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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-449/S-018

Medical Review(s)

Clinical Review Cover Sheet

Application #	**20-449/SE8-018**
Drug Name	**Taxotere® (docetaxel)**
Medical Reviewer	**Ramzi Dagher, M.D.**
Medical Team Leader	**Donna Griebel, M.D.**
Documents reviewed	**SE-018 2/1/02, 3/28/02,8/13/02, 8/19/02,8/20/02, 10/17/02,10/14/02, 9/05/02,9/30/02, 8/08/02,4/08/02**

Table of Contents

Table of Tables

Clinical Review for NDA 20-449/S-018

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends approval of docetaxel (taxotere) in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition.

The assessment of benefit in this application is based on the clinical benefit endpoint of overall survival. In a phase 3 randomized open-label trial, there was statistical evidence for non-inferiority of docetaxel + cisplatin relative to the active control regimen of vinorelbine + cisplatin for the endpoint of survival. The efficacy results for this endpoint are summarized in section II of this document.

With regard to the risks associated with docetaxel therapy, the FDA's previous review of the safety databases submitted in prior NDA's that resulted in the approval of docetaxel for the treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy and for use in locally advanced or metastatic NSCLC after failure of platinum based therapy has identified a number of safety concerns. The review of the new database of patients with locally advanced or metastatic NSCLC who have not previously received chemotherapy for this condition who received docetaxel in combination with cisplatin or carboplatin in a randomized comparison to vinorelbine+cisplatin has allowed identification of the following issues, which are common to those noted in prior reviews. Furthermore, no new toxicites have been identified in this treatment setting :

The most commonly occurring clinically relevant adverse events (greater than or equal to 50% of patients) included alopecia, nausea, vomiting, asthenia, and pain. Most of these AE's were grade 1 or 2 by NCI term (or mild to moderate by COSTART term), with grade 3 or 4 events occurring in 15% or less of patients. Myelosuppression was noted in most patients, with leucopenia, neutropenia, and anemia each occurring in greater than 85% of patients across the three treatment arms.

Other commonly occurring AE's (20%-50% of patients) included diarrhea, weight loss, stomatitis, infection, hemoptysis, constipation, fluid retention, and neurosensory events.

Less commonly occurring AE's (less than 20%) included hypersensitivity reactions, neuro-hearing cerebellar or motor AE's, myalgia, arthralgia, nail disorders, dehydration, taste perversion, and dizziness.

In general, the safety profile of docetaxel + cisplatin was comparable to vinorelbine + cisplatin. Alopecia, fluid retention (especially peripheral edema and weight gain), myalgia, arthralgia, and nail disorders occurred more frequently in the docetaxel + cisplatin arm compared to the vinorelbine + cisplatin arm. Diarrhea and hypersensitivity reactions occurred more frequently and with more severity in the docetaxel + cisplatin arm compared to the vinorelbine + cisplatin arm. In contrast, hearing loss and constipation occurred less commonly in the docetaxel + cisplatin arm compared to the vinorelbine + cisplatin arm.

It is the judgement of the FDA clinical review team that the potential benefits outweigh the risks associated with docetaxel therapy in combination with cisplatin in patients with stage IIIB or stage IV NSCLC who have not received prior chemotherapy. The toxicity profile relative to cisplatin + vinorelbine does not preclude approval based on efficacy non-inferiority.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The previously outlined phase IV commitments which are yet to be fulfilled will be reiterated. The status of clinical trials being conducted in relation to these commitments are outlined below :

1. TAX311 " Phase III Comparison of Taxotere and Taxol in Patients with Advanced Breast Cancer " is ongoing. The sponsor is contemplating halting accrual at his point as 445 of a planned 490 patients have been enrolled.

2. TAX313 titled " A Multicenter, Randomized, Phase III study of docetaxel 100 mg/m^2 versus 75 mg/m^2 versus 60 mg/m^2 as Second-Line Chemotherapy for Patients with Advanced Breast Cancer" was submitted to FDA on October 3 , 2002.

3. TAX259 titled " A Phase I Dose Escalation Study of Docetaxel with Lenograstim Support in Patients with Advanced Solid Tumors " has completed accrual. The sponsor has projected submission of a final study report in Q1, 2003.

4. T96-0028 " Phase I study of Taxotere in Patients with Advanced Malignancies and Varying Degrees of Liver Dysfunction " is ongoing. TAX008 " Phase I Study of

Taxotere for Cancer Patients with Liver Dysfunctions Due to Malignancies " has been completed and submission of a study report is expected in Q1, 2003.

5. TAX

" is ongoing.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions.

The outcome for NSCLC patients with locally advanced or metastatic disease (stage IIIB or IV) remains poor despite multimodality approaches utilizing surgery and chemotherapy with or without radiation. Although multiple platinum-based regimens are widely utilized, none of the regimens is clearly superior to the other. The ideal combination regimen for use in patients with advanced disease has yet to be defined.

Aventis has submitted data for a docetaxel/platin combination regimen for first line treatment of advanced NSCLC from an open-label, randomized phase 3 study of docetaxel used in combination with cisplatin versus vinorelbine + cisplatin versus docetaxel + carboplatin. One-thousand two hundred and twenty patients with stage IIIB or stage IV NSCLC were randomized, 1203 of whom received chemotherapy on one of the three treatment arms (TAX326). The sponsor has also submitted data from one phase 1 (TAX012, N = 64) and one phase 1 / 2 (TAX018, N = 71) study of docetaxel + cisplatin in advanced solid tumors and metastatic or locally advanced NSCLC respectively in addition to one phase 1 study of docetaxel + carboplatin in advanced solid tumors (TAX049, N = 22).

The applicant has previously established the single agent activity of docetaxel in first line treatment of advanced NSCLC in a study that randomized patients between docetaxel 100 mg/m^2 and best supportive care with a small survival benefit. In addition, the applicant has obtained approval of single agent docetaxel at a dose of 75 mg/m^2 for second line treatment of NSCLC after failure of prior platinum therapy based on a survival benefit.

B. Efficacy

The DODP is recommending approval of this sNDA based on the clinical benefit endpoint of overall survival, which was the primary endpoint of TAX326. Kaplan-Meier median estimates of overall survival were 10.9 months, 9.1 months, and 10.0 months for the docetaxel + cisplatin, docetaxel + carboplatin, and vinorelbine + cisplatin arms respectively (estimated hazard ratio of docetaxel + cisplatin / vinorelbine + cisplatin = 0.884). There was no statistical evidence for survival superiority of either docetaxel-containing regimen relative to the active control of vinorelbine + cisplatin. There was statistical evidence for survival non-inferiority of docetaxel + cisplatin relative to the active control regimen with preservation of at least 62% of the vinorelbine + cisplatin effect.

There was no statistically significant finding of superiority in analysis of the secondary endpoints of response rate, duration of response, or time to progression (comparison of either docetaxel-containing regimen to vinorelbine + cisplatin). The sponsor's conclusions regarding QoL analyses were not considered to be reliable by FDA reviewers.

C. Safety

1. Adequacy of safety testing

The following table summarizes the exposure to docetaxel in TAX326 presented as a comparison of mean and median number of cycles on therapy in the three treatment arms.

Table 1 : Drug Exposure in TAX326

Treatment Cycles	Docetaxel Cisplatin N = 406	Docetaxel Carboplatin N = 401	Vinorelbine Cisplatin N = 396
Mean	4.6 (4.4, 4.8)	4.7 (4.5, 4.9)	3.9 (3.7, 4.1)
Median	5	6	4
Min			
Max			

With respect to specific dosing, the following table summarizes cumulative dose and weekly dose intensity of each drug across the three treatment arms. Docetaxel dose intensity was comparable in the two docetaxel-containing regimens. The cisplatin dose intensity was comparable between the docetaxel + cisplatin arm and the vinorelbine + cisplatin active control.

Table 2 : Cumulative Dose and Dose Intensity in TAX326

Treatment Group and Component	Docetaxel Cisplatin N = 406		Docetaxel Carboplatin N = 401		Vinorelbine Cisplatin N = 396	
	Docetaxel	Cisplatin	Docetaxel	Carbop	Vinorelbine	Cisplatin
Cumulative Dose (mg/m^2)						
Mean	340	339	342	1730	284	354
Median	378	377	379	1802	275	353
Min			—			
Max			—			
Dose Intensity (mg/m^2/week)						
Mean	23.44	23.42	23.36	117.37	16.75	22.09
Median	24.21	24.27	24.13	113.83	16.91	23.24
Min			—			
Max			—			

The incidence of deaths attributed to malignant disease or study drug was comparable across treatment arms, with a toxic death rate of 2.2% in the docetaxel+cisplatin arm and 2% in each of the docetaxel+carboplatin and vinorelbine+cisplatin treatment arms.

Overall, 23% of patients discontinued treatment due to an AE in the vinorelbine+cisplatin group, 15.8% in the docetaxel+cisplatin group, and 9.2% in the docetaxel+carboplatin group. This may explain, to some extent, the slightly decreased mean # of cycles of therapy administered on the cisplatin+vinorelbine arm compared to either docetaxel-containing regimen (see table 1 above).

In addition to the 807 patients with previously untreated NSCLC who received docetaxel in TAX326, the FDA has previously reviewed data from 250 patients with NSCLC who received docetaxel on TAX320, 100 NSCLC patients who received docetaxel on TAX317, 138 patients with previously untreated NSCLC who received docetaxel on TAX — and 364 patients with advanced breast cancer who received docetaxel in two randomized trials.

During the period from 4/01/94 until 5/31/01, the sponsor estimates that approximately — patients worldwide have received docetaxel from commercial sources. In addition, approximately 37,500 patients enrolled in clinical trials (post-marketing and investigational) have received docetaxel alone or in combination with other anti-cancer agents in the treatment of various cancers.

2. Serious side effects

Serious or life-threatening adverse events were reported in over 50% of patients in TAX326. However, individual events occurred less commonly. Individual serious or life-threatening adverse events included infection, nausea, vomiting, diarrhea, asthenia, hypersensitivity reaction, fluid retention, neurosensory events, and neutropenia.

Infection : Grade 3 or 4 infections occurred in 8%, 11%, and 8% of patients in the docetaxel + cisplatin, docetaxel + carboplatin, and vinorelbine + cisplatin treatment arms. In patients with death attributed to toxicity from study treatment, infection was the most common investigator assessment as cause of death (19/25 = 76%). There were 6 deaths attributed to infection in the docetaxel+cisplatin group, 5 in the vinorelbine+cisplatin group, and 8 in the docetaxel+carboplatin group.

Nausea: Grade 3 / 4 nausea occurred in 10%, 6%, and 17% of patients in the docetaxel + cisplatin, docetaxel + carboplatin, and vinorelbine + cisplatin treatment groups.

Vomiting : Grade 3 / 4 vomiting was also more commonly observed in the cisplatin-containing regimens than in the docetaxel + carboplatin group (8% for docetaxel+cisplatin and 16% for vinorelbine+cisplatin versus 4% for docetaxel+carboplatin).

Diarrhea : Diarrhea has been a notable toxicity associated with docetaxel use. Grade 3 / 4 diarrhea occurred slightly more commonly in the docetaxel + cisplatin (7%) and docetaxel + carboplatin (5%) arms than in the vinorelbine + cisplatin arm (3%). Grade 4 diarrhea occurred in 1% of patients across the three treatment arms.

Hypersensitivity Reactions : These continue to be observed in docetaxel-containing regimens despite more routine use of dexamethasone pre-medication, although severe reactions are uncommon. In this trial, grade 3 / 4 hypersensitivity reactions were observed slightly more commonly in the docetaxel + cisplatin (3%) and docetaxel + carboplatin (2%) arms than in the vinorelbine + cisplatin arm (< 1%).

Fluid Retention : Pleural effusion, peripheral edema, and weight gain were the major signs of fluid retention. However, severe or life-threatening fluid retention events were uncommon, occurring in approximately 2% of patients across the three treatment arms.

Neutropenia : This was the most commonly observed grade 3 / 4 cytopenia, occurring in approximately 75% of patients across the three treatment arms. Grade 3 / 4 febrile neutropenia occurred in 5% of patients in each of the cisplatin-containing regimens and 4% of patients in the docetaxel + carboplatin arm.

Neuro-sensory events : Although these occurred in more than 30% of patients in TAX326, grade 3 / 4 events were uncommon, occurring in 4% of patients in each of the cisplatin-containing regimens, but less than 1% of patients in the docetaxel + carboplatin arm.

Deaths : Most deaths occurred greater than 30 days after last treatment infusion, and none of these was attributed to study drug. Of the 98 patients who died within 30 days of a treatment infusion 9on all three treatment arms), 25 had deaths attributed to toxicity from study treatment. Deaths due to study drug toxicity were evenly distributed across the three study arms, occurring in 2.2% of patients in the docetaxel + cisplatin group and in 2% of patients in either the docetaxel + carboplatin or vinorelbine + cisplatin group.

3. Drug-drug interactions

There have previously been no formal clinical studies to evaluate the drug interactions of docetaxel with other medications. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving docetaxel as there is a potential for a significant interaction.

Based on results of one phase 1 study in patients with solid tumors and one phase 1 / 2 study of docetaxel given in conjunction with cisplatin in patients with advanced NSCLC submitted with this application, the clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel.

4. Warnings

No other warnings are recommended in addition to those currently outlined in the package insert.

D. Dosing

The recommended dose of docetaxel when administered in combination with cisplatin for the treatment of advanced NSCLC is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.

Based on the dose modification approach utilized in TAX326, the sponsor is proposing the following addition to the label :

" Combination Therapy with TAXOTERE for NSCLC
For patients who are dosed initially at TAXOTERE 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the TAXOTERE dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see manufacturers' prescribing information. "

It should be noted that the protocol design allowed for a second dose modification step down to 50 mg/m^2. In fact, 29 patients (inclusive of both docetaxel-containing regimens) received such a reduced dose of 50 mg/m^2 in 92 cycles of chemotherapy. Therefore, the medical reviewer proposes to add the following statement to the sponsor's suggested addition to the package insert :

" In patients who require a further dose reduction, a dose of 50 mg/m^2 [redacted] ".

E. Special Populations

1. Pediatrics

Although the sponsor has not conducted any clinical trials of docetaxel in the pediatric population, there are two phase 1 trials of docetaxel in children with refractory solid tumors reported in the medical literature.

The first study, conducted at the Children's National Medical Center and the Pediatric Oncology Branch / NCI, adopted a standard dose escalation design using a one-hour infusion of docetaxel given every 21 days. Forty-four children received 103 courses at doses ranging from 55 to 150 mg/m^2. Dose limiting toxicities included neutropenia and constitutional symptoms of myalgia and malaise. Skin rashes, edema, and weight gain were also observed. The recommended phase 2 dose was 125 mg/m^2. Because neutropenia was the major dose-limiting toxicity, further escalation of the dose was proposed with filgrastim support.

The second study also utilized a one-hour infusion given every 21 days, with filgrastim given at a dose of 5 ucg/kg/day 48 hours after docetaxel infusion. Seventeen patients

received 27 courses of docetaxel with G-CSF support at doses ranging from 150 mg/m^2 to 235 mg/m^2. The MTD with G-CSF support was designated at 185 mg/m^2.

2. Elderly

In TAX326, 148 patients (36%) in the docetaxel + cisplatin group were 65 years of age or greater, and 15 patients were 75 years of age and greater. There were 128 patients (32%) in the vinorelbine + cisplatin group 65 years of age or greater. In these patients, no overall differences in effectiveness were observed compared to younger patients. In elderly patients in the docetaxel + cisplatin group, alopecia (68%), diarrhea (55%) and peripheral edema (39%) were observed more frequently in comparison to the vinorelbine + cisplatin group (alopecia 44%, diarrhea 24%, and peripheral edema 20%).

Patients treated with docetaxel + cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%), and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31%, and 21%, respectively).

In the docetaxel + carboplatin group, 114 patients (28%) were 65 years of age or greater, and 15 patients were 75 years of age and greater. In this group, alopecia (69%), diarrhea (46%), peripheral edema (31%) and grade 3/4 infection (18%) were observed more frequently in comparison to the vinorelbine+cisplatin group (alopecia 44%, diarrhea 24%, peripheral edema 20%, grade 3 / 4 infection 11%). Nausea (48%), vomiting (35%), neuro-sensory (32%) and neuro-hearing (8%) were observed less frequently in comparison to the vinorelbine + cisplatin group (nausea 70%, vomiting 63%, neurosensory 41%, neuro-hearing 19%).

3. Renal or Hepatic Impairment

Two phase 1 studies of docetaxel in patients with cancer and varying degrees of liver dysfunction are ongoing.

4. Gender

There were no differences between men and women with regard to efficacy. In general, the incidence of adverse events was comparable between men and women.

5. Ethnicity

The majority of patients enrolled onto TAX326 were caucasian, consisting of 87-89% of the population in each treatment group. Black, hispanic, asian or other groups consisted of 11-13% of the population in each treatment arm. No definitive conclusions can be drawn regarding safety

or efficacy differences among these groups due to the small number of non-caucasian patients in the study population.

6. Pregnancy

Docetaxel can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses ≥ 0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that docetaxel is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

There are no adequate and well-controlled studies in pregnant women using docetaxel. If docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with docetaxel.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: docetaxel
Proprietary Name: Taxotere®

Applicant: Aventis Pharmaceuticals
Route 202-206
PO Box 6800
Bridgewater, NJ 08807-2800

Drug Class: Antineoplastic

Indication:

Current:

Breast Cancer: TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Non-Small Cell Lung Cancer:
TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

Proposed: Addition of the following to the NSCLC indication :

TAXOTERE in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Dosage and Administration

Current Label:

Breast Cancer: The recommended dose of TAXOTERE is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.

Non-Small Cell Lung Cancer: For treatment after failure of prior platinum-based chemotherapy, the recommended dose of TAXOTERE is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials (see **BOXED WARNING, WARNINGS** and **CLINICAL STUDIES** sections).

Premedication Regimen: All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to TAXOTERE administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **BOXED WARNING, WARNINGS,** and **PRECAUTIONS** sections).

Dosage Adjustments During Treatment

Breast Cancer: Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during TAXOTERE therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during TAXOTERE therapy may tolerate higher doses. Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Monotherapy with TAXOTERE for NSCLC

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during TAXOTERE treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Proposed Label:

Addition of the following:

Combination Therapy with TAXOTERE for NSCLC

For chemotherapy-naïve patients, the recommended dose of TAXOTERE is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.

Addition of the following to the section on dose adjustments during treatment :

Combination Therapy with TAXOTERE for NSCLC

For patients who are dosed initially at TAXOTERE 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with

serious non-hematologic toxicities, the TAXOTERE dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see manufacturers' prescribing information.

B. State of Armamentarium for Indication(s)

Lung cancer is a leading cause of cancer death in the United States, with over 150,000 new cases diagnosed yearly. Non-small-cell tumors account for approximately 80% of all lung cancers. The three major histologic tumor types included in this category are adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

For patients with localized disease, surgical resection is the mainstay of treatment, with 5-year survival rates of 40-60% for patients with stage I or II disease. However, over 50% of patients have advanced or metastatic disease at the time of diagnosis. (1) The outcome for these patients with locally advanced or metastatic disease (stage IIIB or IV) remains poor despite multimodality approaches utilizing surgery as well chemotherapy with or without radiation.

A number of single and combination drug regimens have been utilized in the treatment of patients with stage IIIB or stage IV disease. In the United States, a number of drugs are currently approved for the treatment of NSCLC. These include docetaxel (after failure of platinum-based chemotherapy), vinorelbine (first-line treatment of inoperable stage IIIA or IIIB or stage IV NSCLC), and gemcitabine (first-line in combination with cisplatin), paclitaxel (first-line in combination with cisplatin).

The ideal combination regimen for the treatment of patients with advanced/metastatic disease remains to be defined, although platinum-based regimens are widely employed. (2, 3, 4)

Safety – The treatment related mortality in TAX the application's only randomized, controlled trial conducted in the first-line setting, appeared unacceptably higher than that associated with other agents approved for first-line treatment of non-small cell lung carcinoma. The treatment related mortality associated with docetaxel 100 mg/m^2 was similar in the application's first-line phase 2 studies and the supportive second-line randomized, controlled second line trials. Moreover, use of the 100 mg/m^2 dose was not recommended for second line patients in product labeling. Subset analysis demonstrated that treatment related mortality was also unacceptably high in the locally advanced disease patients, the disease stage subgroup "driving" the survival benefit associated with docetaxel in TAX

In a trial with an active control arm (TAX326), vinorelbine administered weekly at a dose of 25 mg/m^2 along with cisplatin 100 mg/m^{2}on day 1, repeated once every 4 weeks was chosen as an active control regimen based on data from a randomized study conducted by the Southwest Oncology Group (SWOG) where patients with stage IIIB or Stage IV disease were randomized to cisplatin 100 mg/m^2 or the cisplatin + vinorelbine combination regimen just described. (1) The combination regimen demonstrated a survival advantage over cisplatin alone (8 months versus 6 months ; p-value 0.0018). Nausea, vomiting, renal insufficiency, ototoxicity and neuropathy were reportedly similar between the two treatment arms. There was more hematologic toxicity with the combination regimen (81% grade 3 / 4 neutropenia versus 5% with cisplatin alone).

The two test arms, docetaxel with cisplatin and docetaxel with carboplatin, were designed to reflect the different medical practices and ongoing controversy surrounding the respective merits of carboplatin and cisplatin. (5, 6, 7) As a single agent, carboplatin is associated with decreased renal, gastrointestinal, and neurotoxicity compared to cisplatin in a number of disease settings. However, the combination with docetaxel had not been previously tested against cisplatin and docetaxel in this clinical setting. Furthermore, it is not clear whether substitution

of carboplatin for cisplatin in combination regimens results in a similar or more favorable toxicity profile without compromising efficacy.

A recently reported comparison of paclitaxel/carboplatin to paclitaxel/cisplatin in patients with inoperable NSCLC illustrates some of these issues. In this large, randomized European trial, Rosell et al. demonstrated non-inferiority in response rates between the two treatment regimens (25% for paclitaxel/carboplatin and 28% for paclitaxel/cisplatin). (8) However, median progression-free survival and median survival were significantly higher in the paclitaxel/cisplatin arm compared with paclitaxel/carboplatin (median survival 9.8 months versus 8.2 months ; p = 0.019). There was no apparent advantage in the safety profile of paclitaxel/carboplatin compared to paclitaxel/cisplatin.

C. Important Milestones in Product Development

05/14/96 Approved for use in patients with locally advanced or metastatic breast cancer who have progressed or relapsed during anthracycline-based therapy (original NDA 20449).

[redacted]

12/23/99 Approved for use in locally advanced or metastatic breast cancer after failure of prior chemotherapy (S-005).

12/23/99 Approved for use in locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy (S-011).

02/01/02 NDA 20449 S-018 was submitted to support the use of docetaxel plus cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition.

D. Other Relevant Information

As of 10/24/02, docetaxel is approved in 103 countries around the world including the United States. In the United States, the indication is currently limited to the treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, and locally advanced or metastatic NSCLC after failure of prior platinum-based therapy. Outside the United States, indications include first and second line

breast cancer, NSCLC, squamous cell carcinoma of the head and neck, and ovarian cancer.

E. Important Issues with Pharmacologically Related Agents

No issues exist.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Clinical Pharmacology and Biopharmaceutics

Clinical pharmacology/biopharmaceutics reviewers agree with the sponsor's proposal to add the following statement to the CLINICAL PHARMACOLOGY / HUMAN PHARMACOKINETICS section of the package insert :

" Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination with docetaxel was similar to that observed with cisplatin alone. "

This assessment was based on review of data submitted from two phase I studies and one phase I/II study in which a total of 159 patients were evaluated; TAX012, TAX049, and TAX018 respectively.

B. Statistics

Statistical reviewers' conclusions focused on the primary endpoint of overall survival as determined in TAX326. In this trial, two test regimens (docetaxel+cisplatin, docetaxel+carboplatin) were compared to the active control (vinorelbine+cisplatin). The Kaplan-Meier median estimates of overall survival were 10.9 months for test regimen A (docetaxel+cisplatin), 9.1 months for test regimen B (docetaxel+carboplatin), and 10.0 months for the active control (vinorelbine+cisplatin). There was no statistical evidence for survival superiority for either test regimen relative to the control regimen. There was statistical evidence for survival non-inferiority of docetaxel in combination with cisplatin relative to the control regimen. There was no statistically significant finding in any secondary efficacy endpoint. For more information, see Integrated Review of Efficacy.

C. Chemistry

Chemistry reviewers have determined that this efficacy supplement qualifies for a categorical exclusion from the requirement to prepare an Environmental Assessment.

D. Animal Pharmacology and Toxicology

No animal data were submitted.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 $L/h/m^2$ and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

A population pharmacokinetic analysis was carried out after docetaxel treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC).

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding.

IV. Description of Clinical Data and Sources

A. Overall Data

NDA 20449/SE8-018 contains the primary data from two phase 1 studies, one phase 1 / 2 study, and a single open-label randomized trial as listed in section IV.B. below. These trials were all conducted by the sponsor.

B. Table Listing the Clinical Trials

Table 1 lists the clinical trials submitted by the sponsor and reviewed by medical, statistical, and clinical pharmacology reviewers.

Table 1 : Clinical Trials Submitted to sNDA

Protocol	Design	Population, N	Endpoints
TAX012	Single-center dose escalation of cisplatin/docetaxel	Advanced solid tumors, 64	MTD PK Protein binding
TAX018	Phase 1 / 2 of docetaxel/cisplatin	Metastatic and/or locally advanced NSCLC, 71	MTD PK Response Rate
TAX049	Dose escalation phase 1 of docetaxel and carboplatin	Advanced solid tumors, 22	MTD PK
TAX326	Randomized Phase 3 of docetaxel + cisplatin, docetaxel + carboplatin, or vinorelbine + cisplatin	Metastatic and/or locally advanced NSCLC, 1220	Survival RR and duration TTP QOL

C. Postmarketing Experience

The sponsor provided a summary of the post-marketing experience covering the period from 4/01/94 until 5/31/01. During this period, the sponsor estimates that approximately patients worldwide have received docetaxel from commercial sources. In addition, approximately 37,500 patients enrolled in clinical trials (post-marketing and investigational) have received docetaxel alone or in combination with other anti-cancer agents in the treatment of various cancers.

As exposure to docetaxel was increasing over time and new safety information was becoming available, the safety related sections of the docetaxel company core safety information and the US Package Insert have been updated.

D. Literature Review

The sponsor conducted an extensive literature search. References 1-5 and 7 below are listed among the sponsor's references. Reference 6 was listed in a preliminary fashion (abstract form) in the sponsor's literature search. References 8 and 9 represent an addition by the medical reviewer to reflect the pediatric experience with docetaxel.

1. Wozniak AJ, Crowley JJ, Balcerzak SP et al. Randomized Trial Comparing Cisplatin with Cisplatin Plus Vinorelbine in the Treatment of Advanced Non-Small-Cell Lung Cancer: A Southwest Oncology Group Study. JCO 16:2459-2465, 1998.

2. Kelly K, Crowley J, Bunn PA et al. Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Vinorelbine Plus Cisplatin in the Treatment of Patients with Advanced Non-Small-Cell Lung Cancer: A Southwest Oncology Group Trial. JCO 19:3210-3218, 2001.

3. Comella P, Frasci G, Panza N et al. Randomized Trial Comparing Cisplatin, Gemcitabine, and Vinorelbine with Either Cisplatin and Gemcitabine or Cisplatin and Vinorelbine in Advanced Non-Small-Cell Lung Cancer: Interim Analysis of a Phase III Trial of the Southern Italy Cooperative Oncology Group. JCO 16:2459-2465, 1998.

4. Le Chevalier T, Brisgand D, Douillard JY et al. Randomized Study of Vinorelbine and Cisplatin Versus Vindesine and Cisplatin Versus Vinorelbine Alone in Advanced Non-Small-Cell Lung Cancer: Results of a European Multicenter Trial Including 612 Patients. JCO 12:360-367, 1994.

5. Fossella FV, DeVore R, Kerr RN et al. Randomized Phase III Trial of Docetaxel Versus Vinorelbine or Ifosfamide in Patients With Advanced Non-Small-Cell Lung Cancer Previously Treated With Platinum-Containing Chemotherapy Regimens. JCO 18:2354-2362, 2000.

6. Schiller JH, Harrington D, Belani CP et al. Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. NEJM 346:92-98, 2002.

7. Georgoulias V, Papadakis E, Alexopoulos A et al. Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomized multicentre trial. The Lancet 357:1478-1484, 2001.

8. Rosell R, Gatzemeier U, Betticher DC et al. Phase 3 randomized trial comparing paclitaxel/carboplatin versus paclitaxel/cisplatin in patients with advanced NSCLC: a cooperative multinational trial. Annals of Oncology 13:1539-1549, 2002.

9. Blaney SM, Seibel NL, O'Brien M et al. Phase I trial of docetaxel administered as a 1-hour infusion in children with refractory solid tumors: a collaborative pediatric branch, National Cancer Institute, and Children's Cancer Group trial. JCO 15:1538-1543, 1997.

10. Seibel NL, Blaney SM, O'Brien M et al. Phase I Trial of docetaxel with Filgrastim Support in Pediatric Patients with Refractory Solid Tumors: a collaborative pediatric branch, National Cancer Institute, and Children's Cancer Group Trial. CCR 5:733-737, 1999.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy review is based primarily on data from TAX326, the open-label, randomized phase III trial of docetaxel in combination with cisplatin or carboplatin versus vinorelbine+cisplatin in patients with stage IIIB or IV NSCLC with no prior chemotherapy.

B. Overview of Materials Consulted in Review

The following materials were reviewed:

- The regulatory history of the application
- Electronic submission of the sNDA
- NDA Volumes 1-185
- Relevant published literature
- Sponsor's presentation slides of 3/13/02
- Relevant submissions in response to medical officer's questions

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A number of methods were utilized in order to evaluate the quality and integrity of the data from TAX326 as outlined below :

1. Clinical Inspections : The Division of Scientific Investigations (DSI), Clinical Practice Branch I, conducted clinical inspections of 3 sites in the United States and one site in Brazil. Sites were selected based on a number of factors, including median survival and response rates that appeared to be higher than those reported for the overall analysis. DSI's overall assessment from was that data from the site in Brazil, as well as from two of the USA sites can be used for evaluation of the reported results of TAX326. DSI personnel expressed concerns regarding patients from the Kansas City site, where the pharmacist supplying chemotherapy agents has been charged with dilution of chemotherapy drugs. However, DSI personnel note that records for the 14 patients randomized at that site were available and in order. Furthermore, these patients exhibited toxicities consistent with the administration of chemotherapy in substantial doses. Finally, there is no evidence that any of these 14 patients specifically had dilution of their chemotherapy doses. Therefore, the medical reviewer has decided not to exclude these patients from safety or efficacy analyses.

2. The reviewers have conducted independent efficacy and safety analyses based on the primary data submitted in SAS transport files after conversion to JUMP format. Any discrepancies between the reviewer's results and those of the sponsor are discussed in relevant sections of the medical review.

3. Copies of the case report forms (electronic or hard copy) were reviewed in select patients.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Consent was required prior to enrollment.

E. Evaluation of Financial Disclosure

Certification of financial disclosure was provided by Steve Caffe, Vice President of Aventis, North America. Of the 688 investigators who participated in the trial, financial disclosure information was obtained in 603, with 85 investigators not responding despite a written request and at least two documented phone contacts.

It was disclosed that — a study investigator at the — — received , — — . His department also received an additional — to support . — The medical reviewer does not believe that this disclosure casts doubt on the findings for the following reasons : 1) only 26 patients were enrolled at Dr. — institution 2) the primary endpoint of survival was objective and well-defined 3) the institution was one of 3 U.S. sites inspected by our Division of Scientific Investigations 4) potential selection bias was minimized by randomization via an interactive voice randomization system in this open-label study.

In addition, it was disclosed that — an investigator at the — — , received — — . There were 19 patients enrolled onto TAX326 at this center. The medical reviewer does not believe that this disclosure casts doubt on the findings for reasons similar to those outlined above.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The results of an international, open-label randomized phase 3 trial of combination chemotherapy in patients with previously untreated locally advanced and/or recurrent or metastatic non-small cell lung cancer (TAX326) were submitted. Patients were randomized to docetaxel + cisplatin, docetaxel + carboplatin, or an active control of vinorelbine + cisplatin.

The primary endpoint was overall survival. According to the sponsor's primary analysis, the docetaxel + cisplatin arm was superior to the vinorelbine + cisplatin arm with a median survival of 11.3 months versus 10.1 months (p value = 0.044). The sponsor is also claiming that non-inferiority of docetaxel + carboplatin relative to vinorelbine + cisplatin was achieved, with a non-inferiority margin up to 0.89 (estimated hazard ratio 1.048). According to FDA reviewers, Kaplan-Meier median estimates of overall survival were 10.9 months, 9.1 months, and 10.0 months for the docetaxel + cisplatin, docetaxel + carboplatin, and vinorelbine + cisplatin arms respectively (estimated hazard ratio of docetaxel + cisplatin / vinorelbine + cisplatin = 0.884). Based on FDA analysis, there was no statistical evidence for survival superiority of either docetaxel-containing regimen relative to the active control of vinorelbine + cisplatin. There was statistical evidence for survival non-inferiority of docetaxel + cisplatin relative to the active control regimen with preservation of at least 62% of the vinorelbine + cisplatin effect.

The sponsor claims a statistically significant difference in response rates between the docetaxel + cisplatin arm and the vinorelbine + cisplatin arm (31.6% [95% confidence interval 27.1%, 36.4%] versus 24.6% [95% confidence interval 20.4%, 29.0%]). According to the FDA analysis, there is no statistically significant finding in analysis of response rates (comparison of either docetaxel-containing regimen to vinorelbine + cisplatin).

No statistically significant finding is evident in sponsor or FDA analysis of time to progression.

The sponsor claims benefit for patients in changes of pain scores, global rating of QOL by EuroQoL5D (EQ5D) and Lung Cancer Symptom Scale (LCSS), and changes in performance status and body weight. FDA reviewers have concluded that these findings are not reliable due to a number of factors including missing data, lack of validation of sponsor's methodology for dealing with missing data, use of post-hoc analyses, and examination of multiple secondary endpoints using multiple analyses without controlling for false-positive rates.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database consists mainly of an open-label, randomized phase 3 trial of docetaxel plus cisplatin versus docetaxel plus carboplatin versus vinorelbine plus cisplatin in chemotherapy naïve patients with unresectable locally advanced and/or recurrent (stage IIIB) or metastatic (stage IV) non-small cell lung cancer.

C. Detailed Review of Trials by Indication

The efficacy review is based primarily on one multicenter trial of docetaxel titled:

A Multicenter, Multinational, Randomized Phase 3 Study of Docetaxel plus Cisplatin versus Docetaxel plus Carboplatin versus Vinorelbine plus Cisplatin in Chemotherapy Naïve Patients with Unresectable Locally Advanced and/or Recurrent (Stage IIIB) or Metastatic (Stage IV) Non-Small Cell Lung Cancer

1. Protocol Review

A total of 140 centers participated in the trial. The distribution of centers by region is outlined in Table 2.

Table 2 : Distribution of Participating Centers by Region

Region	Number of Centers
United States and Canada	52
Europe	63
Australia, New Zealand and South Africa	14
Middle East	11

Table 3 : Protocol Milestones

Milestone	Date	Comments
Protocol open	7/25/98	
Amendment #1	1/29/99	Added further instructions on α1-Acid Glycoprotein collection procedures ; Reference #16 was updated
Amendment #2	3/04/99	Docetaxel pretreatment was modified from oral dexamethasone to oral dexamethasone or equivalent ; eligibility KPS was modified from ≥80% to ≥70% ; DMC first review was modified from Q4, 1998 to Q3, 1999 ; history of substance abuse was added to the exclusion criteria ; it was clarified that only one stepped down change will be made per treatment cycle for dose modifications based on hematologic toxicity ; patients with a symptomatic pleural effusion can receive local treatment with thoracostomy/sclerosis and remain on study provided that evaluable/measurable tumor is not progressing; for AE reporting, the end of the study period was modified from the end of the follow-up period to 30 days after the last study drug infusion; AAG serum sampling was added to the study flowchart;
Administrative changes # 1 and # 2	2/17/99	Study contacts were updated ; references to brand names were removed ; protocol references were updated ; typographical errors corrected
Administrative change # 3	6/19/00	New company name and address change ; study contacts updated
Protocol closed	8/9/01	
sNDA submitted	2/1/02	

Objectives:

Primary

To compare the effects of the drug combinations docetaxel plus cisplatin and docetaxel plus carboplatin to the "standard" regimen of vinorelbine plus cisplatin on overall survival in chemotherapy-naïve patients with unresectable locally advanced and/or recurrent (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC).

Secondary

1. To compare the time to progression , overall objective response rate, and duration of responses between the three treatment regimens.
2. To compare the safety of the three treatment regimens.
3. To compare the quality of life of patients treated with the three regimens, utilizing the Lung Cancer Symptom Scale (LCSS), the EuroQOL Scale and a subset of the neurotoxicity subscale (FACT-NTX) of the Functional Assessment of Cancer Therapy.

Ancillary

1. To collect socioeconomic data in order to perform analyses by country when needed.
2. To collect serum α_1-acid glycoprotein data in order to correlate the incidence and severity of certain adverse experiences.

Selection Criteria

Inclusion Criteria

- Male or female (Female patients of childbearing potential must be nonpregnant, non-lactating, and using adequate contraception) of any ethnic group.
- Age $\geq$ 18 years
- Histologically or cytologically confirmed NSCLC. (a copy of the pathology report was required at the time of randomization)
- Unresectable locally advanced, and/or recurrent (Stage IIIB), or metastatic (Stage IV) disease. Recurrent disease was defined as evident tumor progression after surgical or radiation treatment.
- No previous treatments with a biologic response modifier or chemotherapeutic agent. Previous therapies were limited to : surgery for NSCLC and/or radiation therapy for NSCLC.
- Karnofsky Performance Status $\geq$ 80% (ECOG 0-1)
- At least 1 measurable or evaluable lesion.
- Adequate end organ function defined as follows:
  - Hemoglobin $\geq$ 9.0 gm/dL, no transfusion within 2 weeks of evaluation
  - Neutrophil count $\geq$ 1.5 x 10^9 cells/L
  - Platelet count $\geq$ 100 x 10^9/L
  - Creatinine $\leq$ 1.5 mg/dL, or creatinine clearance $\geq$ 60 mL/min.
  - Total bilirubin $\leq$ 5 x ULN, unless accompanied by extensive bone metastases.
  - AST/SGOT $\leq$ 2.0 times ULN.
  - ALT/SGPT $\leq$ 2.0 times ULN.
  - Serum calcium $\leq$ 1.1 times ULN.

- Signed informed consent.
- Patient participation in quality of life assessments was mandatory, if a validated translation was available; however, refusal to participate by a patient did not make the patient ineligible for the study.

Exclusion Criteria

- Previous or concurrent malignancies at other sites, with the exception of cone biopsied *in situ* carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin
- Symptomatic or history of untreated brain or leptomeningeal metastases. Treated patients must have been stable for 4 weeks after completion of that treatment, with image documentation required.
- Patients who only had ascites, pleural effusion(s), bone metastases, brain or leptomeningeal metastases, previous irradiated lesions(s) (except those lesions which have progressed after completion of radiation therapy), or palpable abdominal masses that could not be measured in two dimensions as their sole indicator of disease; or surrogate serum markers (i.e) enzymes) as the sole indicator of disease.
- Patients whose lesion(s) were assessable only by radionuclide scan.
- Major surgical therapy within 2 weeks prior to study entry.

- Radiotherapy to a major bone marrow area (lower limb girdle, mediastinum or sacrum) within 4 weeks prior to study entry.
- Peripheral neuropathy of NCI grade ≥ 2 not related to a mechanical etiology.
- Serious concomitant illness including but not limited to : myocardial infarction within the last 6 months, uncontrolled cardiac arrhythmias, uncontrolled angina, uncontrolled hypertension, uncontrolled congestive heart failure, uncontrolled diabetes, dementia, uncontrolled seizures, acute hepatitis, acute deep vein thrombosis requiring intravenous or subcutaneous anticoagulant therapy, gastrointestinal bleeding, active peptic ulcer disease or active infection, (including HIV infection).
- Serious complication of malignant disease including but not limited to: untreated superior vena cava syndrome; untreated spinal cord compression; or hypercalcemia of malignancy.
- Clinically significant pericardial effusion (≥ grade 3 NCI criteria)
- Symptomatic (i.e. requiring thoracentesis) pleural effusion.
- Concurrent use of corticosteriods unless chronic treatment (i.e. initiated > 6 months prior to study entry) at low doses (≤ 20 mg methylprednisolone or equivalent).
- History of allergy to drugs containing the excipient TWEEN 80®.
- Psychological, familial, sociological, or geographical conditions which do not permit weekly medical follow-up and compliance with the study protocol.
- Participation in a clinical trial of one or more investigational agents (i.e. antibiotic) or devices within 4 weeks of study entry.

Treatment Plan

Patients were randomized to one of three treatment arms : A, B, or C

Treatment Group A received docetaxel and cisplatin administered as follows :

Docetaxel 75 mg/m^2 (diluted in a minimum of 250 mL 5% dextrose solution or normal saline) administered intravenously over 60 minutes on Day 1, immediately followed by cisplatin 75 mg/m^2 administered over 30-60 minutes.

Dexamethasone (or equivalent corticosteroid) premedication was administered orally as follows

First dose of 8 mg administered on the evening (day –1) before the docetaxel infusion.

Second dose administered on the morning of (day 1) the docetaxel infusion.

Third dose 1 hour before docetaxel.

Fourth dose on the evening of (day 1) the docetaxel infusion

Fifth dose on the morning of day 2

Sixth dose on the evening of day 2

Each chemotherapy cycle was repeated every 21 days

Treatment Group B received docetaxel and carboplatin administered as follows :

Docetaxel 75 mg/m^2 (diluted in a minimum of 250 mL 5% dextrose solution or normal saline) administered intravenously over 60 minutes on Day 1, immediately followed by carboplatin AUC = 6 mg/mL.min as calculated by the Calvert Formula administered IV over 30-60 minutes.

Dexamethasone premedication was administered orally as previously described.

Each chemotherapy cycle was repeated every 21 days

Treatment Group C received vinorelbine and cisplatin administered as follows :

Vinorelbine 25 mg/m^2 administered IV over 6-10 minutes into a free-flowing IV infusion of NS or 5% dextrose in water (D5W) on days 1, 8, 15, and 22, followed by cisplatin 100 mg/m^2 administered IV over 30-60 minutes on day 1 only.

It was recommended that following the weekly vinorelbine infusions, the vein be flushed with sufficient volume to prevent injection site reactions.

Each chemotherapy cycle was repeated every 28 days.

Concomitant Treatments

No systemic anticancer agents other than assigned study drugs were permitted.
All ancillary treatments (inlcuding OTC drugs) were to be recorded on the appropriate CRF.
No concomitant treatment with corticosteroids for reasons other than the study was allowed. However, patients receiving chronic treatment with corticosteroids (> 6 months) at a low dose (≤ 20 mg of prednisone or equivalent) for whatever reasons could continue.
G-CSF was not used prophylactically against neutropenia in the first cycle of treatment, but could be added in subsequent cycles as clinically indicated.
Amifostine was not used prophylactically against renal toxicity in the first cycle of treatment, but could be added in subsequent cycles as clinically indicated. In such cases, amifostine was added to all subsequent cycles of chemotherapy.

Dose Modifications

Each patient was scheduled to receive all cycles of treatment at the starting dose assigned, except for appropriate dose modifications for toxicity. Dose modifications for toxicity were made according to the following guidelines.

The dose reductions were supposed to be limited to a preset pattern, without the need to make any calculations or resolve conflicting recommendations if two or more toxicities occurred within the same cycle.

Except for carboplatin, a maximum of two dose reductions for any one of the chemotherapeutic agents was allowed per patient. Dose modifications were to be reported as either a STEP DOWN, STEP UP, NO CHANGE, or OMIT and applied directly to the Dose Modifications grids outlined in Tables 4 and 5 below. Only one STEP DOWN for each chemotherapeutic agent was required per treatment cycle. For carboplatin, there were to be no dose reductions.

Table 4 : Docetaxel Dose Modification Grid

Steps Down ⇓	**Docetaxel Dose to Administer 75 mg/m^2 (Starting Dose)**
Step 1	65 mg/m^2
Step 2	50 mg/m^2
	Discontinue drug therapy

Table 5 : Dose Modification for Other Study Treatments

Starting Dose	**Cisplatin 75 mg/m^2**	**Carboplatin AUC = 6.0**	**Vinorelbine 25 mg/m^2**	**Cisplatin 100 mg/m^2**
Steps Down ⇓	60 mg/m^2	AUC = 6.0	15 mg/m^2	60 mg/m^2
	50 mg/m^2	AUC = 6.0	10 mg/m^2	50 mg/m^2
	Discontinue drug therapy	Discontinue drug therapy	Discontinue drug therapy	Discontinue drug therapy

Dose modifications made for non-hematologic adverse events were to be permanently reduced.
Dose modifications made for hematologic adverse events were to be permanently reduced except for vinorelbine.
Treatment could be delayed for no more than three weeks, except for hematologic, hepatic, renal, and neurologic toxicities, in which case treatment could be delayed no more than two weeks.
All toxicities were graded using the NCI Common Toxicity Criteria (Version 1)

Pertinent toxicity sections for each of the 3 treatment groups are outlined below :

Treatment Group A : Docetaxel / Cisplatin

Table 6 : Dose Modifications Based on Absolute Neutrophil Count (ANC) - Group A

Nadir of ANC X 10^9/L during last course	Docetaxel dose to be administered ANC on Day 1 of cycle
	< 1.5 x 10^9/L	≥ 1.5 x 10^9/L
> 1.0 OR <1.0 for <7 days	Delay[1]	No change
<1.0 for ≥ 7 days	Delay[1]	No change
Febrile neutropenia[2] (regardless of duration)	Delay[1]	Step Down

[1]Delay (for up to 2 weeks) until counts reach lower limits for treatment.
[2]Febrile neutropenia is defined as : ≥ Grade 2 temperature (≥ 38.1 C), and Grade ¾ neutropenia (<1.0 x 10^9/L cells), and IV antibiotics and/or hospitalization.

Table 7 : Dose Modifications Based on Platelet Count - Group A

Nadir of Platelet Count During Last Course	Docetaxel dose to be administered Platelet count on Day 1 of cycle
	< 100 x 10^9/L	≥ 100 x 10^9/L
≥ 25 x 10^9/L	Delay[1]	No change
< 25 x 10^9/L	Delay[1]	Step Down

[1]Delay (for up to 2 weeks) until counts reach lower limits for treatment

Table 8 : Dose Modifications for Hepatic Toxicity - Group A

Serum liver Function Test Results at Day 1						Docetaxel dose to be administered
SGOT/AST X ULN		Alkaline phosphatase X ULN		Total Bilirubin		
≤ 2.0	and	≤ 5.0	and	WNL		No change
> 2.0 - ≤ 5.0	and	≤ 2.5	and	WNL		No change
> 2.0 - ≤ 5.0	and	> 2.5 - ≤ 5.0	and	WNL		Step Down[1]
> 5.0	or	> 5.0	or	> ULN		Delay[2]

[1]If liver toxicity worsens after dose reduction, patients should go off treatment.
[2]Delay (up to two weeks) until liver function tests reach lower limits for each treatment.

Table 9 : Dose Modifications for Renal Toxicity – Group A

Serum Creatinine Mg/dL		Creatinine Clearance ml/min[1]	Docetaxel dose to be administered	Cisplatin dose to be administered
≤ 1.5	and	≥ 50	No change	No change
≤ 1.5	and	< 50	No change	Delay[2]
> 1.5 – 2.0	and	≥ 50	No change	Step down
> 1.5	and	< 50	No change	Delay[2]
> 2.0	and	any	Delay	Delay[2]

[1]Cisplatin may be dose reduced using the calculated creatinine clearance of the Cockcroft-Gault Formula or the actual 24 hour creatinine clearance measurement.
[2]If cisplatin is delayed for any length of time (1-2 weeks), the next dose is Stepped Down.

Table 10 : Dose Modifications Based on Neurologic Toxicity - Group A

Grade of neurologic toxicity at the time of planned treatment	**Docetaxel and Cisplatin doses to be administered**
0 or 1	No change
2 / 3	Delay cisplatin and docetaxel treatment doses by one week, if Grade ≥ 2 persists for > 2 weeks patients is off study. If patient recovers to Grade 1 toxicity, then Step Down both drugs. If not recovered to Grade 1 in two weeks, discontinue from treatment.
4	Patient is discontinued from study.

Auditory Toxicity : Grade 3 / 4 hearing loss is an indication to discontinue the drug. Grade 1 / 2 hearing loss should trigger a consideration of risk/benefit of continuing cisplatin.

Nausea and Vomiting : If Grade 4 N/V occurs in spite of antiemetics, the cisplatin dose should be Stepped Down for the next course.

Mucositis : If mucositis is present at the time of planned treatment, study treatment is delayed until recovery. If acute grade 3 / 4 mucositis occurs, the next docetaxel dose should be Stepped Down and treatment resumed upon recovery. If docetaxel is delayed due to mucositis, cisplatin should also be delayed.

Hypersensitivity Reactions : Suggested management is outlined in Table 11 below.

Table 11 : Symptoms of Docetaxel Hypersensitivty and Recommendations for Intervention

Mild symptoms: Localized cutaneous reaction such as mild pruritis, flushing, rash	Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside. Then, complete docetaxel infusion at the initial planned rate
Moderate symptoms: any symptom not listed above or below, such as generalized pruritis, flushing, rash, dyspnea, hypotension with systolic blood pressure (BP) > 80 mm Hg	Stop docetaxel infusion Give IV dexamethasone 10 mg and/or diphenhydramine 50 mg IV Resume docetaxel infusion after recovery of symptoms
Severe symptoms: Bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema	Stop docetaxel infusion. Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg and/or epinephrine as needed. Whenever possible resume docetaxel infusion within 3 hours after recovery or reinfuse the patient within 72 hours using dexcamethasone 10 mg IV and/or diphenhydramine 50 mg IV ½ hour prior to resumption of infusion
Anaphylaxis (NCI Grade 4 reaction)	NO FURTHER PROTOCOL THERAPY

Patients with hypersensitivity reactions to docetaxel are at risk for recurrent reactions. For patients who experience moderate or severe hypersensitivity reactions, the docetaxel should be administered over 2 hours for subsequent treatment courses in addition to premedication as noted above.

Fluid Retention : No docetaxel dose reduction was planned for the fluid retention syndrome. For the purposes of toxicity evaluation, fluid retention was defined as the development of edema > trace, or cytologically negative pleural effusion, ascites, or pericardial effusion ; and would be graded as mild, moderate or severe according to the definitions in Table 12 below.

Table 12 : Fluid Retention Grading Criteria – Docetaxel

EDEMA	SEVERITY GRADING	EFFUSION
Asymptomatic	MILD Grade 1	Asymptomatic No intervention required
Symptomatic	MODERATE Grade 2	Symptomatic Intervention may be required
Symptomatic, resulting in drug discontinuation	SEVERE Grade 3	Symptomatic Intervention urgently required

Regimens which have been found to be effective in the management of fluid retention due to docetaxel are listed below:

Spironolactone 50 mg daily up to TID
Furosemide 40 mg PO daily if not responsive to spironolactone. Potassium supplementation may be given as needed
If, after a trial of $\geq$ 2 weeks, this is ineffective, treat with furosemide 20 mg PO daily plus metolazone 2.5 mg PO daily with potassium supplementation as needed.

Treatment Group B : Docetaxel / Carboplatin

For neutropenia, docetaxel dose modifications are identical to those in Table 6. For carboplatin, modifications are identical to those in Table 6 except that febrile neutropenia during the previous course with ANC $\geq$ 1.5 x 10^9/L on day 1 will result in no change in dose.

Dose modifications based on platelet count are outlined in Table 13.

Table 13 : Dose Modifications Based on Platelet Count – Group B

Nadir of platelet count during last course	Docetaxel dose to be administered Platelet count on Day 1 of next cycle		Carboplatin dose to be administered Platelet count on Day 1 of next cycle	
	< 100 x 10^9/L	$\geq$ 100 x 10^9/L	< 100 x 10^9/L	$\geq$ 100 x 10^9/L
$\geq$ 75 x 10^9/L	Delay[1]	No change	Delay[1]	No change
< 75 x 10^9/L	Delay[1]	Step Down	Delay[1]	No change

[1]Delay (for up to 2 weeks) until counts reach lower limits for treatment.

If docetaxel is delayed due to hematologic toxicity, carboplatin should also be delayed and administered unchanged when docetaxel is resumed.

Docetaxel dose modifications for hepatotoxicity for Group B are identical to those oultined for Group A in Table 8. No dose reduction for carboplatin will be made for hepatic toxicity.

Dose modifications for Group B based on renal toxicity are outlined in Table 14.

Table 14 : Dose Modifications Based on Renal Toxicity - Group B

Creatinine at the time of treatment **Mg/dL**	**Docetaxel dose to administer**	**Carboplatin dose to administer**
≤ 2.0	No change	Calculate dose based on Calvert Formula
> 2.0	Delay	Delay

For treatment delays, creatinine should be re-evaluated weekly. If criteria for treatment are not met in 2 weeks, patients should go off protocol treatment.

Docetaxel dose modification for Group B based on neurologic toxicity is outlined in Table 15.

Table 15 : Dose Modifications Based on Neurologic Toxicity - Group B

Grade of neurologic toxicity at the time of planned treatment	**Docetaxel dose to administer**
0 / 1	No change
2 / 3	Delay treatment until patient recovers to Grade 1, then Step Down dose. If not recovered to Grade 1 in 2 weeks, discontinue from protocol.
4	Patient is discontinued from study

Mucositis : If mucositis is present on Day 1, treatment is delayed until recovery.If acute Grade 3 / 4 mucositis occurs at any time, the docetaxel dose should be Stepped Down and treatment resumed upon recovery. If docetaxel is delayed due to mucositis, carboplatin should be delayed and administered when docetaxel is resumed.

Diarrhea : Appropriate symptomatic treatment should be given.

Hypersensitivity Reactions : See Treatment Group A above and Table 11.

Fluid Retention : See Treatment Group A above and Table 12.

Other Toxicities Not Defined Above : For Grade ≤ 2, manage symptomatically and retreat without dose reduction. For Grade ≥ 3, withold suspect drug until resolution to

Grade ≤ 1 or baseline, then reinstitute. If appropriate restart Stepped down one dose level.

Treatment Group C : Vinorelbine / Cisplatin

Dose modifications for neutropenia and thrombocytopenia are outlined in Tables 16, 17, and 18 below.

Table 16 : Dose Modifications Based on ANC - Group C – Day 1 Combination

Nadir of ANC during last course	Cisplatin Dose to be administered – ANC x 10^9/L			Vinorelbine dose to be administered – ANC x 10^9/L		
	≤ 1	> 1 and < 1.5	≥ 1.5	≤ 1	> 1 and < 1.5	≥ 1.5
> 0.5 x 10^9/L	Delay[1]	Step Down	No change	Delay[1]	Step Down	No change
< 0.5 x 10^9/L	Delay[1]	Step Down	Step Down	Delay[1]	Step Down	No change
Febrile neutropenia[2] (regardless of duration)	Delay[1]	Step Down	Step Down	Delay[1]	Step Down	Step Down

[1]Delay (for up to 2 weeks) until counts reach lower limits for treatment

[2]Febrile neutropenia is defined as: ≥ Grade 2 temperature (≥ 38.1 C), and Grade 3 / 4 neutropenia (<1.0 x 10^9/L cells) and IV antibiotics and/or hospitalization

Table 17 : Dose Modifications Based on Platelet Count - Group C - Day 1 Combination

Nadir of platelet count during last cycle	Cisplatin dose to be administered – platelet count on day 1		Vinorelbine dose to be administered – platelet count on day 1	
	< 100 x 10^9/L	> 100 x 10^9/L	< 100 x 10^9/L	> 100 x 10^9/L
≥ 50 x 10^9/L	Delay[1]	No change	Delay[1]	No change
< 50 x 10^9/L	Delay[1]	Step Down	Delay[1]	No change

[1]Delay (for up to 2 weeks) until counts reach lower limits for treatment.

Table 18 : Vinorelbine Dose Modifications for Days 5, 8, 15 and 22 ANC and Platelet Count - Group C

ANC x 10^9 Day of Treatment		Platelets x 10^9 Day of Treatment	Vinorelbine Dose
≥ 1.5	and	≥ 100	No change[1]
1 - < 1.5	or	≥ 75 - < 100	Step Down[1]
< 1	and	< 75	Omit Dose[2]

[1]Dose may be increased at the next administration if hematologic counts permit, but may not exceed the starting dose, or permanent dose reduction (s) for non-hematologic toxicity.

[2]If a weekly vinorelbine dose is omitted, do not make the dose up.

Vinorelbine dose modification based on hepatotoxicity is oultined in Table 19.

Table 19 : Vinorelbine Dose Modification for Hepatic Toxicity - Group C

Total Bilirubin	Vinorelbine Dose
≤ 2.0	No change
2.1 – 3.0	Step Down
> 3.0	Delay

Dose modifications of cisplatin for renal toxicity are based on Day 1 of each cycle and are outlined in Table 20.

Table 20 : Dose Modifications for Renal Toxicity - Group C

Serum Creatinine mg/dL		Creatinine Clearance ml/min[1]	Vinorelbine dose to administer	Cisplatin dose to administer
≤ 1.5	and	≥ 50	No change	No change
≤ 1.5	and	< 50	No change	Delay[2]
> 1.5 – 2.0	and	≥ 50	No change	Step Down
> 1.5	and	< 50	No change	Delay[2]
> 2.0	and	any	Delay	Delay[2]

[1]Cisplatin may be dose reduced using the calculated creatinine clearance of the Cockcroft-Gault Formula or the actual 24 hour creatinine clearance measurements.
[2]If cisplatin is delayed for any length of time (1-2 weeks), the next dose is Stepped Down.

Vinorelbine and cisplatin dose modification based on neurologic toxicity are outlined in Table 21.

Table 21 : Dose Modifications Based on Neurologic Toxicity - Group C

Grade of neurologic toxicity at the time of treatment -	Cisplatin and Vinorelbine doses to be administered
0 / 1	No change
2 / 3	Delay cisplatin and vinorelbine doses by one week, if Grade 2 or 3 persists for > 2 weeks, patient is off study. If patient recovers to Grade 1, then Step Down both drugs
4	Patient is discontinued from study.

Auditory Toxicity : Grade 3 / 4 hearing loss is an indication to discontinue the drug. Grade 1 / 2 hearing loss should trigger a consideration of risk/benefit of continuing cisplatin.

Nausea and Vomiting : If Grade 4 N/V occurs in spite of antiemetics, the cisplatin dose should be Stepped Down for the next course.

Constipation : An appropriate bowel regimen with stool softeners shoould be given to patients receiving vinorelbine.

Other Toxicities : If $\leq$ Grade 2, manage symptomatically, if possible and retreat without dose reduction. If $\geq$ Grade 3, the suspected drug should be witheld until resolution to $\leq$ Grade 1 or baseline, if baseline was greater than Grade 1, then reinstitute, if medically appropriate STEPPED DOWN one dose level.

Duration of Treatment

Patients will be treated with 6 cycles, unless evidence of progressive disease occurs. After completion of 6 cycles of therapy, patients may be continued on their randomized treatment regimen at the discretion of the treating physician.

Off-Study Criteria

1. Completion of 6 cycles of treatment
2. Intercurrent illness, which in the judgement of the investigator, affected assessments of clinical status to a significant degree or required discontinuation of study drugs
3. Unacceptable toxicity
4. Disease progression
5. Withdrawal of consent
6. Treatment delay greater than 3 weeks for any toxicity, except hematologic, hepatic, renal, and neurologic toxicity, in which case a treatment delay greater than 2 weeks
7. Concomitant treatment with a systemic anticancer drug that was not one of the study drugs for the patient's randomized treatment groups
8. Patients who did not have satisfactory compliance with study procedures
9. Major protocol violations, including, but not limited to :

- failure to meet major inclusion/exclusion criteria
- use of disallowed concomitant therapies
- failure to complete full tumor evaluations as required by the protocol

Safety Considerations

Clinical and laboratory assessments at screening, during the chemotherapy treatment phase, and during the followup period are outlined in Table 22.

Table 22 : Clinical and Laboratory Assessments

Study Parameter	Maximum Time Prior to Randomization for pre-study screening	Every Cycle	Every Other Cycle	≥ 30 days after last treatment	Post-Chemo followup every 2 months (discontinued with a response)	Post Chemo followup Every 2 months (any other patients)
Informed consent	4 weeks					
Past Medical History	4 weeks					
QOL Instruments	10 days prior to infusion	X		X	X[6]	X[6]
Socioeconomic Data	2 weeks	X		X	X[6]	X[6]
AE Reporting		X		X	X[5, 6]	X[5, 6]
KPS	2 weeks	X		X	X[6]	X[6]
Vital Signs	2 weeks	X		X		
Weight	2 weeks	X		X	X[6]	X[6]
Physical Exam	2 weeks	X		X		
Hematology[1]	2 weeks[2]	Weekly		X		
Chemistries	2 weeks [3, 3A, 2]	X[3, 4]		X[3, 3A]		
Safety ECG, CXR	2 weeks	As indicated		X		
Post Study Treatments					X[5]	X[5]

1 Hematology = CBC with differential and platelet count
2 if any parameter is abnormal, must repeat again within 7 days of randomization
3 Serum Chemistries = alkaline phosphatase, total bilirubin, AST, ALT, LDH, creatinine
3A Serum

Efficacy Assessment Methods

Tumor Response

All sites of potential malignant disease were to be documented at baseline. Those tests positive for tumor were to be repeated every two cycles, as well as any other test for tumor progression that would be clinically indicated.

Disease was defined as follows:

Measurable Disease – Bidimensionally Measurable Only :

This was defined as a tumor deposit with identifiable margins measurable in two dimensions by ruler or calipers and with the longest diameter and its perpendicular applied at the widest portion of the tumor, with recording in millimeters. The following minimum size was required at baseline:

CT scan or MRI – both diamters greater than the distance between cuts of the scan
Chest X-ray – 1 cm in at least one dimension
Skin lesion or superficial node – 1 cm x 1 cm (documented by photographs-optimal but optional)

Evaluable Disease – Unidimensional Measurable Disease

This was defined as a tumor deposit with only one identifiable margin, measurable by ruler or calipers, such as abdominal tumor masses, or lung lesions not completely surrounded by aerated lung. The following minimum size was required at baseline:

CT scan or MRI – one diameter must be greater than the distance between cuts of the scan.
Chest X-ray – 1 cm.
Skin lesion or superficial node – 1 cm (documented by photographs-optimal but optional)

Evaluable Non-Measurable Disease

This was defined as a tumor deposit, evident on clinical (inspection or palpation) or radiographic examination, without clear margins (i.e. lymphangitic pulmonary metastases), but a decrease in the size of the tumor can be determined; or any tumor below the minimum size limits given above, or bone disease.

Non Evaluable Disease

This was defined as lesions that are not measurable or evaluable, as defined above. Examples include : osteoblastic bone lesions, any lesion in a previously irradiated field which has not clearly progressed, malignant effusions (pleural, pericardial), any lesion only inferred from abnormal laboratory tests, and diffuse hepatomegaly.

Determination of Therapeutic Response

All responses were to be confirmed at the next cycle of treatment (3 weeks later). All measurable and evaluable disease was to be assessed by the identical method as used at baseline. Cr and PR was determined in comparison with baseline. PD was determined in comparison to the smallest size the tumor achieved during the study.

Complete Response (CR)

Complete disappearance of all measurable and evaluable tumor. No new malignant lesions. No evidence of non-evaluable disease. A patient with radiographic evidence of bony metastases prior to study therapy must have had normalization of radiographs or complete sclerotic healing of lytic metastases in association with a normal bone scan. A patient with an abnormal bone scan and normal radiographs prior to study therapy, must have had normalization of the bone scan.

Partial Response (PR)

A 50% or greater decrease in the sum of the products of the perpendicular diameters of all bidimensionally measurable lesions. No progression of evaluable disease. No new lesions.

Partial Response in Evaluable Disease

A 30% or greater decrease in the sum of the diameters of all unidimensionally measurable lesions. Definite improvement in evaluable non-measurable lesions estimated to be greater than 50%. No new lesions. Bony metastases must have decreased in size, or have blastic transformation of lytic lesions.

No change (NC)

Any variation not meeting the criteria of a complete response (CR), partial response (PR), or progressive disease (PD).

Progressive Disease (PD)

An increase of 50% or of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over the smallest sum observed in the trial, or a clear worsening of any evaluable disease (estimated to be > 50% over smallest observed), or the

appearance of any unequivocal new lesion. (In the case of a new onset pleural effusion – a positive cytology was required to determine progressive disease). Worsening of a pleural or pericardial effusion was not considered as progression.

Unknown (NE)

Progression not documented, and one or more measurable or evaluable lesions have not been assessed.

Determination of Response at a Tumor Evaluation Visit

This determination was to be made according to the following table.

Table 23 : Determination of Response at Tumor Evaluation Visit

Response in bidimensional measurable lesions only	Response in evaluable lesions only	Response in non-evaluable lesions only	Tumor response at visit[1]
CR	CR	CR	CR
CR	Any except PD	Any except PD	PR
PR	Any except PD	Any except PD	PR
NC	Any except PD	Any except PD	NC
No bidimensional measurable lesion	NC, PR	Any except PD	NC
No bidimensional measurable lesion	CR	Any except PD, CR	NC
No bidimensional measurable lesion	CR	CR	CR

[1]If there is a PD in any response category or appearance of an unequivocally new lesion, the overall response is PD.

Determination of Best Overall Response for the Study is outlined in Table 23. The overall response rate was to be determined as the number of patients with a confirmed response (CR + PR) plus the number of patients with an unconfirmed response (unconfirmed CR + unconfirmed PR) designation from the start of treatment until removal from study treatment.

Reviewer Comment : The inclusion of unconfirmed responses was planned as an exploratory analysis only.

Table 24 : Determination of Best Overall Response for the Study

Overall Response	Definition
Complete Response	Two documented CR's not less than three weeks apart before progression
Partial Response	Two documented PR's or better, not less than three weeks apart but not qualifying as a CR
Unconfirmed Complete Response	One documented CR before progression but not less than three weeks from initial treatment, and not qualifying as CR
Unconfirmed Partial Response	One documented PR before progression but not less than three weeks from initial treatment, and not qualifying as CR, PR or unconfirmed CR
Stable Disease/No Change	One documented NC, not less than three weeks from initial therapy, and not qualifying as anything else above
Early Progression	Documented progressive disease within 6 weeks from initiation of treatment
Response Unknown	PD documented greater than 6 weeks from initiation of treatment and either all evaluations are unknown or the only evaluation was less than three weeks after initiation of treatment.

Duration of Response : For CR's, this is defined as the interval from the date of initial documentation of a CR to the date of documented disease progression. For PR's, it is the time interval from the date of randomization to the date of documented disease progression.

Time to disease progression is defined as the interval from the date of randomization to the date of documentation of disease progression.

Survival is defined as the time interval from the date of randomization to the date of death.

Statistical Methods

Design

This was a three arm, randomized study comparing either of two docetaxel combinations to the control group receiving vinorelbine/cisplatin in patients with advanced/recurrent or metastatic NSCLC. The intent to treat (ITT) population was to include all randomized patients. Survival analysis was planned for the ITT population. Patients evaluable for other efficacy parameters, such as time to progression or quality of life measures, included those who met the eligibility criteria and had at least one cycle of the assigned treatment.

Patients were evaluable for response if :

1. they were evaluable for efficacy as stated above.
2. All baseline lesions were assessed at least once after the second cycle, with the identical method of assessment as baseline.
3. All baseline x-rays/scans were assessed no longer than 4 weeks prior to randomization.
4. They received at least 2 cycles of treatment, unless having malignant disease progression noted.
5. No major protocol violations had occurred

Safety analyses were to include all patients who received any study drug. These patients were evaluable for safety from the initiation of the first dose of study drugs.

Efficacy Endpoints

Tumor response :	Proportion of patients with objective response. Includes complete and partial confirmed and unconfirmed responses. Duration of tumor response Time to progression
Clinical benefit indicator :	Karnofsky Performance Status Weight changes
Quality of Life :	LCSS scores. EuroQOL (EQ5D) scores. FACT-NTX scores.