CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20449/S11

MEDICAL REVIEW(S)

Slaten
DEC 16 1999

Medical Team Leader Review of Supplemental NDA

Taxotere[R] (docetaxel) for Injection Concentrate
NDA 20-449 SE(011)
Sponsor: Rhone Poulenc Rorer Pharmaceuticals Inc.
Submission Date: June 23, 1999

The sponsor has submitted clinical data in support of the following new indication for docetaxel: "for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy". The submission was granted a priority review and the user fee date is December 23, 1999.

Two multi-center, randomized, controlled trials were conducted in patients with NSCLC whose disease had progressed on or after treatment with one platinum-based chemotherapy regimen. In TAX 317, patients were randomized to treatment with docetaxel 100 mg/m^2 or best supportive care. Upon review of safety in TAX 317, the docetaxel dose was reduced to 75 mg/m^2 because of unacceptable toxicity at the higher dose. In TAX 320, patients were randomized to one of 3 arms – docetaxel 100 mg/m^2, docetaxel 75 mg/m^2, or investigator's choice of vinorelbine or ifosfamide. Because the 100 mg/m^2 dose is not being considered for approval, only data on the efficacy and safety of docetaxel 75 mg/m^2 are clinically relevant.

Efficacy

- Survival

The table below summarizes the median survival and % 1-year survival results for the docetaxel 75 mg/m^2 arms in each of the phase 3 studies submitted in the original supplemental application. The prolongation in median survival time favors the docetaxel 75 mg/m^2 arm over best supportive care in TAX 317, but is not statistically different from active control agents (vinorelbine or ifosfamide) studied in TAX 320. As the efficacy of these control agents as second line therapies for NSCLC has not been definitively proven, the finding of a similar median survival for docetaxel 75 mg/m^2 in this study is not compelling evidence for its efficacy.

Increasingly, the proportion of patients alive at one year from initiation of treatment has been viewed as a clinically meaningful endpoint in disease settings such as metastastic NSCLC in which overall survival times are typically short. In these settings, it is less likely that chemotherapy, even effective chemotherapy, will produce a substantial prolongation of median survival times. The % 1-year survival favors the docetaxel 75 mg/m^2 arm in both studies and is a dramatic finding given its magnitude. A % 1-year survival in the range of 30 – 40% is consistent with % 1-year survivals reported for recently approved agents given in combination with cisplatin for first-line therapy of NSCLC (i.e., vinorelbine, paclitaxel, and gemcitabine).

Note that comparisons of docetaxel 75 mg/m^2 and best supportive care in TAX 317 were not pre-specified in the protocol, necessitating that an unadjusted p value of < 0.05 be reported. The % 1-year survival outcomes were also not pre-specified in either study protocol.

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

*Unadjusted $p < 0.05$, per FDA

An updated analysis of median and % 1-year survival conducted in September 1999 was also submitted. The results of this non-pre-specified analysis are similar to those reported in the original application.

When the Oncologic Drugs Advisory Committee (ODAC) was asked whether the median and % 1-year survival data for docetaxel 75 mg/m^2 were adequate to demonstrate a survival benefit for this docetaxel dose in the second-line treatment of NSCLC, the majority of Committee members agreed (10 – yes; 2 – no; 1 – abstaining).

- **Other Efficacy Outcomes**

Additional efficacy outcomes are tabulated below. The comparisons of docetaxel 75 mg/m^2 with best supportive care in TAX 317 were not pre-specified in the protocol. A modest prolongation of median time to progression (approximately 5 weeks) was shown in this study with an unadjusted $p < 0.05$. A significant prolongation was not demonstrated in the prospectively defined comparison of docetaxel 75 mg/m^2 with active control in TAX 320. Objective tumor responses were reported rarely with docetaxel at this dose.

Original Analyses	TAX317		TAX 320	
	Docetaxel 75 mg/m^2 N = 55	Best Supportive Care/75 N = 49	Docetaxel 75 mg/m^2 N=124	Control (V/I) N= 122
Median Time to Progression	12.3 weeks*	7.0 weeks	8.3 weeks	7.6 weeks
95% CI	(9.0, 18.3)	(6.0, 9.3)	(7.0, 11.7)	(6.7, 10.1)
			log rank p = 0.07	
Response Rate	5.5%	NA	4.8%	0.8%
95% CI	(1.1,15.1)	-	(1.8, 10.2)	(0.0, 4.5)
			Fisher's Exact p = 0.12	

*Unadjusted $p < 0.05$, per FDA

Several additional analyses were performed to assess the impact of docetaxel therapy on patient well-being. These included evaluation of responses on the Lung Cancer Symptom Scale (LCSS), assessment of opioid use on study, and change in performance status on study. No consistent improvement in LCSS scores were noted in either study for patients on docetaxel 75 mg/m^2. In TAX 317, fewer patients on the docetaxel 75 mg/m^2 arm started opioid analgesics on study than those on the best supportive care arm. In that study, analysis of change in performance status from baseline also favored docetaxel 75 mg/m^2 over best supportive care. These trends were not replicated in TAX 320 however. At best, it could be said that treatment with docetaxel 75 mg/m^2 did not worsen patient well-being. When the ODAC was asked whether the data on median time to progression, opioid analgesic use, and mean change in performance status from baseline adequately demonstrate that therapy with docetaxel 75mg/m^2 in second line treatment of NSCLC confers clinical benefit, the Committee disagreed (4 – yes; 7 - no; 2 - abstaining).

Safety

Treatment-related mortality associated with docetaxel 75 mg/m^2 (1.8% in TAX 317 and 3.3 % in TAX 320) was similar to what is currently labeled for second-line treatment of patients with advanced breast cancer treated with 100 mg/m^2 (1.5%). Rates of overall and severe hematologic and non-hematologic toxicities including infection, gastrointestinal and neurologic toxicities, and fluid retention were similar to what is currently labeled for advanced breast patients cancer treated with 100 mg/m^2. The ODAC unanimously agreed with this safety assessment.

Recommended Regulatory Action

Supplemental NDA 20-449, SE(011), submitted on June 23, 1999, for Taxotere^R (docetaxel) for Injection Concentrate is approvable as second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer based on the finding of

improved % 1-year survival observed in two randomized, controlled studies, and a safety profile that is similar to what is currently labeled for docetaxel, albeit at a higher dose. The ODAC overwhelmingly recommended approval (12- yes, 1 – no) but advised that the indication be worded to accurately reflect the characteristics of the patient population studied. Therefore, the patients for which docetaxel would be indicated should be further defined as those in whom the disease has failed "prior cisplatin-based chemotherapy".

The recommended docetaxel dose should be 75 mg/m^2 administered as an intravenous infusion over one hour, every three weeks. Product labeling should warn health care providers that a higher dose of docetaxel in this patient population (i.e., 100 mg/m^2) was associated with increased treatment-related mortality (5 and 14% in each of the two randomized, controlled studies). The current patient package insert should be amended to reflect the addition of the approved lung cancer indication. No post-marketing commitments are requested.

/S/ 12/16/99

Julie Beitz, MD Date

cc:
NDA 20-449: HFD-150 Division File
HFD-150: D. Griebel
HFD-150: A. Staten

STATEN

AUG 11 1999

Medical Team Leader Response to Pediatric Study Waiver Request

Re: **Request for Waiver of Pediatric Study Requirement – Taxotere[R] (docetaxel) for Injection Concentrate NDA #20-449, S-011**

Date of Request: **June 23, 1999**

Background

On June 23, 1999, Rhone-Poulenc Rorer Pharmaceuticals Inc. submitted a supplemental NDA for Taxotere[R] (docetaxel) for Injection Concentrate for **the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy**. The applicant has requested the Agency to consider a waiver of the pediatric study requirement. Under the Pediatric Final Rule that became effective April 1, 1999, a waiver of the pediatric study requirement will be granted "if the product meets both of the following conditions: 1) the product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments, and 2) the product is not likely to be used in a substantial number of pediatric patients". FDA will also waive the pediatric study requirement if the applicant certifies that "the required studies on the product are impossible or highly impractical because, for example, the population is too small or geographically dispersed".

Taxotere[R] (docetaxel) for Injection Concentrate is commercially available and is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Current product labeling for Taxotere[R] states that safety and effectiveness in pediatric patients have not been established.

Rationale for Waiver of the Pediatric Study Requirement

The following considerations speak to the conditions above which, if present, would justify a waiver of the pediatric study requirement.

1. The product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments

Rhone-Poulenc Rorer Pharmaceuticals, Inc. does not intend to label Taxotere[R] for use in pediatric patients and has submitted no data pertinent to the therapeutic benefit of Taxotere[R] for pediatric patients.

2. The product is not likely to be used in a substantial number of pediatric patients

The applicant correctly surmises that non-small cell lung cancer is a rare form of cancer in the pediatric population. According to the American Cancer Society, the prevalence of lung cancer in 1998 for US males was: ages 0-4, 0; ages 5-9, 0; ages 10-14, 0; and ages 15-19, 125. For US females, there were no cases reported for ages 0-19 years. Non-small cell lung cancer represents 75 – 80% of all cancers of the lung. At the time of diagnosis, 25% of these patients are deemed resectable. [1]

Thus, the number of cases of locally advanced or metastatic non-small cell lung cancer developing annually in pediatric patients ($\leq$ 16 years) that would be candidates for Taxotere[R] after failure of prior chemotherapy would be considerably lower than the 50,000 that has been defined as "a substantial number of pediatric patients" by the Pediatric Final Rule.

3. The required studies on the product are impossible or highly impractical because, for example, the population is too small or geographically dispersed

The applicant correctly surmises that studies of Taxotere[R] in pediatric patients with locally advanced or metastatic non-small cell lung cancer, after failure of prior chemotherapy would be highly impractical given the small numbers of such patients in the US population.

References:

[1]American Cancer Society Cancer: 1/28/99; http://www.cancer.org/statistics/cff99;pl

Recommended Regulatory Action

A full waiver of the pediatric study requirement may be granted since the product, Taxotere[R] (docetaxel) for Injection Concentrate, the subject of NDA 20-449, S-011, submitted by Rhone-Poulenc Rorer Pharmaceuticals, Inc., meets the following condition defined by the Pediatric Final Rule which became effective April 1, 1999:
"The required studies on the product are impossible or highly impractical because, for example, the population is too small or geographically dispersed".

/S/ 8/3/99
Julie Beitz, MD

/S/ 8/11/99
Robert Justice, MD

Cancer Facts and Figures 1999.
ICD-9 Code: 162.
Description: Malignant neoplasm of trachea; tracheal cancer (lung cancer)
Source: American Cancer Society; 1/28/99; http://www.cancer.org/statistics/cff99; p1

Statistical Information:
PrimaryHospitalDiagnoses(1):
Gender: Male 57.8% Female 42.2%
Age: <15 *% 15-44 5.6% 45-6435.0% 65+ 59.4%

All-ListedHospitalDiagnoses(1):
Gender: Male 55.7% Female 44.3%
Age: <15 *% 15-44 4.5% 45-64 32.6% 65+ 62.9%

U.S. Trends:
1992 1993 1994 1995 1996 1997
InpatientTrends(1):
A 193,000 172,000 185,000 168,000 180,000 *
B 402,000 372,000 393,000 359,000 377,000 *
C 8.2 8.9 8.3 7.5 7.3 *
A = Primary Diagnosis; B = All Listed; C = Average Stay (days)

PhysicianOfficeVisits(2):
A 798,890 846,591 948,230 724,546 1,504,147 1,368,713
B
A = Office Visits; B = New Patients

HospitalOutpatients(3):
A * 123,915 91,831 275,075 252,578 *
B
A = Total Visits; B = Total New Patients

Geographic Comparisons (4)
U.S. Incidence:
INCIDENCE (1999): For 1999, the incidence of lung cancer was projected at 171,600 cases (males, 94,000; females, 77,600); mortality was projected at 158,900 deaths (males, 90,900; females, 68,000).

INCIDENCE (1998): For 1998, the U.S. incidence of lung cancer was projected at 171,500 new cases (males, 91,400; females, 80,100). Mortality due to lung cancer was projected at 160,100 deaths (males, 93,100; females, 67,000).

INCIDENCE (1997): For the year 1997, the American Cancer Society estimates the number of new cases of lung cancer at 178,100 (98,300 male, 79,800 female), and the number of deaths from lung cancer at 160,400 (94,400 male, 66,000 female).

INCIDENCE (1996): For the year 1996, the American Cancer Society estimates the number of new cases of lung cancer at 177,000 (98,900 male, 78,100 female), and the number of deaths from lung cancer at 158,700 (94,400 male, 64,300 female).

INCIDENCE (1995): In 1995, an estimated 169,900 new cases of lung cancer occurred (men 96,000; women 73,900); estimated deaths 157,400 (men 95,400; women 62,000).

INCIDENCE (1994): In 1994, an estimated 172,000 new cases occurred (men 100,000; women 72,000); estimated deaths 153,000 (men 94,000; women 59,000).

TRENDS: The incidence rate is declining in men, from a high of 87 per 100,000 in 1984 to 77 per 100,000 in 1993. Recently, the rate of increase among women has begun to slow. In 1993, the incidence rate in women was 42 per 100,000.

U.S. Prevalence:

PREVALENCE (1998): Males: (ages 65 and over, 136,802); ages 0-4, 0; ages 5-9, 0; ages 10-14, 0; ages 15-19, 125; ages 20-24, 0; ages 25-29, 261; ages 30-34, 718; ages 35-39, 1364; ages 40-44, 3059; ages 45-49, 6554; ages 50-54, 12,495; ages 55-59, 20,911; ages 60-64, 27,750; ages 65-69, 37,771; ages 70-74, 37,851; ages 75-79, 34,258; ages 80-84, 18,106; ages 85 and over, 8816.Females: (ages 65 and over, 101,864); ages 0-4, 0; ages 5-9, 0; ages 10-14, 0; ages 15-19, 0; ages 20-24, 201; ages 25-29, 249; ages 30-34, 431; ages 35-39, 1604; ages 40-44, 2554; ages 45-49, 6526; ages 50-54, 12,341; ages 55-59, 17,977; ages 60-64, 24,304; ages 65-69, 27,708; ages 70-74, 29,922; ages 75-79, 23,203; ages 80-84, 13,479; ages85 and over, 7552.

NON-SMALL CELL LUNG CARCINOMA (NSCLC):

NSCLC represents 75% to 80% of all cancers of the lung. 25% of these patients have resectable disease at the time of diagnosis, and 50%have disease confined to the thorax. Locally advanced stage III NSCLC accounts for 35% of all lung

1. INTRODUCTION

1.1 Basic Information and Timeline

Table 1 Basic Application Information

Drug Name	Taxotere® (docetaxel)
Sponsor	Rhône-Poulenc Rorer
NDA #20-449 SE-011	
Proposed Indication	Locally advanced or metastatic non-small cell lung carcinoma after failure of prior therapy
Pre-sNDA Meeting	December 22, 1998
sNDA Submission Date	June 23, 1999
NDA Drug Classification	Priority
Pharmacological Category	Semi-Synthetic antineoplastic; member of taxoid family
45-day Meeting	
60-Day Meeting	
ODAC Meeting	December 15, 1999

1.2 Drug Name and Chemical Characteristics

1.2.1 Generic name:

Docetaxel

1.2.2 Trade Name:

Taxotere

1.2.3 Chemical Name:

(2R,3S)-N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

1.2.4 Molecular Weight:

861.9

1.2.5 Chemistry/Manufacturing Controls

See previous review in original NDA.

1.3 Pharmacologic Category:

Antineoplastic agent. Semi-synthetic member of taxoid family. See previous review for original NDA for further details.

1.3.1 Indications and Off-Label Use

Docetaxel was granted accelerated approval in May of 1996 for the treatment of patients with locally advance or metastatic breast cancer who had progressed during anthracycline-based therapy or relapsed during anthracycline-based adjuvant therapy. Full approval for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy in June of 1998.

1.4 Paper and Electronic Submission

The application was submitted on December 23, 1998 and designated a Fast Track supplemental application, and was considered a rolling submission. The data submitted in 1998 was that from TAX 320 and interim data from TAX 317. Electronic data was submitted in SAS and SAS transport files that could utilized with JUMP. The final "paper" submission was filed on June 23, 1999, and consisted of the final analysis of TAX 317. The electronic data (again SAS and SAS transport files) for TAX 317 was filed on June 28, 1999, completing the rolling submission.

A survival update of both phase 3 studies submitted in this application was submitted by the sponsor as the Safety Update on November 5, 1999.

Additional correspondence was received from the sponsor providing information requested from the FDA and comments on review issues conveyed to the sponsor from the FDA reviewer. Those items are tabulated below:

September 9, 1999 – Sponsor submitted response to fax'd FDA questions on August 16.
November 5, 1999 – Sponsor submitted response to 11 FDA questions fax'd October 21. The answers were in response to question 1-9 of that fax
November 10, 1999 – Sponsor submitted response to FDA statistical reviewer regarding Chi-Square methodology utilized in TAX 317.
November 15, 1999 – Sponsor submitted answers to questions 10 and 11 of the FDA's October 21 fax.
November 16, 1999 - Sponsor submitted the briefing document for the NDA.
November 19, 1999 – Sponsor submits requestg for a meeting with the clinical and statistical review team to "ascertain their general impressions regarding the supplement".
November 22, 1999 – Sponsor submitted response to FDA questions fax'd November 8.
December 1, 1999 – Sponsor submitted response to FDA reviewer's fax'd comments regarding deaths that had not been considered treatment related, that were viewed as possibly treatment related by the reviewer, safety issues in the studies, and response assessments sent to sponsor on November 24, 1999.
December 8, 1999 – Sponsor provided draft version of their proposed ODAC presentation slidesl

1.5 *Financial Disclosure of Clinical Investigators*

The sponsor submitted certification that all patients reported in the application completed study before February 2, 1999. The sponsor certified that no investigator who treated patients on the studies presented in the application had received any compensation such as cash, stock royalty interest, etc., which was dependent on favorable study outcome. The sponsor certified that no investigator had ownership in RPR whose value cannot be readily determined through reference to public prices, and that no investigator had proprietary interest in docetaxel such as patent, trademark, copyright or licensing agreement.

2. Summary of Clinical Studies

2.1 *Pivotal Trials*

The sponsor has submitted the data from two phase 3 studies, TAX 320 and TAX 317, conducted in patients with advanced non-small cell lung carcinoma to support their proposal to extend the current indication for docetaxel to include the treatment of patients with locally advanced or metastatic non-small cell lung carcinoma after failure of prior chemotherapy. The sponsor has indicated that it considers TAX 320 the pivotal trial, and TAX 317 as supportive. Six additional phase 2 studies in which docetaxel was administered as second-line treatment for non-small cell lung carcinoma have also been submitted to provide supportive efficacy and safety data. The data from twelve phase 2 studies in which the docetaxel was administered as first-line therapy have also been included in this application as supportive data.

Because TAX 317 is a randomized, controlled trial in which docetaxel was administered in the second-line setting, the reviewer will approach this study as a pivotal trial with equal weight to TAX 320 – the sponsor-specified pivotal trial. These two studies are briefly summarized in the following table.

Table 2 Study Design of TAX 317 and TAX 320

Study No.	Arms	Design	No. Pts.	Population
TAX 317	Docetaxel vs. Best Supportive Care	Phase 3, open label, randomized, multicenter	204	One prior platinum based chemotherapy
TAX 320	Docetaxel vs. Ifosfamide **OR** Vinorelbine (Investigator Choice)	Phase 3, open label, randomized, multicenter	373	One prior platinum based chemotherapy

2.2 *Supportive Studies*

The study reports from six phase 2 studies in which docetaxel was administered as *second-line* treatment for non-small cell lung carcinoma have been submitted as supportive efficacy and safety data. The data from twelve phase 2 studies in which the docetaxel was administered as *first-line* therapy have also been included in this

application as supportive data. The table below summarizes the studies that enrolled second line patients.

Table 3 Supportive Study Summary - Second-Line

Study No.	No. Pts.	Patient Population
TAX 270	N = 44 100 mg	Second Line; Single Center – USA
TAX 271	N=44 100 mg	Second Line; Multi-center – USA
TAX 297	N = 80 100 mg	Second Line; Multi-center – USA
TAX SI002A	N = 72 (2^{nd} line) 100 mg	Second Line (and first line); Multicenter – European
TAX CHI202	N = 10 (2^{nd} line) 75 mg	Second Line (and first line); China
TAX 241	N = 20 60 mg	Second Line (and first line); Japan.

3. Pivotal Study – TAX 320: A Multicenter, Randomized Phase 3 Study of Docetaxel (RP56976, Taxotere®) 100 mg/m^2 or 75 mg/m^2 Versus Vinorelbine or Ifosfamide in Patients with Non-small Cell Lung Cancer Previously Treated with Platinum-based Chemotherapy

Trial Accrual Dates: **June 30, 1995 to April 25, 1997**

Data Cutoff Date: **January 1, 1998**

3.1 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. At an end-of-phase 2 meeting with the Division of Oncology Drug Products the sponsor agreed to a study design that included evaluation of both 100 mg and 75 mg doses of docetaxel, vs. a comparator arm of investigator choice - ifosfamide and vinorelbine. 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. Prior taxane exposure was not excluded.

3.2 Objectives of the Study

- The primary objective was to evaluate the survival.
- Comparison of the quality of life was identified as a secondary objective.

- Determination of the safety, response rate, and response duration associated with docetaxel at either dose were additional secondary objectives.

3.3 Study Design

This study was an open label, randomized, multi-center phase 3 trial with 23 participating centers, all in the United States. A total of 373 patients were stratified by best response to prior platinum-based therapy (progressive disease vs. other response) and ECOG performance status (0-1 vs. 2) for randomization among 3 treatment arms (docetaxel 100 mg/m^2 = 125; docetaxel 75 mg/m^2 = 125; and vinorelbine/ifosfamide = 123). Four possible strata were defined:

Table 4 TAX 320 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 a pre-recorded interactive telephone call.

Reviewer Comment: In its discussion of other protocol violations, the sponsor mentions that although best response to prior cisplatin based chemotherapy was one of the stratification factors for randomization, "some" randomizations were inadvertently stratified on the basis of the overall outcome of that prior therapy instead of best response. This implies that some patients were stratified as PD, when their actual best response to prior cisplatin therapy could have been CR/PR/SD.

In correspondence dated September 9, 1999, the sponsor responded to the Agency's request for further information regarding these stratification errors. The Agency had requested a description of how these stratification errors were discovered, and whether every participant's CRF (case report form) was reviewed to assure the best response to prior therapy had been accurately recorded. The sponsor indicated that the monitoring CRA performed routine verification of the CRF data entries, but there was no systematic review performed for that specific data entry. The incorrect stratifications were found by the monitor in the routine process of verification. The study report indicates that when these errors were discovered the investigator corrected the CRF.

The sponsor provided a list of the 59 (59/373 randomized = 16%) patients who had a discrepancy between stratified and actual best response to prior cisplatin chemotherapy. That list included 42 patients who had been randomized as having had PD as a best response to prior cisplatin therapy, while the CRF indicated the best response was non-

PD, and 17 who had been randomized as having had a non-PD best response, when the CRF indicated it was PD. The errors made in the latter17 patients do not clearly arise from the investigator error described by the sponsor in the study report as the source of these errors – the investigators confusing the ultimate outcome on cisplatin with the best response on therapy - leading the reviewer to believe that the latter group of errors were errors made by the investigators in the randomization process, perhaps through miss-keying answers to randomization questions during the pre-recorded telephone interactive message.

The Agency asked for clarification that only the correct assignments of best response to prior platinum therapy were used in the analyses performed in this trial, and the sponsor confirmed this. Using the electronic dataset, the reviewer checked each patient who appeared on the list of mis-stratification errors submitted by the sponsor to assure that the corrected best response to prior cisplatin was that which appeared in the dataset. ***The list and electronic dataset correlated in all but one patient, Pt. 10486 (a docetaxel 100 mg arm patient), who was randomized as a Non-PD best response to cisplatin, but was corrected in the CRF to PD as best response to cisplatin. In the electronic dataset this patient is coded as "1," which is equivalent to a best response of Non-PD.***

In its response to the Agency's questions regarding stratification errors, the sponsor indicated that there had also been performance status stratification errors. They reported there were 15 patients who had a discrepancy between the PS marked on the CRF and that reported at randomization. Two were mis-stratified both on the basis of PS and response to prior cisplatin. One, Pt. 10517, was a docetaxel 100 mg arm patient who had an actual PS=1 and PD as best response to prior chemotherapy. This patient was stratified as PS=2 and Non-PD as best response to prior cisplatin. The other patient miss-stratified on both counts was Pt. 10097, another docetaxel 100 mg arm patient, who had an actual PS=2 and best response to prior cisplatin = non-PD, but was randomized as a PS=0-1 and a best response to prior cisplatin=PD. The impact of these two mis-stratifications may have been nullified by the fact that the PS and response mis-stratifications trend in opposite directions prognostically. See ***Section 3.7*** *of this review for a detailed discussion of the impact of these stratification errors.*

3.3.1 Treatment Plan

The treatment arms in this study were:

ARM #1: **Docetaxel 100 mg/m^2**, one-hour infusion, cycled every 21 days. Premedication = Dexamethasone 8 mg per os q 12 hours starting 24 hours before the docetaxel infusion and continuing for a total of 5 doses.

ARM #2: **Docetaxel 75 mg/m^2**, one-hour infusion, cycled every 21 days. (Premedicated as in Arm #1.)

ARM #3: Investigator choice of *either* vinorelbine *or* ifosfamide, at the following doses:

Vinorelbine 30 mg/m^2 IV on Days 1, 8, and 15 of each 21-day cycle.

OR

Ifosfamide 2 g/m^2 IV Days 1-3, cycled every 21 days. Mesna was given either as 400 mg/m^2 IV immediately prior to ifosfamide, followed by 800 mg/m^2 IV 4 hours later, or at a ratio of 1:1 to ifosfamide in the same infusion, followed by 500 mg PO 4 hours after completing the mixed-drug infusion.

A maximum of six cycles of treatment was planned in each arm, unless the investigator believed that the patient would benefit from additional cycles.

3.3.2 Dose Modifications

Dose delays and modifications were individualized according to each treatment arm. Common to all docetaxel and ifosfamide arms, no patient could be retreated until the ANC was >1,500 and the platelet count was >100,00 cells/mm^3. Retreatment with vinorelbine at *full dose* was permitted if the ANC was ≥ 1500. Vinorelbine retreatment was also allowed, but only at a reduced dose (15 mg/m^2), if the ANC on the day of treatment was 1,000 – 1499. Vinorelbine was held at least 1 week if the ANC was <1,000, and could be resumed at the appropriate dose when the ANC was ≥ 1000. However, if doses were held for 2 consecutive weeks, the vinorelbine dose had to be reduced to 22.5 mg/ m^2 if the ANC had recovered to a level ≥ 1500, or 11.25 mg/m^2 if the ANC had only recovered to the range of 1000 – 1499 cell/mm^3. If the dose had to be held 3 consecutive weeks, vinorelbine was discontinued. On the ifosfamide and docetaxel 75 mg/m^2 arms, grade 4 neutropenia lasting greater than 7 days, grade 4 neutropenia associated with fever (≥38.0° C x 3 readings within 24 hours or ≥ 38.5° C x 1 reading) or treatment with parenteral antibiotics, and grade 4 thrombocytopenia all prompted 25% dose reductions. On the docetaxel 100 mg/m^2 arm grade 4 neutropenia of >7 days duration or associated with fever or parenteral antibiotics prompted 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 could then be applied.

Reviewer Comment: See Section 3.3.3 Concomitant Therapy, below, for imbalances in G-CSF use that arose from this protocol specified difference in G-CSF administration.

In terms of non-hematological toxicities, the protocol specified that all treatment arms dose reduce 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. Discontinuation from the study was required for grade ≥ 3 peripheral neuropathy. Symptomatic fluid retention prompted administration of diuretics at the investigator's discretion.

Dose adjustments for abnormal liver function tests specifically tailored to individual treatment arms follow:

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%

Vinorelbine:

Total Bilirubin (mg/kg)	Dose of Vinorelbine (mg/m^2)
≤2.0	30
2.1 to 3.0	15
>3.0	7.5

3.3.3 Concomitant Therapy

G-CSF could be administered therapeutically in the first cycle "as clinically indicated", but its prophylactic use was limited to cycles beyond cycle 1 "as clinically indicated". As discussed above, dose modification instructions for neutropenic fever differed among the arms. Dose reduction was protocol-specified in the control and docetaxel 75 mg arms, but prophylactic G-CSF without dose reduction was the specified response to neutropenic fever on the docetaxel 100 mg arm.

Reviewer Comment:

G-CSF: Queries of the PCTX (prior and concomitant medication list) electronic data base using "GCSF, G-CSF, Neupogen, Leukine, GMCSF" identified 53 patients (42%) on the docetaxel 100 mg/m^2 arm, 21 patients (17%) on the docetaxel 75 mg/m^2 arm, and 16 patients (13%) on the control arm (6 patients treated with ifosfamide and 10 patients treated with vinorelbine) who were treated with G-CSF. The following table compares the relative administration of GCSF by cycle among the 3 treatment arms aver the first 6 cycles of therapy.

Table 5 Relative GCSF Administration by Cycle in the First Six Cycles

Cycle	Docetaxel 100 mg		Docetaxel 75 mg		V/I	
	Total No.	No. Starting	Total No	No. Starting	Total No	No. Starting
000	1	0	0	0	2	2
001	27	26	12	12	11	11
002	34	15	7	6	3	2
003	27	6	5	0	1	0

004	22	3	7	3	2	2
005	18	1	4	0	1	0
006	11	O	4	0	2	0

The coded reasons for administering the first dose of G-CSF to the 53 ***docetaxel 100 mg*** *patients were "prophylaxis" (code=5) in 17 patients, "adverse event" (code=4) in 34, "pre-existing", in one, and "other" in one. The majority of AE coding for first cycle of G-CSF administration occurred in cycle 001 - 22 in cycle 001, while there were 8 in cycle 002, and 1 in cycles 003, 004, and 005.. On the* ***docetaxel 75 mg/m^2 arm*** *the reasons for the first use of G-CSF were "prophylaxis" in 9 patients and "adverse event" in 13. On the* ***control arm*** *"adverse event" was the coded reason for the first dose of G-CSF in 9 patients, "prophylaxis" in 6, and "tumor related" in one.*

Antibiotics, prophylactic: The sponsor reported this data as a "by-cycle" analysis in **section 8.2.5 Prophylactic Therapies** of the application's TAX 320 Study Report. On the docetaxel 100 mg arm 87/452 (19%) of cycles were administered with prophylactic antibiotics, and on the docetaxel 75 mg arm, 89/518 cycles (17%) were administered with prophylactic antibiotics. Twenty-one of 305 vinorelbine cycles (7%) and 9/96 ifosfamide cycles (9%) were administered with prophylactic antibiotics.

Erythropoietin: A query of the electronic dataset using "Epogen," "Procrit," and "erythropoietin" identified 10 patients on the 100 mg/m^2 arm (2 patients coded "adverse event" in the first cycle of administration, 1 coded "prophylaxis" 5 coded "preexisting signs and symptoms", 1 coded both "adverse event" and "prophylaxis", and 1 coded "other"), 6 patients on the docetaxel 75 mg/m^2 arm (2 coded "prophylaxis" and 4 coded "preexisting signs and symptoms"), and 6 patients on the control arm (4 coded "adverse event" and 2 coded "prophylaxis"). Eight of the 10 docetaxel 100 mg patients started erythropoietin in cycle 000 or 001, and 3 of those patients had a PS of 2 at study entry. Similarly, on the docetaxel 75 mg arm most patients started erythropoietin in cycle 000 (4/6). All had a baseline PS better than 2. On the control arm 2/6 started in cycles 000 or 001, one of which had a baseline PS of 2.

Megestrol: A query using the medication "megace," "megestrol" and "megestrol acetate" identified 12 patients on the docetaxel 100 mg/m^2 arm (9.6%), 11 patients (9.2%) on the docetaxel 75 mg/m^2 arm, and 13 (10.6%) on the control arm (5 patients treated with ifosfamide and 8 patients treated with vinorelbine). Because differences in baseline megestrol administration could reflect differences in overall baseline status among the treatment groups, bias in supportive care provided, differences in perceived anticipated toxicity by prescribing physician at baseline, or differences in perceived toxicity once treatment had started, the reviewer examined the relative distribution of cycle of first megestrol administration among arms, relative distribution of reasons coded for starting it, and the relative distribution of performance status among patients treated with megestrol on the treatment arms. Those queries were conducted in JUMP and are shown below.

Table 6 Distribution of Cycle of Megestrol First Administration Across Treatment Arms

Cycle	Docetaxel 100 mg	Docetaxel 75 mg	Vinorelbine	Ifosfamide	V/I

000	4 (33%)*	8 (73%)	2 (25%)	1 (20%)	3 (23%)
001	4 (33%)	1 (9%)	1 (13%)	3 (60%)	4 (31%)
002	1	0	2 (25%)	0	2 (15%)
003	1	1	0	0	0
004	1	0	1	0	1
005	1	0	0	0	0
006	0	1	1	0	1
007	0	0	1	1	2
Total	**12**	**11**	**8**	**5**	**13**

*Percentages in the above table are of the total in the column.
The V/I column = Vinorelbine + Ifosfamide

The table above reveals a higher percentage of megestrol-treated patients were on the docetaxel arms at baseline or started in cycle 001 - 66% on Docetaxel 100, 82% on 75 mg and 54% on the V/I arm. The dataset was queried to see how the administration of megestrol correlated with baseline performance status among the treatment arms. The table summarizing this correlation below demonstrates that approximately 50% of the patients administered megestrol on the docetaxel arms had a baseline PS of 0-1, compared to 69% on the control arm.

Table 7 TAX 320 Distribution of Megestrol Administration by Baseline Performance Status Among Treatment Groups

Performance Status	Docetaxel 100 mg	Docetaxel 75 mg	Vinorelbine	Ifosfamide	V/I
PS = 0-1	6 (50%)	6 (55%)	6 (75%)	3 (60%)	9 (69%)
PS = 2	6	5	2	2	4
Total	12	11	8	5	13

Examination of the reasons coded in the dataset for initiating megestrol on study was compared among arms in the table below which shows fewer docetaxel 75 mg arm patients had megestrol initiated for an adverse event.

Table 8 TAX 320 Distribution of Coded Reasons for Initiating Megestrol Among Treatment Groups

	Docetaxel 100 mg	Docetaxel 75 mg	Vinorelbine	Ifosfamide	V/I
Tumor Related	1	0	1	0	1

Pre-existing Symptoms	4 (33%)	6 (55%)	3	3	6 (46%)
Adverse Event	6 (50%)	2 (18%)	4	2	6 (46%)
Prophylaxis	0	2	0	0	0
Other	1	1	0	0	0
Total	12	11	8	5	13

3.3.4 Evaluation on Study

Monitoring in this study included a baseline history and physical examination (including a complete neurological examination); blood work including hematology, chemistry, and urine or serum HCG in patients of childbearing potential; 12 lead ECG; ECOG performance status assessment and a quality of life assessment using the LCSS. 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, clinical tumor measurements, and quality of life assessment were to be repeated. The LCSS was to be completed prior to administration of dexamethasone in each cycle. Serial CBC's were to be performed on a weekly basis. Radiographic tumor assessments were to be repeated (using the same methodology as baseline) every 2 cycles "as required".

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 assessed every 2 months after completing therapy.

3.3.5 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.

Reviewer Comment: The protocol appeared to consider pulmonary lymphangitic metastases as both evaluable and non-evaluable disease. In addition, although pleural effusions appear to meet the protocol's definition of non-evaluable disease, the dataset reveals that pleural effusions were sometimes coded as evaluable (code = "3" in the Tumor dataset). In none of those patients, was the pleural effusion the only evidence of disease, and the additional disease present was measurable or evaluable. The reviewer identified 48 patients in the Tumor dataset who had pleural effusions reported in the baseline assessment, Cycle 000. (One patient in the 48 counted by the reviewer, Pt. 10501, was presumed to have pleural effusion by the reviewer, based on the data recorded in the electronic dataset – "right pleural cavity.") The majority of 31 patients' effusions were coded "3" for evaluable. The remaining 17 patients' effusions were coded non-evaluable, "4".

The protocol defined osteolytic metastases and lymphangitic metastases as evaluable disease. When the reviewer examined the Tumor dataset for patients whose only disease fell into one of these categories, she only found 4 such patients and they were all on a docetaxel treatment arm. Pt. 10035's only disease was a left lung infiltrate coded evaluable ("3") on CT. This patient's best response on the docetaxel 75 mg arm was NC. Pt. 10036, on the docetaxel 100 mg arm, had only bone lesions. Two of the lesions – one in the femoral neck and one in the iliac wing were considered bidimensionally measurable by MRI, and this patient's best response was PD. The remaining two patients were both treated on the docetaxel 100 mg arm and assigned a best response of NC. Pt. 10451 had multiple rib metastases evaluated by bone scan and Pt. 10682 had a vertebral lesion (evaluable, not measurable) evaluated with CT and two areas of pulmonary infiltrate, also evaluated with CT.

There were 42 participants in this study who had evaluable only disease. Their distribution across treatment arms, and the relative distribution of disease response in this subgroup of patients is summarized in the following table.

Table 9 Distribution of Evaluable-Only Disease and Response Category Assignment Among the Treatment Arms

	Docetaxel 100 mg (% Total)	Docetaxel 75 mg (%Total)	V/I (%Total)
All Disease = Evaluable Only	17 (14%)	15 (12%)	10 (8%)
Total NC = Best Response	8/17	6/15	2/10
Total = PR Best Response	**1/17**	**1/15**	**0**
Total = IMP Best Response	**1/17**	**2/15**	**1/10**

A slightly higher percentage of patients on the docetaxel arms had evaluable only disease, and of these patients, a higher percentage were assigned a NC response on the docetaxel arms than the control arm. The protocol specified that only patients with at least one bidimensionally measurable lesion could be assigned a response of PR. Patients with unidimensional (defined in

the protocol as evaluable only) or otherwise evaluable only disease could at best be assigned a response of IMP. ***It was not clear why the sponsor assigned a PR to some of these patients and an IMP to others, and in correspondence with the Agency the sponsor concurred with the protocol specified IMP assignments (rather than PR) in those patients with evaluable-only disease.***

3.4 Inclusion/Exclusion Criteria

3.4.1 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

3.4.2 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
- 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
- Prior treatment with BOTH vinorelbine and ifosfamide. Prior treatment with only one was not grounds for exclusion.
- Serious intercurrent illness
- Participation in a clinical trial or one or more experimental agents within 30 days of entry
- Inadequate marrow, hepatic, or renal function as evidence by:
  - ✓ ANC < 2.0 x 10^9/L
  - ✓ Platelet count < 100 x 10^9/L
  - ✓ Total bilirubin > ULN
  - ✓ Alkaline phosphatase > 5 x ULN
  - ✓ AST or ALT > 1.5 x ULN
  - ✓ Creatinine > 2.0 mg/dL or creatinine clearance < 60 mL./min.

3.5 Protocol Amendments

The content and dates of a single protocol amendment and a single administrative change are summarized below. Enrollment on the study started June 30, 1995 and completed April 25, 1997.

3.5.1 Amendment #1: June 22, 1995

- The minimum liver function requirements for eligibility were revised.
- Dose adjustments for abnormal liver function tests were revised.
- The instructions for dose adjustment for grade 4 neutropenia associated with fever or parenteral antibiotics in the docetaxel 100 mg/m^2 group were modified to substitute initiation of prophylactic G-CSF for dose reduction.
- The ifosfamide administration instructions were modified to allow the investigator to choose between two mesna administration schedules.
- The instructions for dose adjustment for granulocytopenia and hyperbilirubinemia on the vinorelbine arm were revised based on the package insert.
- Use of either AST or ALT was allowed for serial evaluation in the serial serum chemistries to be performed on study.
- The dexamethasone prophylaxis schedule on the docetaxel arms was modified to 5 doses – a decrease from the original five days administration schedule.
- A requirement to document a participant's prior history of febrile neutropenia associated with prior chemotherapy and/or prior growth factor use in the past in the past medical history,
- The definition of calculation of time to progression was modified from beginning at the date of first study drug administration to beginning at the date of randomization.

3.5.2 Administration Change #1: August 17, 1995

The protocol was changed to make to the dexamethasone prophylaxis instructions consistent throughout the protocol.

3.6 Enrollment, Protocol Violations, Removal From Study

Five of the 23 active sites participating in this study entered 53.9% of the patients (201/373). Twelve patients entered at 10 sites were found to be ineligible. Three (one on each treatment arm) were ineligible on the basis of histology (small cell lung carcinoma=1; renal cell carcinoma=1; and no tumor=1). **Those patients were excluded from the sponsor's efficacy analyses.** Elevated liver function test levels made 4 docetaxel patients (three on the 75 mg/m^2 arm and 1 on the 100 mg/m^2 arm) and only one control patient ineligible. The remaining four ineligible patients (three on the docetaxel arms and one on the vinorelbine/ifosfamide arm) were distributed among reasons that included concurrent lymphoma, uncontrolled brain metastases (the vinorelbine/ifosfamide patient), radiation to >10% of bone marrow within 30 days, and no evaluable lesions. There were twelve additional patients who were never treated after randomization (four in each treatment arm) because of rapid disease progression (N=7), medical insurance (N=1), and withdrawal of consent (N=4). Consent was withdrawn by two patients in each of the docetaxel 75 mg/m^2 and control groups. Three docetaxel 100 mg/m^2 arm patients, 2 control arm patients, and 2 docetaxel 75 mg/m^2 arm patients (one classified in this category because of elevated liver function tests) were never treated because of disease progression/disease complications.

Reviewer Comment: Four of the patients listed by the sponsor as never treated secondary to disease progression/complications were actually not eligible for participation – three on the docetaxel treatment arms and one on the control arm. Patients 10471 and 10445 had baseline liver function tests that made them ineligible for participation. Patient 10081 had a baseline creatinine and performance status rendering this patient ineligible as well. Pt 10467, randomized to the control arm, had active seizure activity at the time of randomization.

The control arm had the highest proportion of patients considered inevaluable for response. Most were considered inevaluable because baseline lesions were not assessed at least once after the second cycle with the baseline method of evaluation. The distribution of inevaluable patients among treatment arms and reasons for inevaluability are shown in the table below.

Table 10 Distribution of Inevaluability for Response Among Treatment Arms (Derived from Sponsor Table 8 Listing of Inevaluable Patients for Response by Treatment Group; Vol. 3 ,page 70.)

Reason for Inevaluability	**Docetaxel 100 mg/m^2**	**Docetaxel 75 mg/m^2**	**Vinorelbine/Ifosfamide**
Ineligible	3	6	3*
Not Treated	4	4	4*
Only one cycle of rx administered despite no PD	2	4	6
Baseline lesions not assessed at least once after cycle 2 with the same baseline method	7	4	9
Greater than 35 days between infusions without medical reason	0	0	1
TOTAL	16	18	22*

* One patient was both ineligible and not treated.

Reviewer Comment: It appears that there was better compliance with lesion assessments on the docetaxel 75 mg arm. The reason for this is unclear but could be related to investigator bias, a perception of better efficacy, and possibly better tolerability that enhanced patients' willingness to comply with reassessment procedures. In its discussion of other protocol violations, the sponsor mentions that although best response to prior cisplatin-based chemotherapy was one of the stratification factors at randomization, some randomizations were inadvertently stratified on the basis of the overall outcome of that prior therapy. This implies that some patients were stratified by PD, when their actual best response to prior cisplatin therapy could have been CR/PR/SD. There is no discussion in ***section 6.2 Protocol Violations*** *of the study report regarding how this could have impacted on the study outcome. Refer to* ***Sections 3.3 Study Design*** *and 3.7.1 of this review for a discussion of these errors.*

Protocol violations considered minor by the sponsor included patients who continued chemotherapy administration when they had met criteria for stopping therapy, and dosing errors in two patients —both on docetaxel treatment arms. One of those patients was randomized to 75

mg/m^2 but received 100 mg/m^2 x 3 cycles. Another, randomized to the same treatment group, received a dose of 150 mg/m^2 because of a BSA calculation error.

3.7 *Patient demographics and baseline characteristics; tumor characteristics*

3.7.1 Patient Characteristics

The median age in the docetaxel 100 mg/m^2 and vinorelbine/ifosfamide arms was 60 years. The median age in the docetaxel 75 mg/m^2 arm was 59. Randomization was stratified for performance status (0-1 vs. 2) and best response to prior cisplatin chemotherapy. There were 59 stratification errors on the basis of best response to prior cisplatin chemotherapy in this study, and 15 patients mis-stratified on the basis of performance status. (Please refer to **Section 3.3 Study Design.**) A discussion of the impact of these stratification errors on the distribution of prognostic factors across the treatment arms follows below.

Of the 59 mis-stratified patients, 16 were treated on the control arm, 22 on the docetaxel 100 mg arm, and 21 on the docetaxel 75 mg arm. To examine the distribution's potential impact on study outcome, the reviewer tabulated the number on each treatment arm that were mis-stratified in such a way that they would give a favorable outcome to that arm – those stratified as poor risk (best response to cisplatin PD) but were actually of more favorable risk (best response to cisplatin Non-PD). ***The distribution of these patients favored the docetaxel 75 mg arm.*** *There was a total of 42 such patients – 11 treated on the control arm, 13 on the docetaxel 100 mg arm, and 18 on the docetaxel 75 mg arm. This group could be further subdivided based on factoring in the performance status to the stratification. Seven of these 42 patients had a PS = 2, while the remaining 35 patients were among the most favorable risk at baseline – Non-PD response to prior cisplatin and PS ≤1. Of those 35 patients 10 were treated on the control arm, 10 on the docetaxel 100 mg arm, and 15 on the docetaxel 75 mg arm –* ***again favoring the docetaxel 75 mg arm.***

The 17 patient subgroup of mis-stratified patients that were stratified as more favorable risk, but were actually poorer risk (PD as best response to prior cisplatin chemotherapy) would be anticipated to worsen the outcome on the arm they were randomized into ***These errors, again, appeared to favor the docetaxel 75 mg arm, and particularly unfavorably affected the docetaxel 100 mg arm.*** *Of these patients, 5 were randomized to the control arm, 9 to the docetaxel 100 mg arm, and 3 to the docetaxel 75 mg arm. All but 4 of these patients had a baseline performance status of ≤1. The 4 patients with the poor prognostic factor combination of a PS = 2 and an actual response to prior cisplatin of PD included 3 patients treated on the docetaxel 100 mg arm (one was Pt. 10517, see below) and 1 patient treated on the control arm.*

Excluding those two patients mis-stratified for both PS and response to prior cisplatin, leaves 13 patients mis-stratified on the basis of errors in PS alone. Those whose actual PS was worse than reported at randomization would be anticipated to worsen the outcome of the arm to which they were randomized. This subgroup included 5 patients (excluding Pt 10097) - 2 on the control arm, 2 on the docetaxel 75 mg arm, and 1 on the docetaxel 100 mg arm. Three of the five had a PD best response to prior cisplatin - two control group patients and one patient treated on the docetaxel 75 mg arm. The remaining 8 patients, whose actual performance status was better than reported, would be anticipated to improve the outcome of the arm to which they were randomized.. (One of these patients was Pt. 10517 who was mis-stratified for both PS and best

response to prior cisplatin). All but one had Non-PD best response to prior cisplatin. That patient with a PD best response to prior cisplatin was treated on the control arm. The seven remaining more favorable prognosis patients were distributed among the arms as follows: 2 treated on the control arm, 2 treated on the docetaxel 100 mg arm, and 3 treated on the docetaxel 75 mg arm.

The relative distribution of the stratification factors among the 3 arms resulting from these stratification errors is shown in the tables below:

Table 11 Relative Distribution of the Stratification Factors Among the Treatment Arms that Resulted from Stratification Errors.

Control (V/I)			
	PS = 0, 1	**PS = 2**	**Total**
Non-PD to prior CDDP	75 (61%)	9	84 (68.2%)
PD to prior CDDP	29	10	39
Total	104	19	123
Docetaxel 100 mg			
	PS = 0, 1	**PS = 2**	**Total**
Non-PD to prior CDDP	72 (71*) (56.8%)	12	84 (68.2%)
PD to prior CDDP	32 (33*)	9	41
Total	104	21	125
Docetaxel 75 mg			
	PS = 0, 1	**PS = 2**	**Total**
Non-PD to prior CDDP	**82** (65.6%)	13	**95** (76%)
PD to prior CDDP	**21**	9	**30**
Total	103	22	125

* The corrected electronic dataset number taking into account Pt. 10485, who did not appear to have had the prior response to cisplatin coding corrected in the electronic dataset.

This table demonstrates that the imbalances in prognostic factor distribution, although small, had a favorable impact on the docetaxel 75 mg arm, relative to both of the other treatment arms, and that the impact primarily occurred in the favorable distribution of patients with non-PD response to prior cisplatin with favorable PS.

The reviewer explored this unequal distribution of prior response to cisplatin among the treatment arms as it correlated with the distribution of extent of disease within each arm – locally advanced vs. metastatic. A table summarizing this data, obtained from the electronic dataset follows, the percentages presented in the table are the percent of the total number of patients enrolled in that arm with that stage of disease:

Table 12 Distribution of the Stratification Factor Response to Prior Cisplatin Therapy Between Disease Extent Categories Among the Three Treatment Arms

Control (V/I)			
	Stage IIIB	**Stage IV**	**Total**
Non-PD to prior CDDP	9	75	84
PD to prior CDDP	2 (18%)	37 (33%)	39
Total	11	112	123
Docetaxel 100 mg			
	Stage IIIB	**Stage IV**	**Total**
Non-PD to prior CDDP	12	72 ** 71	84
PD to prior CDDP	5 (42%)	36 (33%) ** 37 (34%)	41
Total	17	108	125
Docetaxel 75 mg			
	Stage IIIB	**Stage IV**	**Total**
Non-PD to prior CDDP	10	85	95
PD to prior CDDP	3 (23%)	27 (24%)	30

Total	13	112	125

** Numbers corrected for Pt. 10485 who did not appear to have the response to prior cisplatin corrected in the electronic dataset. This patient had metastatic disease at registration.

Percentages presented in the above table are of the column total.

These tables demonstrate that the percentage of patients with metastatic disease at enrollment and PD as the best response to prior therapy was somewhat lower on the docetaxel 75 mg arm than both other arms. It must be kept in mind, however, that these percentages are based on small patient numbers. The docetaxel 100 mg arm had the highest percentage of IIIB patients with PD as a best response to prior cisplatin chemotherapy.

A table summarizing the relative distribution of other clinical features among arms may be found below. The treatment arms appeared balanced in distribution of PS = 2 (16.8%;17.6%;15.4%). A slightly higher percentage of patients on the vinorelbine/ifosfamide treatment arm had a baseline performance status of 0: 16.3% vs. 14.4% and 12.0% on the docetaxel 100 mg and 75 mg arms, respectively. Slight imbalances among treatment arms in clinical features as baseline tumor stage, tumor histologic subtype, percentage weight loss in the 3 months prior to study entry, lung involvement at study entry, liver involvement, and disease that was evaluable-only were noted by the sponsor. **The docetaxel 100 mg/m^2 treatment group had the highest relative distribution of patients who had had more than one prior treatment regimen (see table below). It had the highest percentage of patients with IIIB disease, but within that group, as shown in the tables above, there were more patients with PD as best response to prior cisplatin and the highest exposure to number of prior regimens (see Table 18 below).**

Table 13 Distribution of Select Demographic Features Among Treatment Groups (Derived from Sponsor Table 10 Patient Demographics By Treatment Group –ITT; Volume 3, Page 74 and Sponsor Table 13 Prior Chemotherapy by Treatment Group – ITT; Volume 3, Page 77)

Demographic Feature	Docetaxel 100mg/m^2	Docetaxel 75 mg/m^2	Vinorelbine/Ifos.	Total
Baseline Stage				
Locally Advanced	13.6%	10.4%	**8.9%**	11.0%
Metastatic	86.4%	89.6%	**91.1%**	89.0%
Histology				
Adenocarcinoma	**40.8%**	56.0%	52.0%	49.6%
Squamous Cell	33.6%	**17.6%**	30.1%	27.1%
Large Cell Undifferentiated	17.6%	20.8%	**15.5%**	18.0%
Other	8.0%	5.6%	2.4%	5.4%
Weight Loss in Prior 3 months				
<10%	88.8%	**92.0%**	90.2%	90.3%
≥10%	**11.2%**	7.2%	9.8%	9.4%

Demographic Feature	Docetaxel 100mg/m^2	Docetaxel 75 mg/m^2	Vinorelbine/Ifos.	Total
Organs Involved				
Lung	84.0%	77.6%	83.7%	
Liver	**24.0%**	19.2%	15.4%	
Adrenal	18.4%	20.0%	**10.6%**	
Performance status				
PS = 2	17%	18%	15%	
Lesion Assessment				
Evaluable Disease Only	**13.6%**	10.4% *(12%)*	**8.1%**	10.7%
Prior Treatment				
No. of Prior Regimens > 1	**35.2%**	25.6%	28.5%	
CR to Prior Platinum**	14	9	6	
(Subsequent PD within 3 months)	(0/14)	(0/9)	(2/6)	
Non-PD to Prior Platinum Chemotx	68.2%	76%	68.2%	

* *The reviewer found 15/125 patients with evaluable only disease on this treatment arm in her review of the Tumor electronic dataset.*

** *Only two of the patients with CR to prior therapy experienced a PR on TAX 320, and both were treated on the docetaxel 100 mg arm.*

The only negative feature with highest distribution to the vinorelbine/ifosfamide group was the relative distribution of metastatic disease and locally advanced disease, but the difference was slight. The control arm had the lowest percentage of IIIB patients with PD as a best response to prior therapy among the treatment arms, but there were more patients in the docetaxel treatment groups that had locally advanced disease at the time of study entry. The docetaxel 75 mg treatment arm had a lower percentage of PD as a best response to prior cisplatin patients in both stages of disease than the docetaxel 100 mg group. In the overall study population 70.2% had been treated with only one prior chemotherapy regimen, but there is no information on what proportion had received that prior chemotherapy in the neoadjuvant setting.

Reviewer Comment: There were 17 IIIB patients on the docetaxel 100 mg arm, 13 on the docetaxel 75 mg arm, and 11 on the control arm. Despite the similar length of the time interval between diagnosis and last chemotherapy among the treatment arms, including the IIIB subgroup, the patients on the docetaxel 100 mg treatment had been treated with more regimens of chemotherapy prior to randomization than the other two arms. This is summarized in the following table.

Table 14 Stage IIIB Patient History of Number of Prior Treatment Regimens by Treatment Arm

	Docetaxel 100 mg	Docetaxel 75 mg	V/I
One prior regimen	9	10	11
Two prior regimens	6	3	0
Three prior regimens	2	0	0

Of the IIIB patients who had been treated with one prior regimen, the control arm had the highest proportion of regimens that contained paclitaxel – 4/11 (compared to 1/9 on the docetaxel 100mg arm and 3/10 on the docetaxel 75 mg arm).

Comparison of the arms regarding whether the IIIB patients had received prior radiotherapy demonstrated that the docetaxel 100 mg arm had the lowest percentage of IIIB patients who had not been treated with prior radiotherapy - 2/17 (12%) docetaxel 100 mg IIIB patients had received no prior radiotherapy. Both had experienced PD as the best response to prior cisplatin. Six of 13 (46%) docetaxel 75 mg patients had not been treated with prior radiotherapy and two of those had experienced PD as a best response to prior cisplatin. On the control arm, 6/11 (55%) of the IIIB patients had not been treated with prior radiotherapy and only one of those had experienced PD as the best response to cisplatin.

There were 5 patients with a pleural effusion at baseline in the study whose disease was designated stage IIIB. Three were on the docetaxel 100 mg arm, while there was one patient each on the remaining two treatment arms. Of the total 48 patients on study who had pleural effusion at baseline, 20 were on the docetaxel 100 mg arm (16% of that arm's population), 16 were on the docetaxel 75 mg arm (13% of that arm's population), and 12 were on the control arm (10%).

Patients with asymptomatic and "controlled" brain metastases were eligible for this study. There were five patients with brain metastases at baseline on each of the docetaxel arms . Three patients on the control arm were coded as having brain metastases at baseline, but one actually had a spinal cord lesion.. On the docetaxel 100 mg arm, 2/5 had a PS = 2 at baseline, and one patient had experienced a weight loss of >10% at study entry. Of the 5 docetaxel 75 mg arm patients with brain metastases, 1 had a PS = 2 and none had experienced a weight loss of >10%. The only patient on the control arm with a PS =2 was the patient who had a spinal cord lesion rather than brain metastases. None had experienced a weight loss of >10%.

Another approach the reviewer used to explore for differences in baseline patient characteristics among the treatment arms was to examine the concomitant medication dataset, PCTX, for differences in the distribution of the use of various medications at baseline. These analyses found similarities among treatment arms.

A list of patients was tabulated examining baseline use of morphine – like pain medication. The following group of medications was examined: "morphine", "morphine sulfate", "oramorph", ms contin", "fentanyl", "duragesic", and "levo dromeran". Using Jump the reviewer identified 26/125 (26%) patients on the docetaxel 100 mg arm, 36/125 (29%) on the docetaxel 75 mg arm, and 28/123 (23%) on the control arm using these medications at cycle 000 (baseline).

A JUMP query of the PCTX data set for baseline oxygen use in cycles 000 was performed. Nine of 125 (7%) patients on the docetaxel 100 mg arm were on supplemental oxygen at baseline, 8/125 (4%) on the docetaxel 75 mg arm, and 9/123 (3%) on the vinorelbine/ifosfamide arm.

Baseline prednisone use in cycle 000 was identified in 8/125 docetaxel 100 mg patients (6%), 7/125 docetaxel 75 mg patients (6%), and 11/123 vinorelbine/ifosfamide patients (9%) A similar query in JUMP was conducted to assess baseline use of bronchodilator therapy across treatment arms. The following terms were identified and tabulated: "ventolin", "vanceril", "atrovent", theophylline", "theodur", "alupent", "proventil", "azmacort", "brethine", "albuterol", beclomethasone", iprotropium", "mucomyst", "epinephrine", "beclovent", and "maxair". Twenty-eight of 125 patients (22%) of the docetaxel 100 mg patients, 27/125 (22%) of the docetaxel 75 mg patients, and 22/123 (19%) of the control patients were taking these medications.

There were two patients identified who were treated with vinorelbine on study who were reported to be on G-CSF at baseline (patients 10362 and 10493), and one patient on the docetaxel 100 mg arm (Pt. 10458). There were 5 patients (4%) on the docetaxel 100 mg arm who were identified as being treated with erythropoietin at baseline (cycle 000). Similarly, on the docetaxel 75 mg arm, there were 4 patients (3%) on erythropoietin at baseline, cycle 000. There was only one (1%) vinorelbine/ifosfamide patient reported to be on erythropoietin at baseline..

3.8 On-Study Therapy

Twelve of the 373 randomized patients were not treated on study – 4 in each treatment group (docetaxel 100 mg/m^2, docetaxel 75 mg/m^2, and the ifosfamide/OR vinorelbine groups). Of the 119 control arm patients, 32 were administered ifosfamide and 87 vinorelbine. Docetaxel and ifosfamide were administered on a q 3 week schedule, and vinorelbine on a weekly basis, cycled every 21 days. A total of six cycles was recommended, but treatment could be continued beyond 6 cycles at the investigator and patient's discretion.

Doses were reduced in 19/452 (4.2%) cycles of docetaxel 100 mg/m^2, and delayed in 66/452 (14.6%) **cycles**. Five percent of cycles were delayed longer than 7 days. The total number of **patients** who experienced **delays** longer than 3 days was 50/121 treated (**41.3%**). The most common reason given for treatment delay by cycle and patient was "other" (44.0% by patient), followed by hematological toxicity (15.2% of cycles; 18% of patients). Non-hematological toxicity and non-drug related adverse events followed, both 12.1% by cycle and 16.0% by patient. The 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 **10/121 (8%) treated patients** on the docetaxel 100 mg arm that had planned dose reduction (code = 2). These reductions occurred most commonly in cycle 002 (n=6), (despite the protocol plan to manage neutropenic fever first with G-CSF) followed by cycle 004 (n=2).

Doses were reduced in 101/518 (19.5%) cycles of docetaxel 75 mg/m^2, and delayed in 80/518 (15.4%) cycles. Five percent of cycles were delayed longer than 7 days. The total number of patients who experienced **delays** longer than 3 days was 51/121 (**42%**) treated. The most common reason given for treatment delay by cycle and patient was "other", followed by hematological toxicity (11.3% of cycles and 17.6% of patients) and non-drug related adverse events (7.5% by cycle and 11.8% by patient). The two docetaxel treatment arms were similar in the percentage of cycles and patients impacted by treatment delays, but not dose reduction. The smaller percentage of by-cycle dose reductions on the docetaxel 100 mg arm likely reflects the protocol specified practice of administering G-CSF in lieu of the dose reductions performed in the other treatment arms. The 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 docetaxel 75 mg arm who had

planned dose reduction (code = 2) – a higher percentage than the docetaxel 100 mg arm. These dose reductions occurred most commonly in cycle 002 (n=16), followed by cycles 003, 004, and 005 (n=3 in each).

Doses were reduced in 8/96 (8.3%) of ifosfamide cycles, and delayed in 14/96 (14.6%). Delays by-cycle are similar to that reported on the docetaxel arms, and reductions by-cycle are intermediate between that reported for the two docetaxel arms. Five percent of cycles were delayed longer than 7 days. The total number of patients who experienced delays was 9/32 treated (28.1%), which is lower than both docetaxel arms. The most common reason given for ifosfamide treatment delay by patient was "other" (44.4%), followed by hematological toxicity (33.3% of patients) and non-hematological toxicity (11.1% by patient). The 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 **5/32 (16%) patients** treated with ifosfamide that underwent planned dose reduction (code = 2). These dose reductions occurred one each in cycle 002, 003, 004, 005, and 007 (n=6).

Dose attenuation in the vinorelbine group occurred primarily by holding a weekly dose. One dose was omitted in 147/305 (48.2%) vinorelbine cycles, and two doses were omitted in 31/305 (10.2%) cycles. The total number of patients who experienced delays was 52/87 treated (59.8%) The most common reason given for treatment delay by patient was hematologic toxicity (36.5%), followed by missing reason (30.8%) and "other" (23.1%). "Other" was the most common reason in each treatment arm except the vinorelbine-treated patients for delay of treatment : docetaxel 100 mg/m^2 = 44%, docetaxel 75 mg/m^2 = 61%, ifosfamide = 44%. The designation "Other" included holidays, vacation, clinic scheduling problems, weather, pharmacy out of drug, waiting on staging results, death in family, forgotten appointment, and patient request. *(Reviewer Comment: These reasons could not be confirmed in the electronic database.)* In the vinorelbine group hematological toxicity exceeded other (36.5% vs. 23.1%) and this treatment group was the highest reporting hematological toxicity as a reason for treatment delay (docetaxel 100 mg/m^2 = 18%, docetaxel 75 mg/m^2 = 18%, ifosfamide = 37%). The 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 **50/87 (58%) patients** treated with vinorelbine that underwent planned dose reduction (code = 2). These dose reductions occurred most commonly in cycle 002 (n=27) followed by cycle 003 (n=9) and cycle 004 (n=6). The total percentage of those patients actually treated on the entire control arm (vinorelbine + ifosfamide) who experienced dose reduction was 55/119 (46%).

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 arm dose intensity was 0.99, the docetaxel 75 mg/m^2 arm was 0.98, for those patients treated with ifosfamide it was 0.98, and for the patients treated with vinorelbine it was only 0.67.

Reviewer Comment: The vinorelbine dose intensity was the lowest in the study, and the majority of patients treated on the control arm were treated with vinorelbine (87/119). The protocol's vinorelbine dose modifications are those recommended in the vinorelbine label. The

*vinorelbine dose intensity was reported in the phase 3 study reported by Le Chevalier, et al (JCO, Vol. 12, No 2, 1994: 360-367.) as percentage calculated by Given Dose/Expected Dose (calculated full dose for the period of time when a patient was on treatment). On the single agent vinorelbine arm that percentage was **83%**, higher than the dose intensity found in the vinorelbine patients on the control arm of the TAX 320 study, but the eligible patients in the Le Chavalier study had no prior chemotherapy. A study reported by Crawford, et al, in JCO Volume 14, No 10, 1996: 2774-2784, also limited participation to patients with no prior chemotherapy. The vinorelbine dose intensity in that study was reported as 74% of the intended dose. Vinorelbine doses were delayed in 81/143 (57%) patients in that study - similar to TAX 320 - and decreased in 53/143 (37%) – less than TAX 320.*

Please refer **to Section 3.3.3 Concomitant Medications** in this review for a discussion of pertinent differences among the treatment arms in use of prophylactic G-CSF and antibiotics.

3.9 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 either docetaxel dose group and the control group would be 7.5 months and 5 months, respectively, and that the follow-up after the last patient enrollment would be 12 months. The pre-specified comparisons of interest were the differences between the docetaxel 100 mg arm and the control, and the difference between the docetaxel 75 mg arm and control. The treatment group comparisons would be made with the log rank test. The protocol stated that "equality of survival time" would be evaluated by first comparing the docetaxel 100 mg treatment arm to the control arm at the 5% significance level. If this test was not significant, the docetaxel 75 mg arm would not be compared to the control arm. The latter comparison would only be conducted if the first comparison was significant. This comparison strategy was prospectively defined to "result in an overall type I error of 5%". The statistical analysis plan stated that the median survival time would be reported with the 95% CI, and compared with the log rank test.

Time to progression, a secondary endpoint, was to be measured from the date of randomization to date of disease progression. Kaplan-Meier estimates were to be performed and median times to progression reported with a 95% CI. Comparisons would be made with the log rank test.

Criteria for censoring were not set out in the protocol statistical analysis plan. A statistical analysis plan dated approved January 15, 1998 is included with the application in Appendix II (Appendix II.A2). (The data cutoff for this study was January 1, 1998.) In that plan, survival is defined as the duration between the date of randomization and date of death (from any cause) or the date of last contact if there was no documentation of death. The TTP endpoint was defined in that plan as it was in the protocol, however, the text of the plan indicated that the calculation of TTP would include the duration from the date of randomization to the date of last assessment prior to further therapy and duration from date of randomization to the date of death, as long as that death occurs less than 3 months after the last tumor assessment (otherwise the patient is censored at their last tumor assessment). Appendix 2. of that statistical analysis plan outlines the definitions to be applied in the time-to-event Kaplan-Meier analyses. The reasons for censoring in the survival and TTP analyses are tabulated below:

Survival

Reason	Date

•	Lost to follow-up	Date of last contact
•	No death before cut-off	Cut-off date

TTP

	Reason	Date
•	Lost to follow-up	Date of last contact
•	No PD or death before cut-off	Cut-off date
•	Further therapy before PD (further rx to include XRT, chemotherapy, surgery, immunotherapy)	Date last assessment before rx
•	Death ≥3 months beyond last tumor assessment	Date last assessment

The final study report indicates that the actual time to event analyses were performed with different censoring than set forth in the January '98 statistical analysis plan. Time to progression censoring was performed at the last tumor assessment prior to further anti-cancer therapy, which appears to have included surgery, immunotherapy, and chemotherapy, but not radiotherapy. Additionally, the sponsor performed an unplanned survival analysis that censored patients at the time of subsequent chemotherapy.

Reviewer Comment: The reviewer examined those patients who were treated with radiotherapy after randomization and found no patients whose dates of progression were clearly recorded that would have qualified for censoring on the basis of radiotherapy.

Response and Duration of Response were protocol defined secondary endpoints. 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. 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. The protocol stated that response rates would be evaluated separately in patients with bidimensionally measurable disease and in patients with evaluable disease.

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 to 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.

Reviewer Comment: Although the protocol used only bidimensionally measurable disease to define PR, as discussed in ***section 3.3.5 Efficacy and Evaluation Requirements,*** *there were 2*

*patients on the docetaxel arms assigned a best response of PR despite the fact that their disease was evaluable-only, while there were 4 additional patients (2 on the docetaxel 75 mg arm , 1 on the docetaxel 100 mg arm, and 1 on the control arm) who were assigned a response of IMP. The reviewer reassessed the responses utilizing the protocol-specified response criteria. Refer to section **3.10.2 Response** of this review for a more detailed discussion.*

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

- LCSS score changes in baseline of the mean 100mm visual analog scales. The protocol stated that this analysis would include an analysis of variance method for comparison, "if appropriate".
- Changes of weight. Comparisons would be made using an analysis of variance method for comparison, "if appropriate".
- Changes in ECOG performance status. Comparisons would be made using an analysis of variance method for comparison, "if appropriate".
- Changes in analgesic use. Comparisons would be made using an analysis of variance method for comparison, "if appropriate".

Reviewer Comment: Analyses of changes of weight, performance status, and analgesic use were not presented in the study report, except for a brief summary focused on weight gain in the analysis of fluid retention in the safety section.

3.10 Efficacy Analysis

3.10.1 Survival

The sponsor opens its discussion of the efficacy results with an acknowledgement that the primary efficacy analysis of overall survival in TAX 320 detected no significant difference between either docetaxel treatment arm and the vinorelbine/ifosfamide control. They believe, however, that the study demonstrates a "favorable trend" associated with docetaxel, particularly when considering one-year survival, an unplanned analysis.

The protocol's statistical analysis plan stated that the primary endpoint, survival, was to be examined first by comparing the docetaxel 100 mg arm to the control arm, utilizing the log rank test. If that difference was not significant, the comparison of the 75 mg docetaxel arm to the control arm would not be performed. The median survival was very similar on all 3 arms: docetaxel 100 mg = 5.5 months (95% CI = 4.6, 6.6), docetaxel 75 mg = 5.7 months (95% CI = 5.1, 7.9), and control = 5.6 months (95% CI = 4.3, 7.9). The log rank test comparison of docetaxel 100 mg vs. the control arm yielded a p = 0.93. Despite the prospective plan to not compare the docetaxel 75 mg arm if the docetaxel 100 mg/control comparison was not significant, this test was performed with the log rank and the p = 0.14. (In this analysis, 83.2% of the possible events – deaths – had occurred on the docetaxel 100 mg/m^2 arm, 77.6% on the 75 mg/m^2 arm, and 89.4% on the control arm.) The highest percentage of survival censoring occurred in the docetaxel 75 mg/m^2 arm (docetaxel 100 = 21/125; docetaxel 75 = 28/125; control = 13/123). No censored patient had a known date of death, on review of the electronic dataset. The majority had been censored within 3 months of the study cut-off date. Of the 6 patients who were censored >4 months earlier than the cut-off date, 5 were on the docetaxel 75 mg/m^2 arm and 1 was on the docetaxel 100 mg/m^2 arm. Those on the docetaxel 75 mg/m^2 arm were censored approximately 4 months (survival = 606 days), 5 months (survival = 185 days), 7 months

(survival = 111 days), 8 months (64 days) and 20 months (50 days) earlier than the cutoff. The docetaxel 100 mg patient was censored approximately 9 months prior to the cut-off (survival = 64 days).

Reviewer Comment: The sponsor submitted an updated safety analysis in a FAX dated November 5, 1999. The cutoff date for the update was September 20, 1999. In the updated analysis 23 patients were censored (docetaxel 100 mg/m^2= 7; docetaxel 75 mg/m^2 = 12; and control = 4). The median survivals were: docetaxel 100 mg/m^2 = 5.5 months (95% CI = 4.6, 7.2), docetaxel 75 mg/m^2 = 5.7 months (95% CI = 5.1, 7.1), and control = 5.6 months (95% CI = 4.4, 7.9). These medians are unchanged, except for minor changes in the confidence intervals. The log rank analysis continues to reveal no significant difference between each docetaxel arm and the control: docetaxel 100 mg/m^2 p= 0.577 and docetaxel 75 mg/m^2 , p = 0.131.

The Kaplan-Meier curves for the intent to treat population in each treatment arm can be found on page 84 of the sponsor's Study Report in **section 7. Efficacy Results, Figure 2.** The curves overlie each other until approximately 10 months, when the docetaxel 75 mg treatment arm curve appears to pull away from the other two curves, and remains so out to 18 months. This separation led to the sponsor's unplanned comparison of percent survival at one year, a not uncommon survival comparison in the field of non-small cell lung carcinoma. The one year time interval has been viewed a clinically relevant time point for comparisons in this disease and is commonly reported in phase 3 trials of first-line treatment of advanced stage disease. The probability of survival at one year, obtained from the Kaplan-Meier curves in TAX 320, was 21% (CI = 14,28) on the docetaxel 100 mg/m^2 arm, 32% (CI = 23,40) on the docetaxel 75 mg/m^2 arm, and 19% (CI= 12,26) on the control arm. Time to event analyses, including those reported at a particular time interval, are best conducted utilizing an analysis such as the log rank test, which incorporates censored patients in the analysis, thus yielding the most valid comparison. However, because the log rank test looks at the entire curve prior to the selected time point and the control arm curve was overlying those of both docetaxel arms until approximately month seven, the sponsor selected the Chi Square test to compare survival rates at one year. This test evaluates only the selected time point and ignores the censored patients. Comparisons made with this method utilize a 2 x 2 table. The patients entered into the 2x2 comparison were those who had died prior to their 365th day after randomization and those who were alive as of day 365 after randomization. Only patients who had been followed 365 days could be included in this analysis. Any participant who did not fit in either of the categories was not included in the analysis.

The following table summarizes the extent of the available data that formed the basis for the 1-year survival Chi-Square analysis.

Table 15 Patient Numbers Utilized in the Chi-Square Analysis of Percent One-Year Survival

	Total No. on Study	Total Alive 365 days	Total Dead prior to 365 days	No. Excluded from the Analysis (%)
Docetaxel 100 mg	125	21	96 (77%*)	8 (6%)
Docetaxel 75 mg	125	32	83 (66%*)	9 (7%)
Control (V/I)	123	20	98 (80%*)	5 (4%)

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