 5%, two-sided, utilizing the log rank test. The pre-specified comparison of interest was the differences between the docetaxel arm and the best supportive care control, utilizing the log rank test. An interim analysis was pre-specified to be performed after 50% of patients had completed 6 cycles of docetaxel or discontinued the study. The primary endpoint of interest in the interim analysis was time to death or point of censoring. The log-rank test would have to reach 0.005 to be considered significant in this interim analysis, using the O'Brien-Fleming method. Given the plan for an interim analysis, the protocol specified that to be statistically significant in the final analysis the log rank test must reach 0.047. The protocol's statistical analysis section did not include the criteria for censoring for survival.

The statistical analysis plan, dated 5/26/99, stated that the Kaplan-Meier method would be utilized and that the median survival and the Kaplan-Meier estimates would be reported with a 95% CI. The plan stated that survival would be compared between the two groups with a log rank test, and the criteria for censoring were specified as follows: loss to follow-up, no death before the cut-off date, and further anticancer therapy including radiotherapy, chemotherapy,

surgery, and immunotherapy. The statistical analysis plan stated in its discussion of the interim analysis that its main purpose was to evaluate safety and minimize the number of patients exposed to inferior treatment. Other analyses to be performed at the interim were listed as follows:

- Patient demographics and characteristics
- Number of patients violating the protocol by taking systemic chemo- or immunotherapy
- Drug delivery – cycles, cumulative dose, relative dose intensity
- Survival
- Quality of life, utilizing the LCSS Total scores and subscale scores
- Safety – adverse events, hematologic toxicity, biochemistry.

Time to progression was not included as a secondary endpoint in the protocol, although response and duration of response were. Time to progression does appear in the statistical analysis plan dated 5/26/99. In that plan it was to be measured from the date of randomization to date of disease progression, or to the date of last assessment prior to further antitumor therapy, including radiation. Kaplan-Meier estimates were to be performed and median times to progression reported with a 95% CI. Comparisons between the two groups would be made with the log rank test. The statistical analysis plan's criteria for censoring TTP included: loss to follow-up, no PD or death before study cut-off date, and further anticancer therapy (radiotherapy, chemotherapy, surgery, immunotherapy) before the first progression

Response and Duration of Response were protocol-defined secondary endpoints. The protocol stated that objective responses included CR's and PR's, and that response rates would be evaluated separately in patients with bidimensionally measurable disease and patients with evaluable disease. Duration of response was to be measured from the time of initial dose of docetaxel to the time of progression in PR's. For CR's it was to be measured from the time of initial documentation of CR, according to the protocol. In the 5/26/99 statistical analysis plan the duration of response in responders (CR + PR) was to be determined from randomization to the first documentation of progression, with death considered an event. Censoring specified in the statistical analysis plan included further anticancer therapy (chemotherapy, radiotherapy, surgery) at the date of the last assessment before therapy. The Kaplan-Meier estimates and median duration of response would be expressed with the 95% CI. The best overall response was to be confirmed by two evaluations taken at least 4 weeks apart. An assessment of no change (NC) required at least 6 weeks to have passed from the time of starting treatment.

Response criteria set forth in the protocol indicated that all unidimensional and bidimensionally measurable lesions should be measured at each assessment, but when multiple lesions made it impossible to do, a maximum of 6 measurable target lesions representing all organs involved were to be selected, giving priority to the bidimensionally measurable lesions. Complete response was defined as disappearance of all clinical evidence of tumor for a minimum of 4 weeks, and all disease sites had be reevaluated at the 4 week confirmation examination. PR's were defined in the protocol for bidimensionally measurable lesions only. A PR was defined as a ≥50% decrease in the sum of the products of the perpendicular diameters of bidimensionally measurable lesions for a minimum of 4 weeks, with no simultaneous increase of another lesion by ≥25% or appearance of new lesion. Progressive disease was defined as a ≥25% increase in size of a bidimensionally or unidimensionally measurable lesion, a "clinically significant" increase in size of a non-measurable lesion (as determined by the individual investigator) or the appearance of an unequivocal new lesion. "No change" was any change that did not meet the criteria of CR, PR, or PD. Unidimensionally measurable disease that decreased by at least 50% in the sum of the largest diameters of all lesions could be assigned a response of "Improvement", as could non-

measurable evaluable disease that decreased by at least 50% in the estimated area of tumor mass, if ***agreed upon by two independent observers***. Pleural effusions were not considered eligible for such an assessment.

The quality of life secondary endpoints that were defined in the protocol included:

- LCSS/EORTC Quality of Life Questionnaire for Lung Cancer score changes from baseline. The protocol stated that this analysis would include an analysis of area under the curve of the LCSS/ EORTC Quality of Life Questionnaire for Lung Cancer scores during the first 18 weeks in change from baseline to compare the two study groups, utilizing the analysis of variance method.
- Changes of weight. Comparisons would be made using an analysis of variance method for comparison.
- Changes in ECOG performance status. Comparisons would be made using an analysis of variance method for comparison.
- Changes in analgesic use. Comparisons would be made using an analysis of variance method for comparison.

The statistical analysis plan, 5/26/99, stated that there would be a factor analysis on the baseline evaluation of the LCSS to examine correlation structure of the 15 items, in an attempt to identify any independent clusters of symptoms "so that specificity for the scale will be enhanced". All patients with an evaluable baseline assessment and at least one assessment during the 18 weeks of the study's dosing phase would be included in the analysis of each scale. **If a QoL evaluation was missing data, the missing valued would be replaced by the overall mean of the given item if more than 50% of the items were missing** (page 17 of the statistical analysis plan). The QoL data from both instruments utilized in the study were to be analyzed separately, ant then mapped against each other, utilizing data from a subset of sites that would assess QoL with both instruments.

Reviewer Comment: See Statistical Review for a discussion of the methodologies used by the sponsor to analyze the QoL data.

4.10 Efficacy Analysis

4.10.1 Survival

In addition to the comparison of the two study groups' survival for the overall study period, the sponsor's survival analyses included an evaluation of survival based on what study period the patients were entered – before or after the change in docetaxel dose from 100 mg/m^2 to 75 mg/m^2. This was not pre-specified in the protocol or in the May 26, 1999 statistical analysis plan. The change in dose was an unplanned result of the interim analysis. The sponsor states that these additional survival analyses based on dosing period were performed because the dose changed, there was delayed patient enrollment, and because of the expansion of the investigational sites primarily to Europe for expedition of that enrollment. Differences in patient and tumor characteristics between the two study periods and the distribution of those characteristics between arms have been outlined and discussed in section **4.7 Patient Demographics** of this review.

The cut-off date for survival analysis was April 12, 1999. The protocol did not include specified censoring criteria for Kaplan-Meier analyses, but they are found in the statistical analysis plan dated May 26, 1999. They included censoring for further anti-tumor therapy - radiotherapy, chemotherapy, and surgery.

The median survival, considering the pre-specified overall study period, was longer on the docetaxel arm: docetaxel = **7.2 months** (95% CI = 5.5, 9.2) and control = **4.7 months** (95% CI = 3.7, 6.0) – but not statistically significant, p=0.14 by log-rank test. The Kaplan-Meier probability of 1-year survival was 28% (95% CI = 19, 38) on the docetaxel arm and 23% (95% CI = 13, 32) on the best supportive care arm (an analysis that was not pre-specified). In this time to event analysis 74% of the docetaxel patients had died and 26% were censored, while 75% of the control had died and 25% were censored. The distribution of reasons for censoring are summarized for comparison between study arms and over the study periods in the table below.

Table 47 TAX 317 Reasons for Survival Censoring – Comparison of Study Arms and Study Periods

	Docetaxel			Best Supportive Care		
	100 mg	75 mg	Total	100 mg	75 mg	Total
Chemotherapy	6	2	8	8	6	14
Surgery	1	2	3	0	0	0
"3.1"	0	0	0	1	0	1
XRT	0	0	0	0	0	0
Immunotherapy	0	0	0	1	0	1
Other Further Anti-Cancer Tx	0	1	1	1	3	4
No Death	0	15	15	0	5	5

*Reviewer Comment: The sponsor submitted an updated survival analysis in a Fax dated November 5, 1999. The cut-off date for that analysis was October 1, 1999. The percentage of patients censored in that analysis was 19% on the docetaxel arm and 23% on the best supportive care arm. The percentage of deaths is 81% on the docetaxel arm and 77% on the best supportive care arm. The median survival on the docetaxel arm is now **7.0 months** (95% CI = 5.5, 9.0), while that on the best supportive care arm is **4.6 months** (95% CI = 3.7, 6.0). The reported log rank test now suggests that there is a significant difference between arms – p=0.047.*

The sponsor performed proportional hazard regression modeling of prognostic factors on survival. Variables identified as significant, based on a p<0.10, in the stepwise procedure of the regression model included weight loss<10% (risk ratio = 0.38), performance status ≤1 (risk ratio = 0.40), stage IV disease (risk ratio = 2.53), number of organs involved ≥3 (risk ratio = 1.91), and prior number of regimens >1 (risk ratio = 1.60). Adjusting for the prognostic factors, treatment factor was added into the model, but was not found to be statistically significant. An interaction between treatment and enrollment period was suggested, p=0.09.

In its retrospective comparison of treatment arms by study period, the sponsor found no statistically significant survival advantage associated with docetaxel 100 mg/m^2. The median survival with docetaxel 100 mg/m^2 was 5.9 months (95% CI= 4.5, 8.0) vs. 4.9 months (95% CI = 3.5, 8.0) on best supportive care, p = 0.871. In its comparison of the treatment arms in the docetaxel 75 mg dosing period, the sponsor found the median survival of the patients treated with docetaxel 75 mg/m^2 was significantly longer than those randomized to best supportive care during that randomization period – 9.0 months (95% CI = 5.5, 13.1) vs. 4.6 months (95% CI = 3.7, 6.1), respectively (Log Rank p = 0.016).

Reviewer Comment: In the survival update submitted by the sponsor by Fax November 5, 1999, the median survivals reported by study period and the log rank analyses are in the table below:

Table 48 TAX 317 Updated Sponsor Survival Analysis Cut-off Date October 1, 1999 by Study Period

	Docetaxel 100 mg	BSC/100	Docetaxel 75 mg	BSC/75
Median Survival	5.9 mo	4.9 mo	7.5 mo	4.6 mo
95% Confidence Interval	(4.5, 8.0)	3.5, 8.0)	(5.5, 12.8)	(3.7, 6.1)
Log Rank	P=0.78		P=0.01	
1- year Survival Probability	19%	26%	37%	12%
95% Confidence Interval	(7, 30)	(13, 39)	(24, 50)	(2, 23)
			Chi-Square p=0.003	

The sponsor performed an additional unplanned comparison of 1-year survival utilizing a chi-square analysis, limited to the patients entered during the docetaxel 75 mg/m^2 dosing period. The FDA statistical reviewer requested clarification of the methodology used for this analysis, and in their response dated November 10, 1999, the sponsor indicated that censoring had been incorporated in the analysis. The FDA statistical reviewer indicated that this was appopriate methodology for comparing the rates of 1-year survival. It is of some interest, that although the Kaplan-Meier estimate of survival on the docetaxel 75 mg arm at one year is 40%, when this time point is examined in a 2 x 2 table, ignoring censored patients, one sees that only 9/55 patients on that arm were documented to have survived for at least a year. (See table below.) A much larger proportion of patients were excluded from this analysis in this study than in TAX 320. The sponsor found the Chi-Square comparison significant, favoring the docetaxel arm at p = 0.016.

A stepwise procedure of the proportional hazard regression model identified performance status <2, Stage IV disease, number of organs involved ≥ 3, baseline total LCSS score, and prior number of regimens > 1 as significant. Adjusting for these factors the survival difference remained significant, favoring treatment with docetaxel 75 mg/m^2.

Table 49 TAX 317 Patient Numbers Utilized in the Sponsors Chi-Square Comparison of One Year Survival

	Total No. on Study (75 mg Time Period)	Total Alive 365 days	Total Dead prior to 365 days	No. Excluded from the Analysis (%)
Docetaxel 75 mg	55	9	31 (56%*)	15 (27%) 11=not followed 365 days 4 = censored for further tx

	Total No. on Study (75 mg Time Period)	Total Alive 365 days	Total Dead prior to 365 days	No. Excluded from the Analysis (%)
Best Supportive Care/75	49	3	35 (71%*)	11 (23%) 3=not followed 365 days 8 = censored for further tx

* Percent of the total possible events on study = (Total dead prior to 365 days) ÷ (Total no. in treatment group)

Reviewer Comment: The medical and statistical reviewer explored what impact censoring for further therapy had on the survival curves in the second period of the study. By altering survival dates to account for the additional time a patient was known to be alive after starting further therapy. If no date of death was available, patients were censored at the last follow-up prior to cut-off. The resulting Kaplan-Meier survival analysis of the second portion of the study yielded a similar median survival in each arm (docetaxel 75 mg = 9.0 months and best supportive care/75 = 4.7 months) and the log rank test p = 0.041.

There were 30 patients in the study who lived 365 days prior to any censoring for further therapy, including chemotherapy, immunotherapy, surgery, radiotherapy, and "other" therapy. Twelve of the 30 enrolled during the second portion of the study. The reviewer identified 3 patients who survived 365 days but were censored for further therapy prior to 365 days. The clinical characteristics of the 1-year survivors are summarized in the table below.

Table 50 TAX 320 Clinical Characteristics of Patients with Survival ≥365 Days

	Docetaxel 100 mg	**Docetaxel 75 mg**	BSC/100	**BSC/75**
Total No.	**8 (+1)**	**9**	**10**	**3 (+2)**
Stage IIIB	3 (38%)	3 (33%)	3 (30%)	2 (67%)
Stage IV	5 (+1)	6	7	1 (+2)
Best Response on Study = PR	2 (25%)	1 (11%)	0	0
Best Response on Study = NC	6	6	0	0
Best Response on Study = PD	0	2 (22%)	0	0
Best Response on Study = IMP	0	0	0	0
Best Response on Study = NE	0	2 (22%)	0	0

	Docetaxel 100 mg	Docetaxel 75 mg	BSC/100	BSC/75
Total No.	**8 (+1)**	**9**	**10**	**3 (+2)**
Best Response to Prior Cisplatin Non-PD + PS <2	7 (89%)	8 (89%)	8 (80%)	3 (100%)
Best Response to Prior Cisplatin = PD	1 (13%)	1 (11%)	2 (20%)	0 (+1)
Best Response to Prior Platinum = CR +PR	4 (50%) (+!)	4 (44%)	1 (10%)	2 (67%) (+1)
PS >1 (at study entry)	0 (+1)	0	1	0 (+2)
Weight Loss ≥10%	1	0	0	0
LDH >ULN	1	2	1	0
No. of Prior Regimens 1 2 3	 5 1 2	 8 0 1	 7 3 0	 3 0 0

Reviewer Comment: There were 3 patients censored for further therapy who lived >365 days after randomization. The further therapy electronic dataset identified 22 patients treated with further chemotherapy – 6 in the docetaxel 100 mg group, 2 in the docetaxel 75 mg group, 9 in the best supportive care/100 mg group, and 5 in the best supportive care/75 mg group. There was one additional patient in the best supportive care/100 mg group treated with IL-4. The following table tabulates the number of patients in each treatment group that received each chemotherapy drug in further therapy, whether as a single agent or part of a combination, and the response reported (UK = unknown response). Responses were rarely reported (2 only).

Table 51 TAX 317 Summary of Further Chemotherapy and Responses Reported

	Docetaxel 100 mg	Docetaxel 75 mg	BSC/100	BSC 75
Vinorelbine	05005 PD 05009 NE 05172 PD 05193 NC	05021 NE	05164 ??* 05171 NC 05176 PR	05026 NE 05241 UK 05267 NC

	Docetaxel 100 mg	Docetaxel 75 mg	BSC/100	BSC 75
Gemcitabine		05021 NE 05230 NC	5016 NC 05171 NC 05176 PR 05195 PD	5026 NC 5257 UK 05262 NC
Paclitaxel	05172 PD	05230 NC	5176 NC 05491 UK 05190 ??*	
Docetaxel				05266 UK
Carboplatin	05172 PD		05190 ??*	
Vinblastine	05172 PD			
Mitomycin	05172 PD			
5FU	05208 PD		05326 UK	
Arimidex			05002 UK	
IL-4			05178 NC	
Cyclophosphamide	05001??*		05326 UK	
Epirubicin			05326 UK	

* Patients who do not appear in Table 26 Follow Up in Appendix 4A. Patient Data Listing, but do appear in the Further Therapy Electronic Dataset (which does not include the responses to further therapy)

Pt. 05195, Best Supportive Care, was not censored for further chemotherapy, but further surgery.

4.10.2 Time to Progression

Time to progression was not a protocol-specified secondary endpoint. It appears in the statistical analysis plan dated May 26, 1999. That plan was finalized after there had been an interim analysis of the study, and after the data from TAX 320 had been analyzed and submitted to the Agency. The TTP analysis presented by the sponsor, unlike survival, includes the overall study population and is not broken into study periods (before and after change of docetaxel dose). The median time to progression is longer in the overall docetaxel population compared to the best supportive care population: Docetaxel = 10.6 weeks (95% CI = 7.6, 12.1) and BSC = 6.7 (95% CI = 6.0, 7.3). The time to event comparison was significant, log rank $p<0.001$.

Reviewer Comment: In TAX 320 it was the 100 mg docetaxel arm that reported a time to progression that was significantly longer than the vinorelbine/ifosfamide control An exploratory analysis of the time to progression for the two docetaxel subgroups in TAX 317 revealed that the median TTP in each subgroup was significantly longer than the best supportive care arm: Docetaxel 100 mg = 9.1 weeks (95%CI = 6.1, 10.7); BSC/100 = 5.9 weeks (95% CI = 4.0, 7.3); Docetaxel 75 mg = 12.3 weeks (95% CI = 9.0, 18.3); and BSC/75 = 7.0 weeks (95% CI = 6.0, 9.3). The confidence intervals of the docetaxel 100 mg and the best supportive care/75 mg group are superimposable.

The relative distribution of reasons for TTP censoring among study period groups is shown below.

Table 52 TAX 317 Relative Distribution of Time to Progression Coding of Events and Reasons for Censoring Across Study Periods and Treatment Arms

	Docetaxel 100 mg/m^2 Study Period		Docetaxel 75 mg/m^2 Study Period	
Event/Reason for Censoring	Docetaxel 100 mg (n= 49)	Best Supportive Care/100 (n=51)	Docetaxel 75 mg (n=55)	Best Supportive Care/75 (n=49)
Death	11 (23%)	10 (20%)	4 (7%)	6 (12%)
PD	34 (69%)	35 (69%)	43 (78%)	32 (65%)
Chemotherapy	1	1	0	0
Immunotherapy	0	1	0	0
Surgery/"3.1"	1	1	0	0
No PD before Last Contact	2	1	4	4
No PD Before Cut-off Date	0	0	3	0
No Assessment After Baseline	0	2 (4%)	1	7 (14%)

The reviewer examined the application's tumor assessment data from the standpoint of questioning how meaningful the comparison between the arms was for time to progression when one arm was a best supportive care arm. The protocol specified best supportive care arm patients would have tumor assessments every 6 weeks, mirroring the q 2 cycle reassessment pattern in the active treatment arm. If no tumor reassessment was performed for beyond baseline (as might be expected to happen in a best supportive care arm), the analysis could potentially be flawed by missing data. The coding for censoring for no assessment after baseline -"9" in the electronic dataset – was intended to capture this exact protocol violation. As shown in the last row in the table above, this was primarily coded in the best supportive care arm, and more commonly so in the second half of the study. The reviewer examined the data listings of tumor assessments for undercoding of this violation. Undercoding appeared to have occurred in the following patients.

Table 53 TAX 317 Patients in Whom Data Did Not Strongly Support Time to Progression Coding and Dates

Best Supportive Care/100 (N=8)		
	Actual Code	**Problem**
05014	PD	Only tumor assessment was Baseline on 8/29/96. PD coded on 11/6/96, but no documentation of PD in dataset
05161	PD	Only tumor assessment was Baseline on 11/22/94. PD coded on 1/9/95, but no documentation of PD in dataset
05171	Censored for Further Chemotherapy	No assessment after baseline recorded (8/9/95), though appears to have been followed for 4 "cycles". Censored at randomization date (8/15/95) when started further chemotherapy 1/28/97. This patient handled like a "9" but coded a "chemo" and could have contributed as an event if followed.
05178	Censored for	No assessment after baseline recorded (11/1/95), though

	Immunotherapy	appears to have been followed for 6 "cycles". Censored at randomization date (11/14/95) when started further immunotherapy 5/4/97. This patient handled like a "9" but coded a "immuno" and could have contributed as an event if followed.
05184	PD	Only tumor assessment was Baseline on 2/8/96. PD coded on 3/4/96, but no documentation of PD in dataset
05204	PD	Only tumor assessment was Baseline on 10/21/96. PD coded on 12/7/96, but no documentation of PD in dataset
05491	PD	Only tumor assessment was Baseline on 3/21/96. PD coded on 4/25/96, but no documentation of PD in dataset
05499	PD	Only tumor assessment was Baseline on 11/1/96. PD coded on 12/1/96, but no documentation of PD in dataset
Best Supportive Care/75 (N=2)		
05022	PD	Only tumor assessment was Baseline on 1/10/97. PD coded on 4/29/97, but no documentation of PD in dataset
05517	PD	Only tumor assessment was Baseline (9/16/98, 9/22/98, 10/6/98). PD coded on 10/14/98, but no documentation of PD in dataset

Additional instances of lack of documentation of PD and violations of the assessment schedule are listed below.

Table 54 TAX 317 Review Issues with Time to Progression Data

	Docetaxel 100 mg	**Docetaxel 75 mg**	**BSC/100**	**BSC/75**
Missed or delayed evaluations could falsely prolong TTP	05197 05206 05492 05494 (tumor measurements) 05497 (tumor measurements)	05028 05215 05227 05273 (tumor measurements) 05333 05506	05206 05006 05167 05181 05190 05191 05201 05202 05211	05026 05213 05216 05224 05229 05232 05236 05237 05243 05247 05258 05329 05504
PD date Assigned Appears in Error	**05163** (9/8/95 instead of 12/6/95) 05324 (4/3/96 instead of coded 12/29/95)	**5231** (10/27/97 instead of coded 1/13/98) **05249** (6/9/98 instead of coded 8/31/98)		**05216** (5/23/97 instead of coded 3/11/97)

	Docetaxel 100 mg	Docetaxel 75 mg	BSC/100	BSC/75
Can't confirm PD date with dataset	05175	05030 05259 05272 05515	05326	05252
Incorrectly Censored when an Event Occurred			**05206** (censored on the date PD occurred)	
PD Assessed in Evaluable disease * or Evaluable Only Disease** or Non-Evaluable Disease***			05002* 05007** 05015* 05164** 05190** 5191** 5196* 5200* 05490*** 05495**	05026** 05220* 05232** 05243** 05262**

Reviewer Comment: As an exploratory analysis, the FDA review team "re-ran" the TTP time to event analysis without censoring for further therapy. The statistically significant difference between the docetaxel and best supportive care arms remained, p=0.008.

4.10.3 Response

Response and Duration of Response were protocol-defined secondary endpoints. The protocol defined objective as CR's and PR's, and stated that response rates would be evaluated separately in patients with bidimensionally measurable disease and patients with evaluable-only disease. Three patients in each of the docetaxel dosing periods responded to treatment with a PR, and all had bidimensionally measurable lesions. The characteristics of the patients who achieved PR are summarized below. The median duration of response was 26.1 weeks. The clinical characteristics of the six responders in TAX 317 are shown below.

Table 55 TAX 317 Clinical Characteristics of the Docetaxel Patients Who Achieved PR on Study

	Docetaxel 100 mg (N=3)	Docetaxel 75 mg (N=3)
Stage III IV	 2 1	 2 1
PS <2	3	3
Non-PD Response to Prior Platinum	3	3
CR/PR Response to Prior Platinum	1	2
No. of Prior Regimens 1 2 3	 2 1 0	 2 0 1
Weight Loss ≥10% at Study Entry	1	0
LDH >ULN at Study Entry	0	1

	Docetaxel 100 mg (N=3)	Docetaxel 75 mg (N=3)
No. of Organs Involved 1 2 3	 0 2 1	 2 1 0
Survival	230 d 246 d 309 d 422 d 441 d 481 d	

In the course of evaluating the time to progression data the reviewer identified the following problems with response assignments on the docetaxel arm:

Pt 05231 (docetaxel 75 mg) was coded as NC, but appears to have been a best response of PD.
Pt. 05492 (docetaxel 100 mg) was coded NE, but appears to have been a best response of PD.

The percentage of patients treated with docetaxel 100 mg/m^2 who achieved PR on study was 6.1% (3/49), while the percentage of PR's during the docetaxel 75 mg/m^2 dosing period was 5.5% (3/55). The responses are summarized in the table below. The percentages in parentheses are those reported by the sponsor if the FDA review did not concur.

Table 56 TAX 317 Summary of Docetaxel Response – RPR and FDA

	Docetaxel 100 mg/m^2 N=49	**Docetaxel 75 mg/m^2** N=55	**Overall Docetaxel** N=104
CR	0	0	0
PR	3 /49= **6.1%**	3/55 = **5.5%**	6/104 = **5.8%**
NC	18/49 = **36.7%**	25/55 = **45.5%** (47.3%)	43/104 = **41.4%** (42.3%)
PD	18/49 = **36.7%** (34.7%)	19/55 = **34.6%** (32.7%)	37/104 = **35.6%** (33.7%)
NE	10/49 = **20.4%** (22.5%)	8/55 = **14.6%**	18/104 = **17.3%** (18.3%)

4.10.4 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 – a patient scale and 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 that are targeted at 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), and 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." The sponsor also performed a "factor analysis" of the baseline assessment from the patient scale in order to "identify independent aggregate descriptors". In this process two factors were identified that the sponsor reported explained "approximately 60% of the total variability". Those factors were factor 1 = Fatigue, Appetite, Pain, Normal Activities, Overall Symptoms, and QoL Today; and factor 2 = Shortness of Breath, Coughing and Blood in Sputum. In addition a subgroup of factor 1, "Factor 1A" (Fatigue, Appetite, and Pain), was further defined to be "more specific as opposed to Normal Activities, Overall Symptoms, and QoL Today which are very general". These 3 sponsor-developed factors were analyzed with the validated instrument's QoL descriptors.

Reviewer Comment: The FDA review team requested information validating the "factor analysis" the sponsor conducted to selected additional factors for the QoL analysis. No clearly supportive information was submitted.

The EORTC QLQ-C30 (a core questionnaire that incorporates a global health and quality of life scale, 5 multi-item functional scales –physical, role, cognitive, emotional, and social – 3 multi-item symptom scales – fatigue, pain, nausea/vomiting – and 6 single-item symptom measures – dyspnea, insomnia, appetite, constipation, diarrhea, financial) and the QLQ-LC13 (13 questions that include a multi-item scale assessing dyspnea, a series of single items assessing cough, sore mouth, dysphagia, neuropathy, alopecia, hemoptysis, chest pain, and general pain) were utilized at 21 sites (9 European, 8 Canadian, and 4 USA). The items in the QLQ-C30 are all rated by the patient. The initial 7 items are dichotomous (yes/no) and the last two items covering global health status are rated on a 7 point ordinal scale raging from 1= very poor to 7 = excellent. The remaining items in this instrument are rated on a 4-point ordinal scale with 1=Not at all and 4 = Very much. The lung cancer module, QLQ=LC13 rates each question on a 4-point ordinal scale. The data from the scales were scored from 0-100 and arranged in a linear transformation so that a high scale score represented a higher response level.

All QoL assessments in this study were to be performed at baseline and before the infusion of each treatment. The analyses were conducted utilizing a equally spaced, fixed time interval of 21 days to correspond to an ideal treatment cycle. 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%. There were 77 patients with at least one completed EORTC QoL instruments (one docetaxel 100 mg/m^2 patient, 40 docetaxel 75 mg/m^2 patients, 3 best supportive care/100 patients, and 33 best supportive care/75 patients). Forty-one of those patients had completed both an LCSS and EORTC QoL instrument with evaluable baseline and post-baseline assessments. The sponsor did not perform the planned "mapping of the instruments" because too small a number of patients had completed both. The sponsor did not present a formal analysis of the EORTC data in the study report, except to say that only the docetaxel 75 mg study period patients were compared, and that comparison favored docetaxel [illegible] degree of decline in physical function - 21% vs. 27% decline.

Reviewer Comment: The LCSS was to be completed before starting dexamethasone premedication. There were 38 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 = 101). The sponsor indicated in correspondence dated November 15, 1999 that it concurred with that number, except for 1 QoL assessment, and stated that there were 3 assessments that were completed on the same day that dexamethasone was initiated.

The most common reason for non-evaluability in the LCSS QoL analysis in patient-rated items was "no on-treatment assessment": docetaxel = 13% vs. control = 12 %. The most common reason in the best supportive care group was "no baseline assessment" – 16% best supportive care vs. 8% docetaxel. 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 ≥10% difference between groups are highlighted.

Table 57 TAX 317 Distribution of Evaluable LCSS QoL Assessments Between Treatment Arms

Period	**Docetaxel** No. of Patients Available for Assessment (Percentage with Evaluable QoL Assessment)	**Control** No. of Patients Available for Assessment (Percentage with Evaluable QoL Assessment)
Baseline	104 (75)	100 (68)
1	104 (70)	100 (56)
2	89 (69)	85 (55)
3	62 (71)	75 (56)
4	55 (71)	65 (51)
5	40 (73)	49 (49)
6	31 (65)	34 (32)
Follow-up #1	103 (24)	98 (20)
Follow-up #2	103 (11)	95 (6)
Endpoint*	104 (75)	100 (68)

*Last assessment whether on treatment or in follow-up.

One of the sponsor's QoL analyses is an analysis of covariance, "ANCOVA" - a paired analysis of the difference between the baseline and the last available assessment on study. The FDA does not consider this a valid QoL analysis as it ignores what may have happened between those two points, and prefers longitudinal analysis with 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 sponsor performed QoL analyses on the pooled overall study data, and as subgroups, breaking the data into the two docetaxel dosing periods. The sponsor's longitudinal analysis of the overall study population found a difference favoring docetaxel in patient pain subscore, p=0.005. There were no other patient scores that were significantly different between arms. In the study period subgroup analyses, the longitudinal analysis of the docetaxel 100 mg dosing period also found the only significant difference between arms was limited to the pain score of the LCSS, p=0.003. In the docetaxel 75 mg dosing period, however, there was no significant

difference between arms in any of the patient scales, including pain. The sponsor reported that there were favorable trends in OBSERVER scores for pain (p=0.08), appetite (p=0.1), and fatigue (0.07) in the overall population and the docetaxel 100 mg dosing period group. The pattern mixture longitudinal analysis, which examines for informative missingness (completers were defined as those patients who had a QoL assessment after period #3 and non-completers those whose last assessment occurred before or in period #3), yields similar results.

Reviewer Comment: The statistical reviewer re-evaluated the QoL pattern mixture longitudinal analyses. She found that for the pain subscale, the test for non-ignorable missingness in the docetaxel group was informative, so that dropouts and completers needed to be analyzed separately. Dropouts experienced a decrease in pain with time, while the completers on the docetaxel arm experienced an increase. The missing mechanism was found to be non-informative on the best supportive care arm and inclusion of the dropouts in the analysis was not indicated to produce bias. In the QoL Today analysis, in both treatment groups the test for non-ignorable missingness found that the missing information could be considered ignorable – allowing the completers and non-completers to be combined in the analysis of that subscale. The statistical reviewer found no significant difference between arms in either of those subscales. Please refer to Statistical Review for a detailed discussion.

The sponsor had pre-specified comparative evaluation of analgesic use on study, using an analysis of variance method, as a secondary objective of the study. It is not clear from the study report how this analysis was actually performed, but a comparison of interval need for starting analgesics or for increasing the effective dose (versus being able to stop analgesics, maintain the same dose, or decrease doses) is the type of analysis that would be of interest. It does not appear that this kind of analysis was done. The study report references Table 1.10 in Appendix II. F of the application in its discussion of this endpoint, a table that tabulates the total number of patients in each treatment group on morphinic or non-morphinic analgesics for tumor related pain. Results of the Chi-square test of the overall proportion of patients in each analgesic category from each randomization group are presented. This type of analysis does not seem to get at the issue of correlating this endpoint with real clinical benefit. The analysis of analgesics was reported as "morphine usage as tumor-related medication for pain" and non-morphine analgesics usage as tumor-related medication for pain". The sponsor reports that fewer docetaxel patients were administered morphine for pain – 32% vs. 49%, and that this difference was significant, p=0.01, and that significantly fewer docetaxel patients were administered non-morphine analgesics for pain – 39% vs. 55%, p=0.03. Similar comparisons were made in subgroup analyses of the two dosing periods.

Reviewer Comment: The reviewer attempted to examine the arms for differences in baseline percentage in overall and morphinic analgesic uses for tumor related patient (identified by using the code "1" for "tumor related pain" as the indication for administration of medications listed in the PCTX dataset), as well as differences in initiation of morphinic analgesics after baseline. (The reviewer included morphine, fentanyl, meperidine, hydromorphone, ethylmorphine - "dionin", and buprenorphine - "temgesic" in this category.) The table below summarizes the reviewer findings. The baseline numbers do not correlate with those reported by the sponsor, and the reviewer had difficulty categorizing some of the analgesics utilized at foreign sites as morphinic vs. non-morphinic. In correspondence submitted by the sponsor on November 22, 1999 they identified the analgesics they included as "morphinic". That list included Tylox, Percocet, Oxycocet, and tramadol, which the reviewer did not include in her analysis. Importantly, this analysis does not capture dose changes, or addition of further analgesics after the first start of a morphine-related analgesic. There was an apparent lack of a prospectively defined method of capturing these data and analyzing them in a meaningful fashion. There was

also no apparent attempt to optimize baseline pain control prior to randomization. This open-label study was therefore open to bias in terms of the pain medication data collection. These important and insurmountable issues aside, the table below suggests there was a higher rate of starting morphinic analgesics after baseline on the best supportive care control arms – usually within the first four "cycles" on study (12 weeks).

Table 58 TAX 317 Reviewer Summary of Relative Analgesic Administration Between Treatment Arms

	Docetaxel		Best Supportive Care	
	Docetaxel 100 mg N=49	Docetaxel 75 mg N=55	BSC/100 N=51	BSC/75 N=49
Any Analgesic Medication for Tumor Pain at Baseline	31 (63.3%)	23 (41.8%)	32 (62.8%)	32 (65.3%)
Interim Start of Any Analgesic Medication for Tumor Pain After Baseline (no analgesic at 000, analgesic started in or after cycle 001	6 (12.2%) 001 002 004 005 006 009	2 (3.6%) 003 004	7 (13.7%) 001 x 5 003 x 2	9 (18.4%) 001 x 3 002 003 004 x 3 005
Morphine-Like Analgesic for Tumor Pain at Baseline	14 (28.6%)	12 (21.8%)	11 (21.6%)	8 (16.3%)
Interim Start of Morphine-Like Analgesic After Baseline	4 (8.2%) 001 002 005	2 (3.6%) 001 004	10 (19.6%) 001x 2 002 x 3 003 x 2 004 005 006	16 (32.7%) 001 002 x 5 003 x 3 004 x 4 005 006 008

The results of the LCSS and analgesic "pain comparisons" are summarized in the table below . The rows with asterisks are those analyses not considered clinically meaningful or statistically valid by the Agency.

Table 59 Summary and Comparison of Sponsor and FDA Reviewer Quality of Life Endpoint Analyses

	Overall Docetaxel vs. BSC	Docetaxel 100 mg vs. BSC/100	Docetaxel 75 mg vs. BSC/75
Pattern Mixture Longitudinal - Sponsor	Patient PAIN: P <0.01 favoring docetaxel	Patient PAIN: P <0.01 favoring docetaxel	NS

	Overall Docetaxel vs. BSC	Docetaxel 100 mg vs. BSC/100	Docetaxel 75 mg vs. BSC/75
FDA Pattern Mixture Longitudinal Analysis	NS		
ANCOVA*	P<0.05	P<0.01	NS
Morphine Usage for Tumor-Related Pain*	32% vs. 49% p=0.01	NS	26% vs. 53% p<0.01
Non-morphine Analgesic Usage for Tumor-Related Pain*	39% vs. 55% p=0.03	NS	31% vs. 57% p<0.01

Reviewer Comment: The QoL differences between arms in the overall study population appear to be driven by the differences in the docetaxel 100 mg study period. It is interesting then that the difference in analgesic use seems to be driven by the 75mg dosing period data.

4.10.4.1 Performance Status and Change in Weight

Changes in performance status and body weight were protocol pre-specified secondary endpoints. The methodology for these analyses was not described in the statistical analysis plan. The protocol's statistical methods discussion suggests these comparisons were an analysis of variance comparing baseline to end of study values. The study report does not discuss the methodology of the comparisons, but Tables 1.12 (Summary of Weight Loss from Baseline to Last Assessment of Weight on Study Treatment by Treatment Group) and Table 1.13 (Summary of Change from Baseline to Last Assessment of Performance Status on Study Treatment by Treatment Group) of Appendix II.F in the application indicate that the weight change comparisons among arms were based on proportions of patients who experienced a specified degree of weight loss (≥10%). The comparisons of performance status were made by setting up contingency tables for each treatment arm comparing the number of patients at a baseline PS level to the number of patients at that same level or a different level at the last assessment of PS on study.

The sponsor reports that for the overall study population a similar proportion of patients in each arm experienced deterioration of ECOG performance status between baseline and last performance status on study – 42% of the docetaxel patients and 46% of the best supportive care arm patients. The mean change in performance status was not found to be significantly different between arms either, although there was less of a change on the docetaxel arm – 0.56 for docetaxel vs. 0.80 for best supportive care. In the subgroup analysis by study period, the sponsor found that although there was no significant difference in the proportion of patients who experienced deterioration of performance status between the docetaxel arm in the two dosing periods. The mean change (decline) in performance status was significantly less in those patients treated with docetaxel 75 mg than those on the best supportive care arm during that dosing period – 0.65 vs. 1.09, p<0.05. Differences in the proportion of patients who experienced ≥10% weight loss from baseline to last measure on study was also only found to be significantly different for the 75 mg dosing period subgroup, favoring the docetaxel arm. These analysis of variance data are summarized in the table below.

Table 60 TAX 317 Summary of Sponsor's Performance Status and Weight Loss Analyses

	Overall	Docetaxel 100 mg Dosing Period	Docetaxel 75 mg Dosing Period

	Docetaxel	BSC	Docetaxel 100 mg/m^2	BSC/ 100	Docetaxel 75 mg/m^2	BSC/ 75
Mean Change **Performance Status** (Last PS – Baseline PS)	0.56 SE = 0.09	0.80 SE= 0.11	0.45 SE = 0.14	0.50 SE =0.13	0.65 SE = 0.13	1.09 SE =0.16
	P=0.11		P=NS		P<0.05	
Proportion Experiencing **PS** Worsening	42%	46%	39%	32%	45%	59%
	P=NS		P=NS		P=NS	
Proportion Experiencing ≥10% **Weight Loss** (Baseline – Last Assessment)	7%	15%	12%	8%	2%	22%
	P=0.07		P = NS		P<0.01	

Reviewer Comment: The sponsor presented exploratory analyses of performance status change by cycle in the first 3 cycles on study in TAX320 (submitted in correspondence dated November 5, 1999). In those comparisons the differences between arms (docetaxel 75 mg/m^2 and control) in cycle 003, and averaged over the first 3 cycles was reported to be significant, without apparent adjustment for multiple comparisons. Less than 50% of the patients in each treatment arm were included in that analysis. The electronic dataset of TAX 317 reveals that 67% of the docetaxel 75 mg subgroup and 75% of the BSC/75 group had a performance status evaluation recorded in cycle 003. The same type of analysis was not found to reveal significant differences in TAX 317.

Summary: The prospectively defined primary endpoint of overall survival was not significantly different between docetaxel and best supportive care. An unplanned comparison based on dose of docetaxel administered was utilized and, limiting the best supportive care population of comparison to those randomized during the two dose periods, yielded a significantly longer median survival on the docetaxel 75 mg arm. The response rate was under 10% in this population. Time to progression was significantly longer on both docetaxel subgroups. The LCSS patient pain subscale findings were driven by the 100 mg subgroup, whereas analgesic differences, changes of weight, and change in performance status were confined to the 75 mg group.

4.11 Safety

4.11.1 Adverse Events

The following table summarizes the more common adverse events observed in TAX 317 associated with docetaxel. It compares the two dose levels, and includes overall reported adverse events ("All Events" column) and treatment emergent events ("New Onset" column). The grade ¾ events listed in the table are for the treatment emergent events. All of the events in the following tables are considered without any attribution to treatment. The table summarizes both NCI event terminology and COSTART terminology. The COSTART events are bolded, and the grade 3/4 column in those events refers to the "severe" categorization of COSTART events.

Table 61 TAX 317 Summary of Common Docetaxel Adverse Events – Overall and Treatment Emergent

	Docetaxel Overall N=104			**Docetaxel 100 mg N=49**			**Docetaxel 75 mg N=55**		
	All Events	Grade 3/4*	New Onset	All Events	Grade 3/4*	New Onset	All Events	Grade 3/4*	New Onset
Pain (COSTART)	80.6%	17.3%	39.4%	85.7%	16.3%	30.6%	76.4%	10 18.2%	47.3 %
Asthenia (COSTART)	83.7%	20.2%	57.7%	89.8%	22,4%	61.2%	78.2%	18.2%	54.5 %
Pulmonary	74%	27.9%	45.2%	81.6%	36.7%	53.1%	67.3%	20.0%	38.2 %
Cough Increased (COSTART)	71.9%	3.9%	31.7%	66.9%	4.1%	28.6%	49.6%	3.6%	34.5 %
Alopecia	60.6%	0	33.7%	65.3%	0	34.7%	56.4%	0	32.7 %
Neuro-sensory	44.2%	1.9%	23.1%	51.0%	2.1%	26.5%	38.2%	1.8%	20.0 %
Neuro-motor	23.1%	2.9%	15.4%	20.4%	2.1%	16.3%	25.5%	1.8%	14.5 %
Nausea	48.1%	2.9%	35.6%	44.9%	2.1%	34.7%	50.9%	3.6%	36.4 %
Vomiting	29.8%	1.9%	25.0%	28.6%	0	26.5%	23.5%	3.6%	23.6 %
Fever (infx Absent)	53.8%	0	50.0%	40.8%	0	36.7%	65.5%	0	61.8 %
Anorexia (COSTART)	33.7%	2.9%	17.3%	30.6%	2.1%	20.4%	36.4%	3.6%	14.5 %
Infection	35.6%	9.6%	33.7%	38.8%	14.3%	36.7%	32.7%	5.5%	30.9 %
Peripheral Edema (COSTART)	26.9%	1.9%	25.0%	26.5%	2.1%	26.5%	27.3%	1.8%	23.6 %
Diarrhea	33.7%	2.9%	33.7%	30.6%	2.1%	30.6%	36.4%	1.8%	36.4 %
Constip. (COSTART)	29.8%	0	16.3%	30.6%	0	18.4%	29.1%	0	14.5 %
Skin	36.5%	2.9%	31.7%	46.9%	6.1%	44.9%	27.3%	0	20.0 %