**Safety Endpoints**

Incidence of adverse experiences, including SAE's, recorded during the study.
Changes from baseline in vital signs (blood pressure, heart rate), ECG and weight
Changes from baseline in laboratory parameters (serum chemistry, hematology)

**Ancillary Studies**

Socioeconomic data : data will be collected to perform an analysis by country when needed.

Laboratory data : Serum α1-acid glycoprotein determinations will be collected at medical centers where it is feasible to perform analyses. The incidences of certain adverse event experiences will be analyzed in conjunction with the serum α1-acid glycoprotein levels.

**Sample Size Considerations**

The following assumptions were made in estimating the sample size :

The median survival time for either docetaxel combination regimen and the vinorelbine / cisplatin regimen are 10.5 and 8.0 months, respectively.

The patient accrual time is 18 months.

The follow-up time after the last cycle is 12 months.

Given these assumptions, an estimated sample size of 360 patients per arm will allow the detection of a survival superiority in either of the docetaxel combination treatment arms versus the vinorelbine / cisplatin arm with an alpha level of 5% and a power of about 90%. It will also allow the testing of a modified null hypothesis of median survivals to show that either of the docetaxel combination regimens is better or "not much worse" than the control at an alpha level of 5% and a power of about 85%.

**Randomization**

Randomization was to be administered centrally. Following stratification, patients were to be randomly assigned with an equal probability to one of the three treatment groups.

**Interim analysis**

An interim analysis was to be performed after 50% of patients had completed the chemotherapeutic treatment phase and 9 months of follow-up. The primary parameter for this analysis was to be survival. A formal adjustment for the alpha level of the final analysis was to be made only for this parameter.

## 2. Trial Results

### Study Conduct

### Informed Consent

Prior to the screening evaluation, the patient was to be informed of the nature of the study drug. The procedures and possible hazards were to be explained. An approved informed consent statement was to be read and signed by the patient, a witness, and the investigator. The patient was to be provided with a copy of the signed informed consent statement. Verification of a signed informed consent statement was to be noted on the patient's CRF.

### Treatment Assignment and Randomization

Disease stage (IIIB versus IV) and geographic region (North America ; South Africa/New Zealand/Australia ; Rest of the world) were the two stratification factors for randomization. Patients were randomized and received an allocation number and treatment group assignment only when they were about to start treatment. Computer-generated randomization logs were used for each stratum. The patient was assigned with equal probability to one of the three treatment groups according to the next sequential number in the stratum log.

### Protocol Violations

Thirteen patients were discontinued from the study by the investigator for a major protocol violation. Six of these patients were never treated after randomization. Four patients had a violation of protocol treatment, and the others were recognized as not eligible for the study and discontinued. Table 25 outlines protocol violations.

**Table 25 : Sponsor's List of Major Protocol Violations**

| Protocol Violation | Docetaxel/Cisplatin | Docetaxel/Carboplatin | Vinorelbine/Cisplatin |
|---|---|---|---|
| Elevated serum creatinine | 22322 | 11016 | 12024 |
| Brain metastases | | 12077 , 22160 | 42050 |
| Delayed treatment > 3 weeks | | 12100 | |
| On anticoagulants | | | 11018 , 12243 |
| Symptomatic Pleural Effusion | | | 11020 |
| Discontinued vinorelbine | | | 21016 |
| Acoholism | | 42100 | 22256 |

*Reviewer Comment: The medical reviewer's analysis of the submitted dataset 'feval' reveals 32 patients who were randomized onto the trial although ultimately deemed ineligible due to violation of inclusion/exclusion criteria. The reasons for ineligibility and patient numbers are listed in Table 26. These findings were forwarded to the sponsor on 8/5/02.*

**Table 26 : Medical Reviewer List of Eligibility Violations**

| Eligibility Violation | Patient Identification Number |
|---|---|
| Serious concomitant illness | 11018, 11029, 11039, 12023, 12112, 12243, 22077, 22254, 22357, 32055 |
| Received prior/concurrent anticancer agent | 11034, 22290, 31001 |
| Previous or concurrent history of malignancy | 11062, 12214, 12231, 21037 |
| No histologically or cytologically proven NSCLC | 12017, 41011 |
| Serum creatinine > 1.65 mg/dl + clearance < 54 ml/minute | 12024, 41049, |
| Symptomatic or history of untreated brain mets | 12077, 22160, 41059, 42050 |
| Peripheral neuropathy ≥ grade 2 | 12209, 22141, 21215, 22262 |
| Total bilirubin > 1.1 x ULN | 12239 |
| Major surgical treatment within 14 days of study entry | 42067 |
| Serious complication of malignant disease | 21029 |

**Enrollment, Demographics, Baseline Characteristics**

**Enrollment by Region**

A total of 1218 patients were enrolled into the intent to treat population. The region with the largest accrual was Europe, with 48.5% of patients enrolled. Table 27 outlines accrual by region and study arm.

**Table 27 : Enrollment by Region and Study Arm**

| Region | Docetaxel cisplatin | Docetaxel carboplatin | Vinorelbine cisplatin | Total N (%) |
|---|---|---|---|---|
| US/Canada | 115 | 115 | 113 | 343 (28%) |
| Europe/Lebanon/Israel | 197 | 197 | 197 | 591 (49%) |
| S Africa/Australia/NZ | 33 | 32 | 32 | 97 (8%) |
| S America/Mexico | 63 | 62 | 62 | 187 (15%) |

*Reviewer comment : 1220 patients were randomized to one of the three treatment arms. The sponsor has considered 1218 of these as the intent to treat population. The sponsor has excluded two randomized patients from the ITT population due to an ultimate diagnosis other than NSCLC (one patient with oat cell cancer, another with pancreatic cancer). It is the medical reviewer's opinion that all randomized patients should be considered in the ITT analysis.*

**Baseline Demographics**

Age, gender, race, and Karnofsky performance status at baseline are listed by distribution across the three study arms in Table 28.

**Table 28 : Baseline Patient Characteristics**

| Characteristic | Docetaxel Cisplatin N = 408 | Docetaxel Carboplatin N = 407 | Vinorelbine Cisplatin N = 405 |
|---|---|---|---|
| Age (years) | | | |
| Mean | 60.1 | 58.9 | 59.6 |
| Median | 60.5 | 59 | 61 |
| Range | 30-81 | 23-87 | 35-80 |
| Gender | | | |
| Female | 114 (28%) | 115 (28%) | 102 (25%) |
| Male | 294 (72%) | 292 (72%) | 303 (75%) |
| Race | | | |
| Black | 13 (3%) | 13 (3%) | 6 (1%) |
| Caucasian | 360 (88%) | 353 (87%) | 361 (89%) |
| Hispanic | 23 (6%) | 32 (8%) | 26 (6%) |
| Oriental | 5 (1%) | 2 (<1%) | 7 (2%) |
| Other | 7 (2%) | 7 (2%) | 5 (1%) |
| Karnofsky PS (%) | | | |
| 70 | 15 (4%) | 16 (4%) | 16 (4%) |
| 80 | 157 (38%) | 155 (38%) | 153 (38%) |
| 90 | 171 (42%) | 170 (42%) | 168 (41%) |
| 100 | 65 (16%) | 66 (16%) | 68 (17%) |

**Disease Characteristics of the Patient Population**

Histologic subtype, staging, and time from diagnosis to randomization by treatment group are provided in Table 29.

**Table 29 : Histologic Subtype and Staging**

| Disease Characteristic | Docetaxel Cisplatin N = 408 | Docetaxel Carboplatin N = 407 | Vinorelbine Cisplatin N = 405 |
|---|---|---|---|
| **Histologic Subtype** | | | |
| Adenocarcinoma | 181 (44%) | 169 (42%) | 164 (40%) |
| Squamous Cell Ca | 131 (32%) | 135 (33%) | 140 (35%) |
| Large Cell Ca | 41 (10%) | 46 (11%) | 47 (12%) |
| Bronchoalveolar Ca | 15 (4%) | 11 (3%) | 11 (3%) |
| Other | 40 (10%) | 46 (11%) | 43 (10%) |
| **Staging at Diagnosis** | | | |
| I | 13 (3%) | 18 (4%) | 18 (4%) |
| II | 5 (1%) | 10 (3%) | 15 (4%) |
| IIIA | 9 (2%) | 9 (2%) | 9 (2%) |
| IIIB | 142 (35%) | 123 (30%) | 123 (30%) |
| IV | 224 (55%) | 228 (56%) | 221 (55%) |
| Not assigned | 15 (4%) | 19 (5%) | 19 (5%) |
| **Staging at Randomization** | | | |
| Stage IIIB | 135 (33%) | 133 (33%) | 133 (33%) |
| Stage IV | 273 (67%) | 274 (67%) | 272 (67%) |
| **Time from Diagnosis to Randomization** | | | |
| Mean (months) | 4.6 | 4.2 | 3.8 |
| Median (months) | 0.9 | 0.9 | 0.9 |

*Reviewer Comment : In the study report for TAX326 (section 6.1.6), the sponsor disclosed that 51 patients had a change in staging from randomization due to a variety of factors, such as incomplete availability of results of baseline staging at the time of site personnel contact to randomize a patient. The medical reviewer examined case report forms for these patients and concluded that the modification in staging was supported by the complete data in 50 of 51 patients. Based on these findings, a sensitivity analysis was conducted by statistical reviewers. The results of this analysis were consistent with those of the primary analysis.See Integrated Review of Efficacy for more information.*

A surgical procedure was reported in 96 patients in the docetaxel/cisplatin treatment group, 102 patients in the docetaxel/carboplatin treatment group, and 119 patients in

the vinorelbine/cisplatin treatment group. Table 30 provides the frequency of different surgical procedures across the three treatment arms.



**Table 30 : Prior Anti-Cancer Surgery**

| Procedure | Docetaxel Cisplatin N = 408 | Docetaxel Carboplatin N = 407 | Vinorelbine Cisplatin N = 405 |
|---|---|---|---|
| Complete Pneumonectomy | 3 | 10 | 10 |
| Lobectomy | 32 | 41 | 41 |
| Segmental Lung Resection | 6 | 5 | 3 |
| Excision of Lung Lesion | 2 | 3 | 5 |
| Exploratory Thoracotomy | 22 | 16 | 22 |
| Other Surgical Procedure | 40 | 42 | 56 |

**Efficacy Results**

**Survival**

The primary efficacy endpoint was survival, defined as time from randomization to the date of death (from any cause) or date of last patient contact if lost to follow-up. According to the sponsor, the primary analysis was performed on the intent-to-treat population (ITT). The ITT population consisted of 1218 patients with NSCLC who were randomized.

At the study cut-off date of 4/3/01, 307 patients (75.2% of 408) on the docetaxel + cisplatin arm, 319 patients (78.6% of 406) on the docetaxel + carboplatin arm, and 323 patients (80% of 404) on the vinorelbine + cisplatin arm had died. Ninety-three patients in the docetaxel + cisplatin group, 75 in the docetaxel + carboplatin group,

and 70 in the vinorelbine + cisplatin group were alive at the cutoff date. Eight, twelve, and eleven patients in each of the three groups was lost to followup.

The sponsor's primary analysis was the non-parametric covariate-adjusted stratified log-rank test. The stratification factors were disease stage (IIIB versus IV) and geographical region (USA/Canada versus Europe/Israel/Lebanon versus South Africa/Australia/New Zealand versus South America/Mexico. The covariates utilized in the sponsor's analysis are listed in Table 31 below.

**Table 31 : Covariates Used in Sponsor's Primary Analysis of Survival**

| Covariate | Comparison |
|---|---|
| **Age** | $\leq$ 60 versus > 60 years |
| **Karnofsky Performance Status** | KPS = 100 versus KPS < 100 |
| **Time from diagnosis to randomization** | > 60 days versus $\leq$ 60 days |
| **Weight loss in prior 6 months** | < 5% versus $\geq$ 5% |
| **Histologic subtype** | a. Adenocarcinoma versus other<br>b. Squamous cell versus other<br>c. LCU versus others |
| **Albumin** | $\leq$ 1 versus > 1 |
| **LDH** | > ULN versus $\leq$ ULN |
| **Sex** | Female versus Male |
| **Baseline QoL score** | a. LCSS QoL > 60 versus $\leq$ 60<br>b. EQ5D Global Health Status > 60 versus $\leq$ 60 |
| **Liver involvement** | No versus yes |
| **Bone involvement** | No versus yes |
| **Prior radiotherapy** | Yes versus no |
| **Prior surgery** | Yes versus no |

Based on the sponsor's primary analysis, the p-value for comparing the docetaxel + cisplatin arm to the vinorelbine + cisplatin arm was 0.044 and the p-value for comparing the docetaxel + carboplatin arm to the vinorelbine + cisplatin arm was 0.66. therefore, the sponsor concluded that the docetaxel + cisplatin arm was associated with a longer time to survival as compared to the active control (vinorelbine+cisplatin). Since the hazard ratio cannot be obtained in a non-parametric log-rank test setting, the sponsor employed a stratified proportional hazards model adjusted for the same set of covariates to estimate the hazard ratios. The estimated hazard ratio of the active control to the docetaxel + cisplatin arm was 1.183 with a

95% confidence interval of (1.008, 1.388).The estimated hazard ratio of the active control to the docetaxel + carboplatin arm was 1.048 with a 95% confidence interval of (0.894, 1.229). Although superiority of docetaxel + carboplatin to the active control could not be established (p-value = 0.66), the sponsor concluded that non-inferiority was achieved with a threshold of 0.89.

The adjusted median survival in the sponsor's comparison of docetaxel + cisplatin to the active control regimen was 11.3 months versus 10.1 months, and in the comparison of docetaxel + carboplatin to the active control was 9.4 months versus 9.9 months respectively.

Based on information provided in the JCO report by **Wozniak et al** ( X ), in which a randomized trial of cisplatin versus cisplatin + vinorelbine is described, the sponsor estimated the hazard ratio of vinorelbine + cisplatin to cisplatin to be 0.74 with a 95% confidence interval of (0.65, 0.86) and concluded the following :

1) Preservation of the control effect (based on the hazard ratio) is more than 100% for docetaxel + cisplatin and 66% for docetaxel + carboplatin.
2) Docetaxel + cisplatin preserves more than 75% of the effect size of vinorelbine + cisplatin even under very stringent criteria; i.e. adjusting for multiplicity and using the upper 95% C.I. for the control effect.
3) Docetaxel + cisplatin is non-inferior to vinorelbine + cisplatin

*Reviewer's Comments : The reviewers disagree with a number of aspects of the sponsor's analysis. The problems encountered in the sponsor's analysis are outlined below :*

A. *Changes in the primary analysis for superiority : Since the FDA requested that multiplicity adjustment for the two comparisons (docetacel+cisplatin to active control and docetaxel+carboplatin to active control) be made, the sponsor proposed the Hochberg procedure and changed the primary analysis from the stratified logrank test to the non-parametric covariate-adjusted stratified log-rank test. This change is not acceptable due to a number of factors : 1) The planned primary analysis was changed after the interim analysis had been performed 2) The nominal significance levels for the interim and final analyses were calculated based on the stratified logrank test, not the test adjusted for covariates. To control the false positive rate, nominal significance levels may need to be adjusted with change of analysis because the correlation in test statistics between the interim and final analysis may be changed. 3) Many covariates included in the adjusted analysis are not acceptable to the FDA. Two covariates (prior radiotherapy and prior surgery) were not specified in the SAP. Furthermore, classifications of possible outcomes for some covariates were not pre-specified either.*

B. *Inconsistencies between superiority and non-inferiority analyses : The stratified proportional hazards model adjusted for covariates is different from the stratified*

*non-parametric covariate-adjusted log-rank test. Although both are covariate adjusted analyses, the assumptions required for the analysis are different. The same analysis approach should be used for both superiority and non-inferiority tests to avoid contradictory results.*

C. *Sponsor's non-inferiority analysis : Only one published report was employed in estimating the effect of the active control relative to the best standard of care at the time (i.e. cisplatin). In this report, the logrank test stratified by center and disease stage was used, therefore the sponsor should have used the same analysis (instead of the proportional hazards model) for a meaningful comparison. Furthermore, when estimating the percent of the active control effect preserved by the test treatments, the sponsor did not consider the variability of the estimated active control effect.*

*FDA Analysis :The reviewers considered the stratified logrank test as the primary analysis for both superiority and non-inferiority for the reasons outlined above. The reviewers also included all randomized patients in the ITT population, resulting in 2 more patients than the sponsor-defined ITT. The primary superiority analysis is presented in Table 32 below. This analysis indicates no statistically significant evidence for superiority of either docetaxel-containing regimen over the cisplatin + vinorelbine combination.*

**Table 32 : Reviewer's Primary Analysis of Stratified Logrank Test (on All Randomized Patients)**

| | Comparison 1 | Comparison 2 |
|---|---|---|
| | (docetaxel/cisplatin) vs. (vinorelbine/cisplatin) | (docetaxel/carboplatin) vs. (vinorelbine/cisplatin) |
| P-value [a] | 0.122 | 0.657 |
| Estimated Hazard Ratio [b] | 0.884 | 1.036 |
| 95.3% CI [c] | (0.754, 1.036) | (0.885, 1.212) |
| 97.65% CI [d] | (0.737, 1.059) | Not needed. |

[a] From the superiority test "$H_0$: hazard ratio = 1 vs. $H_1$: hazard ratio ≠ 1".
[b] Hazard ratio of test treatment to the active control. A hazard ratio of less than 1 indicates that the test treatment is associated with a longer time to survival.
[c] Corresponding to a nominal significance level of 0.047.
[d] Corresponding to a nominal significance level of 0.0235.

*An assumption was made that non-inferiority requires the test regimens to preserve 50% of the active control effect. (For more information on the derivation of the non-inferiority margin, see the Statistical Review) The non-inferiority test using the Hochberg procedure to control the error rate for multiple comparisons was conducted as follows :*

*Step 1:*

*Construct 95.3% confidence intervals (corresponding to a nominal significance level of 0.047) for the hazard ratio of each test treatment to the active control. If both confidence intervals lie entirely below 1.078 (refer to the previous bullet), then non-inferiority evidence is shown for each test treatment. Otherwise, there is no non-inferiority evidence in at least one comparison and one should proceed to Step 2 to determine whether lack of non-inferiority evidence is shown in only one comparison or in both comparisons.*

*Step 2:*

*If there is non-inferiority evidence, it should be in the comparison resulting in a smaller p-value, which is in Comparison 1, so construct a 97.65% confidence interval (corresponding to a nominal significance level of 0.0235) for the hazard ratio of test treatment docetaxel + cisplatin to the active control (vinorelbine + cisplatin). If the confidence interval entirely lies below 1.078, then non-inferiority evidence is shown for docetaxel + cisplatin.*

*As seen in Table 32, not both 95.3% confidence intervals for the hazard ratios entirely lay below 1.078, so one should proceed to Step 2. The 97.65% confidence interval for the hazard ratio of D75+Cis to V+Cis was (0.737, 1.059), entirely below 1.078. This suggested statistical evidence for non-inferiority of the test regimen docetaxel + cisplatin. Based on the 97.65% confidence interval, the effect of docetaxel + cisplatin relative to the historical control (cisplatin) was estimated to be 0.910 (=1.059*0.86). Since the effect of the active control was estimated to be 0.86 after incorporating the variability of the point estimate, docetaxel + cisplatin) preserved 62% (= ln 0.910 / ln 0.86) of the active control (vinorelbine + cisplatin) effect. However, it should be cautioned that the results were based on only one historical trial and, in which trial, the stratification factors were not identical to those in this registration trial. Therefore, the non-inferiority results might have been different had more historical trials been available.*

*The reviewers' Kaplan-Meier estimate of median survival is 10.9 months for the docetaxel + cisplatin arm, 9.1 months for the docetaxel + carboplatin arm, and 10.0 months for the vinorelbine + cisplatin arm.*

*Of the covariates listed in Table 31, FDA reviewers consider performance status, gender, and weight loss at baseline to be of higher priority than others listed in terms of potential relevance to outcome. Therefore, a supportive analysis based on the stratified proportional hazards model adjusted for the three covariates was conducted. The results of this analysis were consistent with those of the primary analysis.*

*In the study report for TAX326 (section 6.1.6), the sponsor disclosed that 51 patients had a change in staging from randomization due to a variety of factors, such as incomplete availability of results of baseline staging at the time of site personnel*

*contact to randomize a patient. The medical reviewer examined case report forms for these patients and concluded that the modification in staging was supported by the complete data in 50 of 51 patients. Based on these findings, a sensitivity analysis was conducted by statistical reviewers. The results of this analysis were consistent with those of the primary analysis.*

**Overall Response Rate and Duration of Response**

Response rate was analyzed on the sponsor-defined ITT population as well as the sponsor-defined response-evaluable population.

The sponsor's results are summarized in Table 33 and Table 34. As seen in Table 33, among the three treatment arms, the docetaxel + cisplatin arm yielded the numerically highest, and docetaxel + carboplatin arm the numerically lowest, overall response rate, whether on the sponsor-defined ITT or the sponsor-defined response-evaluable population.

In comparing docetaxel + cisplatin to the active control, the p-value based Fisher's exact test was 0.029 on the sponsor-defined ITT population and 0.074 on the sponsor-defined response-evaluable patients. In comparing docetaxel + carboplatin to the active control, the p-value was relatively large on either population.

**Table 33: Sponsor's Descriptive Results of Response Rate**

| Population [a] | Response Rate | Docetaxel + Cisplatin | Docetaxel + Carboplatin | Vinorelbine + Cisplatin |
|---|---|---|---|---|
| ITT | **Overall (CR+PR) [95% CI[b]]** | **129/408 (31.6%) [27.1%, 36.4%]** | **97/406 (23.9%) [19.8%, 28.3%]** | **99/404 (24.5%) [20.4%, 29.0%]** |
| | Complete (CR) | 8 (2.0%) | 5 (1.2%) | 8 (2.0%) |
| | Partial (PR) | 121 (29.7%) | 92 (22.7%) | 91 (22.5%) |
| Response-Evaluable | **Overall (CR+PR) [95% CI[b]]** | **127/366 (34.7%) [29.8%, 39.8%]** | **96/363 (26.4%) [22.0%, 31.3%]** | **95/336 (28.3%) [23.5%, 33.4%]** |
| | Complete (CR) | 8 (2.0%) | 5 (1.4%) | 7 (2.1%) |
| | Partial (PR) | 119 (32.5%) | 91 (25.1%) | 88 (26.2%) |

[a] Both populations are sponsor-defined.
[b] Nominal 95% confidence interval

**Table 34: Sponsor's P-values for Analysis of Overall Response Rate**

| Population[b] | Comparison 1 | Comparison 2 |
|---|---|---|
| | Docetaxel + Cisplatin Vs. Vinorelbine + Cisplatin | Docetaxel + Carboplatin vs. Vinorelbine + Cisplatin |
| ITT | 0.029 | 0.870 |
| Response-Evaluable | 0.074 | 0.611 |

Note: P-values are based on Fisher's exact test for $H_0$: equal response rates vs. $H_1$: unequal response rates.

[b] Both populations are sponsor-defined.

The sponsor defined the duration of response as the time from the date of randomization to the date of disease progression and obtained the adjusted median duration of survival, based on non-parametric covariate-adjusted stratified logrank test, as in Table 35 below.

**Table 35: Sponsor's Adjusted Median Duration of Response**

| Population | Comparison 1 | | Comparison 2 | |
|---|---|---|---|---|
| | Docetaxel + Cisplatin | Vinorelbine + Cisplatin | Docetaxel + Carboplatin | Vinorelbine + Cisplatin |
| Sponsor-defined evaluable population | 32 weeks | 34 weeks | 31 weeks | 35 weeks |

*Reviewer Comments : Although a p value of 0.029 (Table 34) seemed small, there was no statistically significant evidence that docetaxel + cisplatin yielded a higher overall response rate compared to the active control when the Hochberg procedure was employed for multiple comparisons with the control. In summary, there was no statistically significant evidence that either test regimen was associated with a higher overall response rate as compared with the active control.*

*The reviewer agrees with the sponsor's measurement of duration of response for patients with a complete response. However, for patients with a partial response, the reviewer's assessment is that duration of response should be calculated as time from initial documentation of a PR to the date of documented disease progression, not from date of randomization to date of progression .*

*In addition, the median duration of response should be obtained by the Kaplan-Meier estimates (also pre-specified in the sponsor's statistical analysis plan), not the non-parametric covariate-adjusted stratified logrank test (post-hoc). The latter may lead to different estimates of the median duration of response for the active control arm as seen in Table 35. The FDA's descriptive summary of duration of response can be found in Table 36. As seen in this table, the median duration of response was around 150 days for docetaxel + cisplatin, 141 days for docetaxel + carboplatin and 173 days for vinorelbine + cisplatin. It is to be noted that duration of response is considered on responders only. It should not be compared between treatment groups because the respective responder subgroups are treatment-outcome dependent.*

**Table 36 : Reviewer's Results of Response Rate and Response Duration**

| Population | | Docetaxel + Cisplatin | Docetaxel + Carboplatin | Vinorelbine + Cisplatin |
|---|---|---|---|---|
| All randomized patients | # of responders [95% CI[b]] | 129/408 ( 31.6%) | 97/407 (23.8%) | 99/405 (24.4%) |
| | # censored for duration | 37/129 (28.7%) | 21/97 (21.7%) | 22/99 (22.5%) |
| | Median duration[c] [Adj 95% CI] | 21.3 [18.1, 24.3] | 20.1 [16.6, 23.7] | 24.7 [21.6, 26.1] |
| Response-evaluable [a] | # of responders [Adj 95% CI] | 127/366 (34.7%) [29.2%, 40.3%] | 96/363 (26.4%) [21.4%, 31.6%] | 95/336 (28.3%) [22.9%, 33.8%] |
| | # censored for duration | 36/127 (28.3%) | 21/96 (21.9%) | 21/336 (22.3%) |
| | Median duration [Adj 95% CI] | 21.6 [18.1, 25.4] | 20.1 [16.6, 23.4] | 24.7 [21.0, 27.1] |

[a] Sponsor-defined response-evaluable population.
[b] Adjusted for multiple comparisons on this endpoint based on the Hochberg procedure
[c] Kaplan-Meier estimates in weeks.

**Time To Progression (TTP)**

During the study, greater than 75% of patients had a determination of disease progression. The sponsor reported that most assessments were performed at the end of every other treatment cycle within the first 26 weeks. Since each chemotherapy cycle was repeated every 3 weeks in both docetaxel-containing regimens and every 4 weeks in the active control group of vinorelbine + cisplatin, the sponsor commented

that the assessments of time to progression might have been biased due to the differences in the target tumor assessment intervals. The sponsor further commented that it was more likely that TTP was inflated in the treatment group with longer cycles (i.e., the vinorelbine + cisplatin group).



**Table 37: Sponsor's Descriptive Summary of Time to Disease Progression**

| Population | Comparison 1 | | Comparison 2 | |
|---|---|---|---|---|
| | Docetaxel + Cisplatin [N = 408] | Vinorelbine + Cisplatin [N=404] | Docetaxel + Carboplatin [N = 406] | Vinorelbine + Cisplatin [N=404] |
| Censored patients | 92 (23%) | 91 (23%) | 60 (14.8%) | 91 (23%) |
| Median TTP (weeks) [95% CI[a]] | 22 [21, 25] | 23 [21, 27] | 20 [19.0, 22.5] | 22 [19.0, 25.0] |

[a] Nominal 95% confidence interval based on the sponsor's stratified non-parametric covariate-adjusted analysis.

*Reviewer's Comments : The medians obtained by the sponsor were not based on the Kaplan-Meier method; they were adjusted medians using the sponsor-proposed non-parametric covariate-adjusted stratified logrank test. The sponsor's approach resulted in different median estimates in the same active control group (vinorelbine + cisplatin) between the two comparisons (see Table37 above). The reviewer's descriptive results of median TTP on all randomized patients based on the Kaplan-Meier method is summarized in Table 38.*

*Because of the difference in cycle duration between the docetaxel-containing regimens and the vinorelbine + cisplatin group, a bias may be introduced in analysis of TTP. Therefore, comparisons between the docetaxel-containing regimens and the vinorelbine + cisplatin control must be viewed with caution.*

**Table 38 : Reviewer's Descriptive Summary of Time to Disease Progression**

| | Docetaxel + Cisplatin [N = 408] | Docetaxel + Carboplatin [N = 407] | Vinorelbine + Cisplatin [N=405] |
|---|---|---|---|
| Censored patients | 92 (22.5%) | 60 (14.7%) | 92 (22.7%) |
| Median TTP (weeks) [Adjusted 95% CI[a]] | 21.4 [19.3, 24.6] | 19.4 [18.1, 21.3] | 22.1 [18.1, 25.6] |

[a] Adjusted for multiple comparisons on this endpoint based on the Hochberg procedure.

**Quality of Life (QoL)**

QoL instruments were completed prior to the first treatment infusion (within 14 days or less before initiation of chemotherapy), during chemotherapy administration (prior to each new cycle), at the end of study-treatment and during the follow-up period (every two months). The instruments were administered only in countries where a translated version of the QoL with validation was available. As a result, only patients who participated in QoL evaluation were included in QoL analyses.

Two validated instruments were used: LCSS and EuroQoL. The sponsor considered the global QoL item "Quality of Life Today" as the primary LCSS endpoint and the "Global Health State" item as the primary EuroQoL endpoint and performed two analyses, a longitudinal analysis and an analysis of covariance, for each endpoint. The sponsor used a fixed interval of 21 days (i.e., the sponsor-defined period) for all QoL analyses because the length of treatment cycle in these test regimen groups was different from that in the active control group. The sponsor's results are summarized in Table 39. The Sponsor concluded that an improvement in "Global Health State" was seen in both docetaxel-containing arms compared to the active control in both analyses and an improvement in "Quality of Life Today" was seen in the docetaxel as compared to the active control in both analyses.

**Table 39: Sponsor's Results of QoL Analyses**

| Instrument / Endpoint | Analysis | Docetaxel +Cisplatin vs. Vinorelbine+Cisplatin [N = 313] | Docetaxel+Carboplatin vs. Vinorelbine+Cisplatin [N = 307] |
|---|---|---|---|
| LCSS / Quality of Life Today | Longitudinal | 0.064 | 0.016 |
| | Covariance | 0.216 | 0.012 |
| EuroQoL / Global Health State | Longitudinal | 0.016 | < 0.001 |
| | Covariance | 0.014 | < 0.001 |

*Reviewer's Comments : Due to a number of issues as outlined below, reviewers do not consider the sponsor's conclusions regarding QoL analyses to be reliable:*

A. *Multiple Endpoints : The sponsor states in the SAP that LCSS will be the primary instrument to assess quality of life and the primary LCSS score will be the global QoL item rated by the patient. The EuroQoL scale will be the secondary instrument. Based on the Based on the sponsor analysis results from the LCSS instrument, no statistical significance was found in comparing docetaxel + cisplatin to vinorelbine + cisplatin. Therefore, analysis based on the secondary instrument should not be considered. If the sponsor intends to make a claim based on either instrument, then a procedure for controlling the false positive rate should be pre-specified in the SAP, which was not done in this case.*

B. *Multiple Analyses: Several statistical procedures (analyses) for the primary score were performed, such as "longitudinal" and 'covariance" as in Table 39. Other analyses were also proposed in the SAP. It was not clear which was the primary analysis.*

C. *Missing Data: Many patients in countries where translations of QoL instruments were not available did not participate in QoL evaluation. In addition, a proportion of patients who participated in the evaluation had missing values at baseline assessment, and many more at post-baseline assessments. Across the three treamtent arms, 28-29% of patients did not participate in QoL evaluations. Furthermore, only 62-65% of patients had baseline values available. It was not clearly specified in the sponsor's SAP how missing values would be handled. The approach for handling missing data utilized by the sponsor and described in the study report appears to be based on general considerations without a basis of support for this approach in the setting of the specific instruments utilized in this clinical trial.*

D. *The issues related to multiple endpoints and multiple analyses described above also apply to any interpretation of the sponsor's claims regarding change in weight from baseline and change in Karnofsky Performance Status.*

## D. Efficacy 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. 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.

There was no statistically significant finding in analysis of response rates, duration of response, or time to progression (comparison of either docetaxel-containing regimen to vinorelbine + cisplatin). Sponsor's conclusions regarding QoL assessment were not considered to be reliable by FDA reviewers for a number of reasons.

# VII. Integrated Review of Safety

## A. Brief Statement of Conclusions

The most commonly occurring clinically relevant adverse events (greater than or equal to 50% of patients) included alopecia, nausea, vomiting, asthenia, and pain. Of these, alopecia occurred more commonly in either docetaxel-containing regimen than in the vinorelbine + cisplatin arm. Nausea and vomiting occurred less commonly in the docetaxel + carboplatin arm than in either cisplatin-containing regimen. Asthenia and pain were approximately equally distributed in frequency across the three treatment arms. 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.

Other commonly occurring AE's (20%-50% of patients) included diarrhea, weight loss, stomatitis, infection, hemoptysis, constipation, fluid retention, and neurosensory events. Of these, stomatitis, diarrhea, and fluid retention occurred more commonly in either docetaxel-containing regimen than in the vinorelbine + cisplatin control arm. On the other hand, constipation occurred more commonly in the vinorelbine + cisplatin arm than either docetaxel-containing arm. Neuro-sensory events occurred less commonly in the docetaxel + carboplatin arm than either cisplatin-containing regimen.

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.

Myelosuppression was noted in most patients, with leucopenia, neutropenia, and anemia each occurring in greater than 85% of patients across the three treatment arms. Of note, most neutropenic events were of grade 3 / 4 severity (74-78% across the three treatment arms). Thrombocytopenia was less common, occurring in 15% - 25% of patients.

Biochemical abnormalities included elevations in SGOT or SGPT (20-30%), alkaline phosphatase (37-50%), or creatinine (10-37%). Hypocalcemia and hypomagnesemia were also observed. Elevations in creatinine and hypocalcemia were both observed more commonly in the cisplatin-containing regimens than in the docetaxel + carboplatin arm.

Of the 98 patients who died within 30 days of last infusion, 25 had the cause of death listed as toxicity from study drug 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.

Infection was the most common investigator assessment as cause of death in these patients. The vast majority of patients died more than 30 days after the last infusion of study drug. Of these, 830 were attributed to malignant disease and 53 were attributed to other causes. None were attributed to toxicity from study drug treatment.

In summary, the safety profile of docetaxel + cisplatin is generally 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.

**B. Description of Patient Exposure**

A total of 1203 patients (98.6% of the ITT population) received treatment during the study. Patients received between one and thirteen cycles of treatment. The treatment cycle for the docetaxel groups was 21 days and for the

vinorelbine/cisplatin group it was 28 days. Table 40 summarizes the number and percentage of patients treated by cycle and treatment group.



**Table 40 : Number of Patients Treated by Cycle and Treatment Group**

| Cycle Number | Docetaxel Cisplatin | Docetaxel Carboplatin | Vinorelbine Cisplatin | All |
|---|---|---|---|---|
| 1 | 406 | 401 | 396 | 1203 |
| 2 | 370 | 365 | 350 | 1085 |
| 3 | 313 | 308 | 266 | 887 |
| 4 | 280 | 277 | 220 | 777 |
| 5 | 239 | 233 | 173 | 645 |
| 6 | 202 | 206 | 133 | 541 |
| 7 | 36 | 43 | 12 | 91 |
| 8 | 24 | 37 | 6 | 67 |
| 9 | 4 | 9 | 1 | 14 |
| 10 | 2 | 2 | 0 | 4 |
| 11 | 1 | 0 | 0 | 1 |
| 12 | 1 | 0 | 0 | 1 |
| 13 | 1 | 0 | 0 | 1 |

*Reviewer Comment : The sponsor and FDA analyses of number of patients treated by cycle and treatment group are identical.*

The mean and median number of treatment cycles administered to patients in the three treatment arms are provided in Table 41 .

**Table 41 : Treatment Cycles on Study by Treatment Group**

| 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 | | | |

*Reviewer Comment : FDA's analysis of median number of cycles on study by treatment group is identical to that of the sponsor. The mean number of cycles and confidence intervals presented in Table 41 are a reflection of the FDA's analysis. This data is not presented by the sponsor in the study report for TAX326.*



The sponsor's analysis of cumulative dose, weekly dose intensity, and relative dose intensity by treatment group is presented in Table 42. Relative dose intensity was calculated by dividing actual dose intensity by planned dose intensity.

**Table 42 : Sponsor Assessment of Cumulative Dose and Dose Intensity by Treatment Component**

| 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 | 285 | 354 |
| **Median** | 378 | 377 | 379 | 1802 | 276 | 353 |
| **Min** | | | | | | |
| **Max** | | | | | | |
| **Dose Intensity ($mg/m^2$/week)** | | | | | | |
| **Mean** | 23.45 | 23.42 | 23.37 | 117.37 | 16.75 | 22.09 |
| **Median** | 24.22 | 24.27 | 24.14 | 113.83 | 16.91 | 23.24 |
| **Min** | | | | | | |
| **Max** | | | | | | |
| **Relative Dose Intensity** | | | | | | |
| **Mean** | 0.94 | 0.94 | 0.93 | 0.92 | 0.67 | 0.88 |
| **Median** | 0.97 | 0.97 | 0.97 | 0.94 | 0.68 | 0.93 |
| **Min** | | | | | | |
| **Max** | | | | | | |

*Reviewer Comment : The FDA medical reviewer's analysis of the USMA medications dataset revealed similar, but not identical results for cumulative dose and dose intensity. The FDA analysis is presented in Table 43.In both sponsor and FDA*

*analyses, mean and median dose intensity and relative dose intensity of cisplatin in the vinorelbine + cisplatin arm are slightly lower than those of cisplatin in the docetaxel + cisplatin arm. In both analyses, mean and median dose intensity of docetaxel were comparable in the two docetaxel-containing regimens. In the FDA analysis, relative dose intensity of docetaxel was slightly lower in the docetaxel+carboplatin than in the docetaxel+cisplatin combination.*



**Table 43 : Reviewer's Analysis of Cumulative Dose and Dose Intensity by Treatment Component**

| 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 | 340 | 342 | 1738 | 284 | 354 |
| **Median** | 378 | 377 | 379 | 1802 | 275 | 351 |
| **Min** | | | | | | |
| **Max** | | | | | | |
| **Dose Intensity ($mg/m^2$/week)** | | | | | | |
| **Mean** | 24 | 24 | 23 | 118 | 18 | 22 |
| **Median** | 24 | 24 | 24 | 115 | 18 | 23 |
| **Min** | | | | | | |
| **Max** | | | | | | |
| **Relative Dose Intensity** | | | | | | |
| **Mean** | 0.95 | 0.96 | 0.92 | 0.91 | 0.72 | 0.88 |
| **Median** | 0.96 | 0.96 | 0.92 | 0.92 | 0.72 | 0.92 |
| **Min** | | | | | | |
| **Max** | | | | | | |

## C. Methods and Specific Findings of Safety Review

Incidence of Adverse Events

According to the sponsor, fewer grade 3 / 4 or severe AE's were reported in the docetaxel/cisplatin and docetaxel/carboplatin groups compared with the control. The sponsor's assessment of distribution of serious adverse events in the three treatment arms is listed in Table 44.



**Table 44 : Sponsor Assessment of Patients with an Adverse Event**

| Percent of Treated Patients | Docetaxel Cisplatin | Docetaxel Carboplatin | Vinorelbine Cisplatin |
|---|---|---|---|
| At Least One AE | 100 % | 99.5 % | 97.9 % |
| At Least One Severe or Grade ¾ AE | 51.7 % | 49.8 % | 59.6 % |

*Reviewer Comment : The medical reviewer agrees with the sponsor's assessment. However, it would be more informative to illustrate the distribution of AE's by NCI CTC Grade across the 3 treatment arms as follows in Table 45 :*

**Table 45 : Reviewer's Assessment of Patients with an AE by Treatment Group**

| NCI-CTC Grade | Docetaxel Cisplatin N = 406 | Docetaxel Carboplatin N = 401 | Vinorelbine Cisplatin N = 396 |
|---|---|---|---|
| **Grade 1** | 399 (98%) | 397 (99%) | 392 (99%) |
| **Grade 2** | 390 (96%) | 390 (97%) | 392 (99%) |
| **Grade 3** | 225 (55%) | 222 (55%) | 335 (85%) |
| **Grade 4** | 78 (19%) | 78 (19%) | 233 (59%) |

*This analysis suggests a greater number of patients experiencing a grade 3 or grade 4 toxicity in the control arm compared to either docetaxel-containing regimen.*

The sponsor presented all adverse events reported by ≥ 10% of patients in Appendix II.F of the study report. In table 52 of the study report, these findings were presented by treatment group and the sponsor's conclusions regarding these are as follows :

A larger percentage of patients in the docetaxel/cisplatin arm than in the vinorelbine/cisplatin arm experienced alopecia, diarrhea, peripheral edema, nail disorder, allergy, myalgia, arthralgia, taste perversion and weight gain. However, fewer docetaxel/cisplatin patients than vinorelbine/cisplatin patients experienced local toxicity, weight loss, vomiting and dizziness. The same incidence of patients in both arms experienced overall neurotoxicity, as represented by the grouping of NCI neurolgical events. Neuro-sensory had a greater frequency in the docetaxel/cisplatin than the vinorelbine/cisplatin group. However, there were fewer neuro-hearing and neuro-constipation events in the docetaxel/cisplatin than in the vinorelbine/cisplatin group.

A larger percentage of patients in the docetaxel/carboplatin group than the vinorelbine/cisplatin group experienced alopecia, diarrhea, nail disorder, skin, allergy, increased cough, peripheral edema, myalgia, arthralgia, hemoptysis and infection. However, fewer docetaxel/carboplatin than vinorelbine/cisplatin patients experienced nausea/vomiting, local toxicity, weight loss, anorexia, dizziness, asthenia, constipation, decreased cardiac function, dehydration and overall neurotoxicity. Individually, neuro-hearing, neurosensory, and neuro-constipation were of lower frequency in the doctaxel/carboplatin than vinorelbine/cisplatin group.

Among the grade 3 / 4 or severe adverse events that were reported, more patients in the docetaxel + cisplatin arm experienced grade 3 / 4 diarrhea and allergy. However, fewer docetaxel + cisplatin patients experienced grade 3 / 4 nausea/vomiting, neurotoxicity, asthenia and local toxicity. More docetaxel + carboplatin than vinorelbine + cisplatin patients experienced grade 3 / 4 infection and diarrhea. However, fewer docetaxel + carboplatin patients experienced grade 3 / 4 nausea/vomiting, neuro-toxicity, asthenia, local toxicity and dehydration.

*Reviewer comment : The sponsor's analysis and presentation include AE's by COSTART term or NCI term. For NCI term, data is provided as any AE or grades 3 / 4. For COSTART term, data is provided as any or severe. The medical reviewer has analyzed AE data by NCI term with a calculation of number of patients experiencing an AE with distribution by maximum grade experienced. This data is presented in Table 46. An analysis of the data by COSTART term is presented separately below in Table 47. A key difference between the sponsor's approach and that of the reviewer is that the reviewer has included all treated patients in the analysis, whereas the sponsor has used a "treatment emergent" principle, where events are included only if they developed during treatment. Although the sponsor's*

*statements about relatively greater or smaller frequencies in the docetaxel-containing regimens compared to the cisplatin + vinorelbine regimen are genrally supported by the FDA analysis, the individual frequencies of several AE's are higher in the reviewer's analysis than in the sponsor's analysis. This is likely due to the differences in strategies used as discussed above.*

**Table 46 : Reviewer Analysis of AE's Reported by NCI Term, Maximum Grade, and Treatment Group**

| Adverse Event | Docetaxel Cisplatin N = 406 | Docetaxel Carboplatin N = 401 | Vinorelbine Cisplatin N = 396 |
|---|---|---|---|
| **Alopecia Grade** | | | |
| 1 | 104 | 96 | 102 |
| 2 | 199 | 178 | 64 |
| 3 | 3 | 4 | 0 |
| 4 | 0 | 0 | 0 |
| TOTAL | 306 (75%) | 278 (69%) | 166 (42%) |
| **Nausea Grade** | | | |
| 1 | 120 | 117 | 102 |
| 2 | 131 | 78 | 133 |
| 3 | 38 | 26 | 65 |
| 4 | 2 | 0 | 1 |
| TOTAL | 291 (72%) | 221 (55%) | 301 (76%) |
| **Vomiting Grade** | | | |
| 1 | 98 | 76 | 87 |
| 2 | 95 | 52 | 92 |
| 3 | 22 | 17 | 48 |
| 4 | 10 | 1 | 16 |
| TOTAL | 225 (55%) | 146 (36%) | 243 (61%) |
| **Diarrhea Grade** | | | |
| 1 | 86 | 70 | 59 |
| 2 | 78 | 63 | 30 |
| 3 | 22 | 16 | 7 |
| 4 | 6 | 5 | 4 |
| TOTAL | 192 (47%) | 154 (38%) | 100 (25%) |
| **Weight Loss Grade** | | | |
| 1 | 71 | 66 | 74 |
| 2 | 41 | 31 | 54 |
| 3 | 5 | 5 | 9 |

| | | | |
|---|---|---|---|
| 4 | 0 | 0 | 0 |
| TOTAL | 117 (29%) | 102 (25%) | 137 (35%) |
| **Neuro-Constipation** | | | |
| Grade | | | |
| 1 | 38 | 49 | 60 |
| 2 | 33 | 22 | 29 |
| 3 | 2 | 1 | 8 |
| 4 | 0 | 1 | 0 |
| TOTAL | 73 (18%) | 73 (18%) | 97 (24%) |
| **Stomatitis Grade** | | | |
| 1 | 53 | 53 | 45 |
| 2 | 35 | 48 | 35 |
| 3 | 8 | 1 | 5 |
| 4 | 0 | 0 | 0 |
| TOTAL | 96 (24%) | 102 (25%) | 85 (21%) |
| **Infection Grade** | | | |
| 1 | 49 | 49 | 51 |
| 2 | 58 | 81 | 65 |
| 3 | 24 | 31 | 24 |
| 4 | 10 | 14 | 8 |
| TOTAL | 141 (35%) | 175 (44%) | 148 (37%) |
| **Local Toxicity** | | | |
| Grade | | | |
| 1 | 14 | 16 | 31 |
| 2 | 14 | 13 | 37 |
| 3 | 1 | 2 | 13 |
| 4 | 0 | 0 | 0 |
| TOTAL | 29 (7%) | 31 (8%) | 81 (20%) |
| **Skin** Grade | | | |
| 1 | 47 | 59 | 40 |
| 2 | 16 | 28 | 11 |
| 3 | 3 | 2 | 4 |
| 4 | 0 | 0 | 0 |
| TOTAL | 66 (16%) | 89 (22%) | 55 (14%) |
| **Neuro-hearing** | | | |
| Grade | | | |
| 1 | 15 | 10 | 21 |
| 2 | 32 | 15 | 55 |
| 3 | 5 | 3 | 7 |
| 4 | 0 | 0 | 0 |
| TOTAL | 52 (13%) | 28 (7%) | 83 (21%) |

| | | | |
|---|---|---|---|
| **Neuro-sensory** | | | |
| **Grade** | | | |
| **1** | 128 | 96 | 112 |
| **2** | 45 | 17 | 38 |
| **3** | 16 | 4 | 15 |
| **4** | 0 | 0 | 1 |
| **TOTAL** | 189 (47%) | 117 (29%) | 166 (42%) |
| **Neuro-cerebellar** | | | |
| **Grade** | | | |
| **1** | 7 | 4 | 8 |
| **2** | 2 | 1 | 2 |
| **3** | 2 | 1 | 1 |
| **4** | 0 | 0 | 0 |
| **TOTAL** | 11 (3%) | 6 (1%) | 11 (3%) |
| **Neuro-motor** | | | |
| **Grade** | | | |
| **1** | 34 | 27 | 21 |
| **2** | 31 | 21 | 26 |
| **3** | 13 | 14 | 21 |
| **4** | 1 | 2 | 1 |
| **TOTAL** | 79 (19%) | 64(16%) | 69 (17%) |

**Table 47 : Reviewer Analysis of AE's Reported by COSTART Term, Maximum Severity*, and Treatment Group**

| Adverse Event | Docetaxel Cisplatin N = 406 | Docetaxel Carboplatin N = 401 | Vinorelbine Cisplatin N = 396 |
|---|---|---|---|
| **Asthenia Severity** | | | |
| 1 | 121 | 104 | 110 |
| 2 | 128 | 126 | 130 |
| 3 | 49 | 42 | 56 |
| 4 | 1 | 2 | 1 |
| TOTAL | 299 (74%) | 274 (68%) | 297 (75%) |
| **Pain Severity** | | | |
| 1 | 126 | 118 | 123 |
| 2 | 119 | 132 | 142 |
| 3 | 50 | 55 | 48 |
| 4 | 0 | 3 | 2 |
| TOTAL | 295 (73%) | 308 (77%) | 315 (80%) |
| **Anorexia Severity** | | | |
| 1 | 88 | 63 | 63 |
| 2 | 59 | 60 | 74 |
| 3 | 21 | 12 | 20 |
| 4 | 1 | 0 | 1 |
| TOTAL | 169 (42%) | 135 (34%) | 158 (40%) |
| **Peripheral Edema Severity** | | | |
| 1 | 80 | 58 | 46 |
| 2 | 54 | 35 | 25 |
| 3 | 2 | 3 | 1 |
| 4 | 1 | 0 | 0 |
| TOTAL | 137 (34%) | 96 (24%) | 72 (18%) |
| **Myalgia Severity** | | | |
| 1 | 44 | 52 | 33 |
| 2 | 25 | 11 | 12 |
| 3 | 3 | 3 | 1 |
| 4 | 0 | 0 | 0 |
| TOTAL | 72 (18%) | 66 (16%) | 46 (12%) |
| **Arthralgia Severity** | | | |
| 1 | 39 | 41 | 31 |
| 2 | 26 | 23 | 17 |
| 3 | 2 | 3 | 4 |
| 4 | 0 | 0 | 0 |
| TOTAL | 67 (17%) | 67 (17%) | 52 (13%) |
| **Constipation Severity** | | | |
| 1 | 75 | 71 | 103 |
| 2 | 43 | 34 | 43 |

| | | | |
|---|---|---|---|
| **3** | **6** | **2** | **13** |
| **4** | **0** | **1** | **0** |
| **TOTAL** | 124 (31%) | 108 (27%) | 159 (40%) |

| | | | |
|---|---|---|---|
| **Nail disorder Severity** | | | |
| **1** | 40 | 30 | 2 |
| **2** | 12 | 11 | 1 |
| **3** | 3 | 0 | 0 |
| **4** | 0 | 0 | 0 |
| **TOTAL** | 55 (14%) | 41 (10%) | 3 (<1%) |
| **Hemoptysis Severity** | | | |
| **1** | 78 | 75 | 58 |
| **2** | 11 | 16 | 12 |
| **3** | 1 | 5 | 1 |
| **4** | 2 | 1 | 0 |
| **TOTAL** | 82 (20%) | 95 (24%) | 71 (18%) |
| **Dehydration Severity** | | | |
| **1** | 11 | 3 | 5 |
| **2** | 18 | 7 | 16 |
| **3** | 9 | 7 | 15 |
| **4** | 3 | 0 | 2 |
| **TOTAL** | 41 (10%) | 17 (4%) | 38 (10%) |
| **Pleural Effusion Severity** | | | |
| **1** | 65 | 70 | 54 |
| **2** | 20 | 30 | 27 |
| **3** | 10 | 9 | 6 |
| **4** | 0 | 0 | 1 |
| **TOTAL** | 95 (23%) | 109 (27%) | 88 (22%) |
| **Weight Gain Severity** | | | |
| **1** | 41 | 39 | 27 |
| **2** | 18 | 14 | 8 |
| **3** | 2 | 2 | 1 |
| **4** | 0 | 0 | 0 |
| **TOTAL** | 61 (15%) | 55 (14%) | 36 (9%) |
| **Taste Perversion Severity** | | | |
| **1** | 31 | 24 | 17 |
| **2** | 7 | 4 | 3 |
| **3** | 1 | 0 | 0 |
| **4** | 0 | 0 | 0 |
| **TOTAL** | 39 (10%) | 28 (7%) | 20 (5%) |
| **Dizziness Severity** | | | |
| **1** | 22 | 18 | 45 |
| **2** | 14 | 7 | 9 |
| **3** | 0 | 1 | 1 |
| **4** | 0 | 0 | 0 |
| **TOTAL** | 36 (9%) | 26 (6%) | 55 (14%) |

1 = mild ; 2 = moderate ; 3 = severe ; 4 = life threatening

*COSTART terms for which frequencies obtained by reviewer analysis are notably greater than those obtained by the sponsor's analysis include asthenia, pain, anorexia, arthralgia, hemoptysis and pleural effusion.*

The following sections are devoted to specific clinical toxicities associated with docetaxel administration :

Fluid Retention : There is no single NCI or COSTART term for fluid retention. Signs of fluid retention may include peripheral edema, weight gain, or pleural effusion. In some patients, ascites or pericardial effusion may occur. Sponsor findings regarding the incidence of signs of fluid retention are summarized in section 8.4.2.10 of the final study report for TAX326. The sponsor's assessment of the frequency of patients with the more common signs of fluid retention or any sign of fluid retention are presented in Table 48 below. In both docetaxel-containing regimens, the incidence of fluid retention (as a whole) appears to be greater than that observed in the vinorelbine + cisplatin arm.

**Table 48 : Sponsor Assessment of Fluid Retention by COSTART Term**

| Signs of Fluid Retention | Docetaxel + Cisplatin N = 406 | Docetaxel + Carboplatin N = 401 | Vinorelbine + Cisplatin N = 396 |
|---|---|---|---|
| **Weight Gain** | 30 (7.4%) | 26 (6.5%) | 24 (6.1%) |
| **Edema** | 81 (20%) | 46 (11.5%) | 51 (12.9%) |
| **Pleural Effusion** | 41 (10.1%) | 62 (15.5%) | 53 (13.4%) |
| **All patients*** | 229 (56.4%) | 200 (49.9%) | 168 (42.4%) |

*Includes sponsor assessment of weight gain, pleural effusion, edema, lung edema, pericardial effusion, ascites

*Reviewer Comments : Of note, although the sponsor's presentation includes an incidence of signs of fluid retention of 56.4%, 49.9%, and 42.4% across the three treatment arms as seen above, the sponsor's suggested labeling includes frequencies of fluid retention as an overall adverse event of 25.9%, 18.7%, and 8.3% respectively. These frequencies are much lower than those presented in the study report. Furthermore, the suggested labeling only provides overall frequencies without attention to individual signs. The reviewer analyzed individual signs of fluid retention and found that the main contributing COSTART terms in terms of patients with a reported AE were weight gain, peripheral edema, and pleural effusion. The reviewer's analysis by sign (COSTART term) and maximum grade is presented in Table 49 below.*

**Table 49 : Reviewer Assessment of Fluid Retention by COSTART Term and Worst Grade**

| Signs of Fluid Retention and Maximum Severity* | Docetaxel + Cisplatin N = 406 | Docetaxel + Carboplatin N = 401 | Vinorelbine + Cisplatin N = 396 |
|---|---|---|---|
| **Weight Gain** | | | |
| 1 | 41 | 39 | 27 |
| 2 | 18 | 14 | 8 |
| 3 | 2 | 2 | 1 |
| 4 | 0 | 0 | 0 |
| TOTAL | 61 (15%) | 55 (14%) | 36 (9%) |
| **Peripheral Edema** | | | |
| 1 | 80 | 58 | 46 |
| 2 | 54 | 35 | 25 |
| 3 | 2 | 3 | 1 |
| 4 | 1 | 0 | 0 |
| TOTAL | 137 (34%) | 96 (24%) | 72 (18%) |
| **Pleural Effusion** | | | |
| 1 | 65 | 70 | 54 |
| 2 | 20 | 30 | 27 |
| 3 | 10 | 9 | 6 |
| 4 | 0 | 0 | 1 |
| TOTAL | 95 (23%) | 109 (27%) | 88 (22%) |
| **All patients**** | | | |
| 3 or 4 | 9 (2%) | 10 (2%) | 6 (1.5%) |
| Any | 220 (54%) | 205 (51%) | 168 (42%) |

* 1 = mild ; 2 = moderate, 3 = severe ; 4 = life-threatening

** patients with weight gain, pleural effusion and/or peripheral edema

Hypersensitivity Reaction : The sponsor concluded that hypersensitivity reactions were reported by more patients in either docetaxel-containing regimen than those in the vinorelbine + cisplatin arm. Although the incidence of grade 3 / 4 reactions was low, it also appeared to occur slightly more frequently in either docetaxel-containing regimen than in the vinorelbine + cisplatin group. (See Table 50 below) No deaths occurred due to hypersensitivity reactions in any of the three treatment arms.

*Reviewer's Comments : In general, the reviewer agrees with the sponsor's conclusions. The reviewer's analysis results in frequencies similar to those of the sponsor. The sponsor is proposing inclusion of treatment-related events in the proposed label. The reviewer proposes presentation of all events irrespective of whether they are considered treatment-related.Both sponsor and reviewer proposals are presented in Table 50.*

**Table 50 : Sponsor and Reviewer Assessment of Hypersensitivity Reactions**

| Hypersensitivity Reactions based on NCI term Allergy | Docetaxel + Cisplatin N = 406 | Docetaxel + Carboplatin N = 401 | Vinorelbine + Cisplatin N = 396 |
|---|---|---|---|
| **Sponsor** | | | |
| **Grade 3 / 4** | 2.5% | 2.0% | 0.3% |
| **Any** | 10.6% | 10.2% | 3.0% |
| **Reviewer** | | | |
| **Grade 3 / 4** | 3% | 2% | < 1% |
| **Any** | 12% | 11% | 4% |

Neurologic Toxicity : The sponsor's assessment of individual neurologic toxicities is presented in section 8.4.2.2 of the study report. The sponsor concluded that the overall incidence of neurotoxicity was comparable between the docetaxel + cisplatin and vinorelbine + cisplatin arms, but occurred less frequently and with less severity in the docetaxel + carboplatin arm than in the active control. With respect to individual toxicities, the sponsor concluded that more patients in the docetaxel + cisplatin arm experienced neuro-sensory events but fewer experienced neuro-hearing and neuro-constipation events than in the vinorelbine + cisplatin arm. The sponsor's assessment of neurologic toxicities is presented in Table 51 below.

**Table 51 : Sponsor's Assessment of Neurologic Toxicities by NCI Term**

| Adverse Event NCI Term | Docetaxel + Cisplatin N = 406 | Docetaxel + Carboplatin N = 401 | Vinorelbine + Cisplatin N = 396 |
|---|---|---|---|
| **Neuro-sensory** | | | |
| **Grade 3 / 4** | 16 (3.9%) | 3 (0.7%) | 15 (3.8%) |
| **All** | 174 (42.9%) | 100 (24.9%) | 146 (36.9%) |
| **Neuro-constipation** | | | |
| **Grade 3 / 4** | 2 (0.5%) | 2 (0.5%) | 8 (2.0%) |
| **All** | 68 (16.7%) | 56 (14.0%) | 87 (22.0%) |
| **Neuro-motor** | | | |
| **Grade 3 / 4** | 14 (3.4%) | 15 (3.7%) | 18 (4.5%) |
| **All** | 67 (16.5%) | 54 (13.5%) | 49 (12.4%) |
| **Neuro-mood** | | | |
| **Grade 3 / 4** | 5 (1.2%) | 3 (0.7%) | 10 (2.5%) |
| **All** | 54 (13.3%) | 60 (15.0%) | 64 (16.2%) |
| **Neuro-hearing** | | | |
| **Grade 3 / 4** | 3 (0.7%) | 1 (0.2%) | 7 (1.8%) |
| **All** | 42 (10.3%) | 16 (4.0%) | 73 (18.4%) |
| **Neuro-headache** | | | |
| **Grade 3 / 4** | 5 (1.2%) | 2 (0.5%) | 4 (1.0%) |
| **All** | 25 (6.2%) | 21 (5.2%) | 26 (6.6%) |
| **Neuro-cortical** | | | |
| **Grade 3 / 4** | 12 (3.0%) | 8 (2.0%) | 14 (3.5%) |
| **All** | 24 (5.9%) | 17 (4.2%) | 26 (6.6%) |
| **Neuro-vision** | | | |
| **Grade 3 / 4** | 2 (0.5%) | 1 (0.2%) | 3 (0.8%) |
| **All** | 14 (3.4%) | 11 (2.7%) | 17 (4.3%) |
| **Neuro-cerebellar** | | | |
| **Grade 3 / 4** | 2 (0.5%) | 1 (0.2%) | 0 |
| **All** | 8 (2.0%) | 5 (1.2%) | 11 (2.8%) |

*Reviewer's Comments : As with other analyses, the sponsor utilized an emergent strategy for assessing frequencies of individual toxicities. The reviewer analyzed neurologic adverse events, including all reported patients irrespective of whether an individual AE was present at baseline in any individual patient. The reviewer's results are presented in Table 52 below. The conclusions reached by the sponsor are confirmed by the reviewer's analysis. However, the incidence of some individual toxicities is higher in the reviewer's analysis.*

**Table 52 : Reviewer's Assessment of Neurologic Toxicity by NCI Term**

| Adverse Event NCI Term | Docetaxel + Cisplatin N = 406 | Docetaxel + Carboplatin N = 401 | Vinorelbine + Cisplatin N = 396 |
|---|---|---|---|
| **Neuro-sensory** | | | |
| **Grade 3 / 4** | 16 (4%) | 4 (1%) | 16 (4%) |
| **All** | 189 (47%) | 117 (29%) | 166 (42%) |
| **Neuro-constipation** | | | |
| **Grade 3 / 4** | 2 (< 1%) | 2 (< 1%) | 8 (2%) |
| **All** | 73 (18%) | 73 (18%) | 97 (24%) |
| **Neuro-motor** | | | |
| **Grade 3 / 4** | 14 (3%) | 16 (4%) | 22 (4.5%) |
| **All** | 79 (19%) | 64 (16%) | 69 (17%) |
| **Neuro-mood** | | | |
| **Grade 3 / 4** | 5 (1%) | 5 (1%) | 10 (3%) |
| **All** | 88 (22%) | 96 (24%) | 95 (24%) |
| **Neuro-hearing** | | | |
| **Grade 3 / 4** | 5 (1%) | 3 (< 1%) | 7 (2%) |
| **All** | 52 (13%) | 28 (7%) | 83 (21%) |
| **Neuro-headache** | | | |
| **Grade 3 / 4** | 5 (1%) | 2 (< 1%) | 4 (1%) |
| **All** | 27 (7%) | 28 (7%) | 33 (8%) |
| **Neuro-cortical** | | | |
| **Grade 3 / 4** | 12 (3%) | 9 (2%) | 14 (4%) |
| **All** | 26 (6%) | 18 (4%) | 27 (7%) |
| **Neuro-vision** | | | |
| **Grade 3 / 4** | 3 (< 1%) | 2 (< 1%) | 4 (1%) |
| **All** | 17 (4%) | 14 (3%) | 19(5%) |
| **Neuro-cerebellar** | | | |
| **Grade 3 / 4** | 2 (< 1%) | 1 (< 1%) | 1 (< 1%) |
| **All** | 11 (3%) | 6 (1%) | 11 (3%) |

Laboratory Evaluations

The sponsor states that the incidence of laboratory values abnormalities across the three treatment groups was mostly comparable. Table 53 summarizes the sponsor's assessment of total number and percentage of patients who experienced abnormal values for NCI-gradable parameters.

**Table 53 : Sponsor's Assessment of NCI-Gradable Biochemistry Tests at Worst Grade Under Treatment**

| NCI Parameter | Docetaxel/Cisplatin % | Docetaxel/Carbo % | Vinorelbine/Cispl % |
|---|---|---|---|
| **SGOT** | N = 387 | N = 384 | N = 376 |
| **Gr1** | 11.4 | 16.9 | 11.2 |
| **Gr2** | 0.5 | 1.6 | 1.9 |
| **Gr3** | 0.3 | 1.0 | 1.1 |
| **Gr4** | 0.3 | 0.3 | 0.8 |
| **SGPT** | N = 382 | N = 377 | N = 368 |
| **Gr1** | 15.4 | 21.0 | 16.3 |
| **Gr2** | 1.0 | 3.4 | 1.9 |
| **Gr3** | 1.0 | 0.8 | 0.5 |
| **Gr4** | 0.3 | 0.3 | 0.3 |
| **Total Bilirubin** | N = 389 | N = 384 | N = 377 |
| **Gr1** | 0 | 0 | 0 |
| **Gr2** | 3.3 | 3.6 | 4.8 |
| **Gr3** | 1.8 | 2.6 | 1.6 |
| **Gr4** | 0.3 | 0.3 | 0.5 |
| **Alkaline Phosphatase** | N = 392 | N = 383 | N = 379 |
| **Gr1** | 28.6 | 35.5 | 39.3 |
| **Gr2** | 3.3 | 4.4 | 3.4 |
| **Gr3** | 0.3 | 0.8 | 1.3 |
| **Gr4** | 0 | 0 | 0 |
| **Creatinine** | N = 397 | N = 392 | N = 384 |
| **Gr1** | 19.4 | 7.7 | 21.9 |
| **Gr2** | 7.1 | 2.3 | 10.9 |
| **Gr3** | 1.0 | 0 | 1 |
| **Gr4** | 0.3 | 1 | 1.3 |
| **Hypercalcemia** | N = 382 | N = 376 | 367 |
| **Gr1** | 7.6 | 9.3 | 7.9 |
| **Gr2** | 1.6 | 1.9 | 1.6 |
| **Gr3** | 0.3 | 1.1 | 0.3 |
| **Gr4** | 1 | 1.6 | 0.5 |
| **Hypo-magnesemia** | N = 295 | N = 274 | 277 |
| **Gr1** | 31.5 | 38.3 | 31.4 |
| **Gr2** | 22 | 17.5 | 21.7 |
| **Gr3** | 9.2 | 2.9 | 7.6 |

| | | | |
|---|---|---|---|
| **Gr4** | 3.1 | 1.8 | 1.1 |

Only patients with at least one evaluable assessment during treatment or follow-up are included.

% = number of patients experiencing the laboratory value abnormality Grade/total number of evaluable patients.

Derived from Table 65 of the final study report for TAX326.

*Reviewer Comment :The sponsor's analysis included only those patients who had at least one evaluable assessment during treatment or followup, and appears to have excluded some patients who received chemotherapy. Furthermore, hypocalcemia, hypergylcemia, and hypoglycemia are not included although they are NCI-gradable and the sponsor's submitted dataset includes data for these abnormalities. The reviewer has analyzed the data including those for the aforementioned abnormalities and has considered the total number of patients who received chemotherapy as the denominator for each treatment group. The results are listed in Table 54 below.*

**Table 54 : Reviewer's Assessment of NCI-Gradable Biochemistry Tests at Worst Grade**

| NCI Parameter | Docetaxel Cisplatin N = 406 | Docetaxel Carboplatin N = 401 | Vinorelbine Cisplatin N = 396 |
|---|---|---|---|
| **SGOT** | | | |
| **Gr1** | 67 (17%) | 83 (21%) | 65 (16%) |
| **Gr2** | 3 (0.7%) | 8 (2%) | 8 (2%) |
| **Gr3** | 1 (0.2%) | 4 (1%) | 4 (1%) |
| **Gr4** | 1 (0.2%) | 1 (0.2%) | 3 (0.8%) |
| **SGPT** | | | |
| **Gr1** | 86 (21%) | 102 (25%) | 92 (23%) |
| **Gr2** | 4 (1%) | 16 (4%) | 9 (2%) |
| **Gr3** | 4 (1%) | 3 (0.7%) | 2 (0.5%) |
| **Gr4** | 1 (2%) | 1 (0.2%) | 1 (0.3%) |
| **Total Bilirubin** | | | |
| **Gr1** | 0 | 0 | 0 |
| **Gr2** | 14 (3%) | 20 (5%) | 22 (6%) |
| **Gr3** | 9 (2%) | 11 (3%) | 7 (2%) |
| **Gr4** | 1 (0.2%) | 1 (0.2%) | 4 (1%) |
| **Alkaline Phosphatase** | | | |
| **Gr1** | 134 (33%) | 157 (39%) | 171 (43%) |
| **Gr2** | 16 (4%) | 22 (5%) | 21 (5%) |
| **Gr3** | 1 (0.2%) | 3 (0.7%) | 7 (2%) |
| **Gr4** | 0 | 0 | 0 |
| **Creatinine** | | | |

| | | | |
|---|---|---|---|
| **Gr1** | 80 (20%) | 33 (8%) | 94 (24%) |
| **Gr2** | 31 (8%) | 10 (2%) | 43 (11%) |
| **Gr3** | 4 (1%) | 1 (0.2%) | 4 (1%) |
| **Gr4** | 2 (0.5%) | 3 (0.7%) | 5 (1%) |
| **Hypercalcemia** | | | |
| **Gr1** | 31 (8%) | 41 (10%) | 41 (10%) |
| **Gr2** | 7 (2%) | 10 (2%) | 6 (2%) |
| **Gr3** | 1 (0.2%) | 5 (1%) | 3 (0.8%) |
| **Gr4** | 4 (1%) | 6 (1%) | 2 (0.5%) |
| **Hypocalcemia** | | | |
| **Gr1** | 73 (18%) | 39 (10%) | 63 (16%) |
| **Gr2** | 24 (6%) | 18 (4%) | 14 (4%) |
| **Gr3** | 11 (3%) | 5 (1%) | 4 (1%) |
| **Gr4** | 3 (0.7%) | 2 (0.5%) | 2 (0.5%) |
| **Hypomagnesemia** | | | |
| **Gr1** | 102 (25%) | 116 (29%) | 94 (24%) |
| **Gr2** | 68 (17%) | 53 (13%) | 59 (15%) |
| **Gr3** | 29 (7%) | 9 (2%) | 22 (6%) |
| **Gr4** | 9 (2%) | 5 (1%) | 4 (1%) |
| **Hyperglycemia** | | | |
| **Gr1** | 5 (1%) | 2 (0.5%) | 3 (0.8%) |
| **Gr2** | 4 (1%) | 4 (1%) | 4 (1%) |
| **Gr3** | 4 (1%) | 4 (1%) | 3 (0.8%) |
| **Gr4** | 0 | 0 | 1 (0.3%) |
| **Hypoglycemia** | | | |
| **Gr1** | 3 (0.7%) | 0 | 1 (0.3%) |
| **Gr2** | 0 | 0 | 0 |
| **Gr3** | 0 | 0 | 0 |
| **Gr4** | 0 | 0 | 0 |

*As expected, the incidence of creatinine elevations was higher in both cisplatin-containing arms than in the docetaxel/carboplatin arm. The same was true for hypocalcemia and hypomagnesemia.*

Hematological toxicity

As expected, some degree of leucopenia, anemia, and neutropenia was reported in most patients. Thrombocytopenia was less commonly reported. Table 55 presents the sponsor's analysis of incidence of NCI-hematological parameters by worst grade and treatment group. Note that the sponsor only included patients with an evaluable cycle in this analysis. A cycle was considered evaluable if there was $\geq$ 1 blood count between Day 2 and the next cycle. Furthermore, the sponsor did not consider cycles where patients received G-CSF as evaluable, unless neutropenia was equal to grade 4.

**Table 55 : Sponsor Assessment of NCI-Hematological Parameters by Worst Grade and Treatment Group**

| NCI Parameter | Docetaxel Cisplatin N = 404 | Docetaxel Carboplatin | Vinorelbine Cisplatin |
|---|---|---|---|
| **Leucopenia** | | | |
| Gr 3 | 140 (34.7%) | 164 (41.2%) | 161 (41.2%) |
| Gr 4 | 33 (8.2%) | 33 (8.3%) | 52 (13.3%) |
| Gr 1-4 | 359 (88.9%) | 340 (85.4%) | 358 (91.6%) |
| **Neutropenia** | | | |
| Gr 3 | 94 (23.3%) | 100 (25.3%) | 99 (25.3%) |
| Gr 4 | 208 (51.5%) | 194 (49.1%) | 210 (53.7%) |
| Gr 1-4 | 368 (91.1%) | 339 (85.8%) | 356 (91.0%) |
| **Thrombocytopenia** | | | |
| Gr 3 | 9 (2.2%) | 20 (0.5%) | 8 (2.0%) |
| Gr 4 | 2 (0.5%) | 8 (2.0%) | 7 (1.8%) |
| Gr 1-4 | 60 (14.9%) | 100 (25.1%) | 60 (15.3%) |
| **Anemia** | | | |
| Gr 3 | 22 (5.4%) | 34 (8.5%) | 80 (20.4%) |
| Gr 4 | 6 (1.5%) | 8 (2.0%) | 14 (3.6%) |
| Gr 1-4 | 358 (88.6%) | 357 (89.5%) | 368 (93.9) |

*Reviewer's Comment :The reviewer disagrees with some aspects of the sponsor's approach. Evaluation of safety data should include all treated patients, irrespective of number of blood counts per cycle. In addition, the reviewer does not believe that administration of G-CSF should abrogate consideration of reported neutropenia in individual patients. In fact, a report of neutropenia in the face of G-CSF administration is even more compelling, and should be included. Therefore, the reviewer has analyzed the NCI-hematological parameters included in the dataset ULAB while considering all treated patients and listing the results by worst grade and treatment group in Table 56 below. Of note, the incidence of grade 3 / 4 hematologic toxicities of neutropenia, anemia and thrombocytopenia in the vinorelbine + cisplatin arm is virtually identical to those observed in the vinorelbine = cisplatin arm of the phase III SWOG trial reported by Wozniak et al. (1)*

**Table 56 : Reviewer's Assessment of Hematological Parameters by Worst Grade and by Treatment Group**

| NCI Parameter | Docetaxel Cisplatin N = 406 | Docetaxel Carboplatin N=401 | Vinorelbine Cisplatin N=396 |
|---|---|---|---|
| **Leucopenia** | | | |
| Gr 1 | 67 (17%) | 43 (11%) | 36 (9%) |
| Gr 2 | 119 (29%) | 100 (25%) | 109 (28%) |
| Gr 3 | 141 (35%) | 164 (41%) | 163 (41%) |
| Gr 4 | 33 (8%) | 33 (8%) | 52 (13%) |
| TOTAL | 360 (89%) | 340 (85%) | 360 (91%) |
| **Neutropenia** | | | |
| Gr 1 | 17 (4%) | 18 (4%) | 16 (4%) |
| Gr 2 | 49 (12%) | 26 (6%) | 32 (8%) |
| Gr 3 | 94 (23%) | 101 (25%) | 100 (25%) |
| Gr 4 | 208 (51%) | 194 (48%) | 210 (53%) |
| TOTAL | 368 (91%) | 339 (85%) | 358 (90%) |
| **Thrombo-cytopenia** | | | |
| Gr 1 | 34 (8%) | 42 (10%) | 29 (7%) |
| Gr 2 | 15 (4%) | 31 (8%) | 16 (4%) |
| Gr 3 | 11 (3%) | 21 (5%) | 8 (2%) |
| Gr 4 | 2 (<1%) | 8 (2%) | 8 (2%) |
| TOTAL | 62 (15%) | 102 (25%) | 61 (15%) |
| **Anemia** | | | |
| Gr 1 | 151 (37%) | 166 (41%) | 83 (21%) |
| Gr 2 | 180 (44%) | 153 (38%) | 193 (49%) |
| Gr 3 | 24 (6%) | 40 (10%) | 83 (21%) |
| Gr 4 | 6 (1%) | 8 (2%) | 15 (4%) |
| TOTAL | 361 (89%) | 367 (91%) | 374 (94%) |

Deaths

Of the 1220 patients enrolled, 949 died prior to the cut-off date for the survival analysis of 4/3/01. An additional 44 patients died between 4/3/01 and 8/9/01, and these were included in the final database for the ITT population. Of the 1203 patients who received any chemotherapy, 981 died. Ninety-eight (8.1% of 1203) died within 30 days after last infusion of study treatment, while 883 (73.4% of 1203) died more than 30 days after last infusion of study treatment.

According to the sponsor, of the 98 patients who died within 30 days of last infusion, 41 had malignant disease as cause of death, 25 had the cause of death listed as toxicity from study drug treatment, and 32 had other causes of death listed. The incidence of deaths attributed to malignant disease or study drug was comparable across treatment arms, with a toxic death rate of 2.2%, 2%, and 2% in the three 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%), followed by grade 4 cardiac dysfunction (5/25 = 20%) and dehydration (1/25 = 4%).

*Reviewer Comment : Of the 32 patients who died within 30 days of last infusion and had the cause of death listed as 'other', review of patient narratives indicates that some patients had occurrence of adverse events likely initiated or exacerbated by chemotherapy which contributed to their demise although not listed as the primary cause of death. Some had clinical symptoms suggestive of progressive disease. In these patients, it is arguable whether the deaths can be reclassified as due to malignant disease or toxicity from study treatment. An example is patient # 11050, who had multiple lesions at diagnosis, including subcarinal lesions. This patient died 7 days after cycle 1 of cisplatin + vinorelbine with hemoptysis due to an intrapulmonary hemorrhage. It is difficult not to consider a likely linkage between the circumstances of death and progressive disease. Another is patient #11048, who died 9 days after cycle 1 of docetaxel + cisplatin due to a cardiopulmonary event. At the time of death, the patient had anemia, thrombocytopenia, and neutropenia. Although the cause of death was listed as pulmonary embolism, it is possible that pancytopenia resulting from cytotoxic therapy was a contributing factor influencing a pulmonary process.*

The vast majority of patients died more than 30 days after the last infusion of study drug. Of these, 830 were attributed to malignant disease and 53 were attributed to other causes. None were attributed to toxicity from study drug treatment.

Treatment Discontinuation Due to Adverse Events

Criteria for treatment discontinuation included unacceptable toxicity or a treatment delay greater than 3 weeks for any toxicity, or greater than 2 weeks for hematologic, renal, hepatic, or neurologic toxicity. Overall, 91 patients (23%) discontinued treatment due to an AE in the vinorelbine+cisplatin group, 64 patients (15.8%) in the docetaxel+cisplatin group, and 37 patients (9.2%) in the docetaxel+carboplatin group. The AE's most commonly associated with treatment discontinuation in either cisplatin-containing regimen were neuro-sensory and neuro-motor AE's (3-4%).

Comparisons to historical data :

Grade 3 / 4 or severe / life-threatening adverse events on the vinorelbine + cisplatin arm of TAX 326 were comparable to those seen on the vinorelbine + cisplatin arm of the SWOG trial published by Wozniak et al. (1) See Table 57 below.

**Table 57 Comparison of AE's : Vinorelbine + Cisplatin in TAX326 and SWOG Trial**

| **Grade 3 / 4 or severe/life-threatening AE** | **TAX326 N = 396** | **SWOG N = 204** (Wozniak et al JCO, 1998) |
|---|---|---|
| Neutropenia | 78% | 81% |
| Anemia | 25% | 24% |
| Thrombocytopenia | 4% | 6% |
| Nausea/vomiting | Nausea 17%<br>Vomiting 16% | 20% |
| Malaise/weakness | Asthenia 14% | 15% |
| Constipation | 3% | 3% |
| Stomatitis | 1% | 2% |

A comparison of docetaxel + cisplatin arm of TAX326 with docetaxel dose of 75 mg/m$^2$ alone of TAX320 with respect to select adverse events is shown in Table 58 below. Overall, toxicities were comparable. Grade 3 / 4 diarrhea and neuro-sensory events occurred more commonly on the docetaxel + cisplatin arm of TAX326, likely due to the additional effect of concurrent cisplatin administration. Severe or grade 3 / 4 infection was reported less commonly on the docetaxel + cisplatin arm of TAX326.

**Table 58 : Adverse Events in Two Docetaxel Containing Arms of TAX326 and TAX320**

| Adverse events | TAX326 docetaxel + cisplatin N = 406 | TAX320 docetaxel 75 mg/m$^2$ N = 121 |
|---|---|---|
| Infection<br>Any<br>Severe or grade 3 / 4 | <br>35%<br>8% | <br>35.5%<br>12.4% ; 18.1% SAE |
| Diarrhea<br>Any<br>Grade 3 / 4 | <br>47%<br>7% | <br>11.8%<br>1.7% |
| Stomatitis<br>Any<br>Grade 3 / 4 | <br>24%<br>2% | <br>27.3%<br>1.7% |
| Neuro-sensory<br>Any<br>Grade 3 / 4 | <br>47%<br>4% | <br>54.5%<br>0.8% |
| Neuro-motor<br>Grade 3 / 4 | <br>3% | <br>2.5% |
| Fluid Retention<br>Any<br>Severe/life-threatening | <br>54%<br>2% | <br>41.3%<br>3.3% |
| Septic Death or Treatment Related Death | 2.2% | 1.7% |

## D. Adequacy of Safety Testing

In addition to 807 NSCLC patients who received docetaxel as a component of their participation in TAX326, the safety database also includes 250 NSCLC patients previously treated with a platinum drug who were randomized to either 75 mg/m$^2$ or 100 mg/m$^2$ of docetaxel on TAX320, 104 patients treated with docetaxel (49 patients treated with 100 mg/ m$^2$

and 55 patients with 75 mg/m$^2$) on TAX317, 137 patients with previously untreated metastatic or locally advanced NSCLC treated with docetaxel at a dose of 100 mg/m$^2$ and thousands of patients in the post-marketing phase worldwide who have received docetaxel alone or in a combination setting for the treatment of advanced NSCLC as well as those receiving docetaxel as a component of therapy for breast cancer or other malignancies.

### E. Summary of Critical Safety Findings and Limitations of Data

In summary, the safety profile of docetaxel + cisplatin is generally 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.

The medical reviewer agrees with many of the sponsor's conclusions. However, the medical reviewer disagrees with the sponsor's results with regards to the frequencies of a number of adverse events. Clinical adverse events where these disagreements are most notable include asthenia, pain, hemoptysis, and pleural effusion.

With some adverse events such as nausea/vomiting, the sponsor is proposing presenting these as a combination in the label. The medical reviewer suggests presenting these separately, in order to provide more detailed and interpretable information to the reader. Another example is fluid retention, which is presented as an overall group of events in the sponsor's suggested labeling. The reviewer suggests providing frequencies for the three major contributing signs of fluid retention (weight gain, pleural effusion, peripheral edema) in addition to overall frequencies across the three treatment arms.

For some events such as diarrhea, there may not be major differences between sponsor and reviewer analyses. However, the sponsor is proposing to include only patients with adverse events considered as treatment related, whereas the reviewer is proposing presentation of AE's irrespective of perceived relationship to study treatment.

## VIII. Dosing, Regimen, and Administration Issues

Based on the approach utilized in this trial for dose modification, 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 included allowing for a second dose modification step down to 50 mg/m$^2$. In fact, 29 patients 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$^2$ should be utilized ".

## IX. Use in Special Populations

### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

There were no differences between men and women with regard to efficacy.

The sponsor analyzed all AEs and grade 3 / 4 or severe AEs by gender. The sponsor concluded that the incidences of patients with an adverse event were comparable in men and women in all treatment groups. For both docetaxel containing groups, nausea and vomiting occurred less frequently in male patients than female patients for grade 3 / 4 events.

When comparing both docetaxel-containing groups to the vinorelbine + cisplatin group, grade 3 / 4 events of asthenia and neurotoxicity were observed in a lower percentage of females than males in both docetaxel-containing groups. For all other AEs, the treatment differences between docetaxel-containing groups and vinorelbine + cisplatin were similar in male and female patients.

*Reviewer Comments : In general, the incidence of adverse events was comparable between men and women. The sponsor's conclusions regarding some grade 3 / 4 events should be interpreted cautiously as these involved small numbers of patients in each subgroup.*

**B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

1. Age

The sponsor conducted a subgroup analysis of adverse events using two categories, patients under 65 years of age and patients 65 years of age or older. Based on this analysis, the sponsor concluded that there was a trend toward more diarrhea and grade 3 / 4 events of neurotoxicity (frequency and severity) in elderly patients in the taxotere/cisplatin group in comparison to the vinorelbine/cisplatin group. According to the sponsor, there was a trend to more diarrhea and grade 3 / 4 infection, but less nausea/vomiting, neurotoxicity and neurosensory events in the docetaxel/carboplatin group in comparison to the vinorelbine/cisplatin group. The sponsor is proposing to include this information in the geriatric section of the package insert.

*Reviewer Comment : As with other adverse event analyses, the sponsor used an 'emergent strategy' approach, where adverse events were excluded from the analysis if they had been present at baseline. The reviewer does not agree with this approach. The reviewer analyzed adverse events based on all patients who received chemotherapy, irrespective of whether AE's were present at baseline. Based on this analysis, some adverse events appear to have occurred more or less frequently in either docetaxel-containing arm in comparison to the vinorelbine+cisplatrin control when one examines the population aged 65 or older. These adverse events are presented in Table 57 below. In patients 65 years of age or greater treated with docetaxel + cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine + cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). When docetaxel was combined with carboplatin for the treatment of chemotherapy naïve, advanced non-small cell lung carcinoma, patients 65 years of age or greater experienced higher frequency of infection compared to similar patients treated with docetaxel + cisplatin, and a higher frequency of diarrhea, infection, peripheral edema and weight loss than elderly patients treated with vinorelbine + cisplatin.*

**Table 59 : Reviewer's Assessment of Adverse Events in Patients Aged 65 Years or Older**

| Adverse Event | Docetaxel Cisplatin N = 148 | Docetaxel Carboplatin N = 114 | Vinorelbine Cisplatin N = 128 |
|---|---|---|---|
| Alopecia | 101 (68%) | 79 (69%) | 56 (44%) |
| Diarrhea | 81 (55%) | 53 (46%) | 31 (24%) |
| Peripheral Edema | 57 (39%) | 35 (31%) | 26 (20%) |
| Weight Loss | 46 (31%) | 31 (27%) | 47 (37%) |
| Grade 3 / 4 Infect | 17 (11%) | 20 (18%) | 14 (11%) |
| Nausea | 111 (75%) | 56 (48%) | 89 (70%) |
| Vomiting | 77 (52%) | 40 (35%) | 81 (63%) |
| Neuro-sensory | 64 (43%) | 52 (41%) | 36 (32%) |
| Neuro-hearing | 23 (16%) | 9 (8%) | 24 (19%) |

*In comparing the age group of patients aged 65 years or older to those less than 65 years of age, 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). See Tables 60 and 61 below.*

**Table 60 : All AE's by Age < 65 Years or ≥ 65 Years**

| AE | Age < 65 Years | | | Age ≥ 65 Years | | |
|---|---|---|---|---|---|---|
| | Doc/Cis N = 258 | Vin/Cis N = 268 | Doc/Car N = 287 | Doc/Cis N = 148 | Vin/Cis N = 128 | Doc/Car N = 114 |
| Alopecia (N) | 205 (79) | 110 (41) | 199 (69) | 101 (68) | 56 (44) | 79 (69) |
| Nausea (N) | 180 (70) | 212 (79) | 166 (58) | 111 (75) | 89 (70) | 56 (48) |
| Asthenia (C) | 185 (72) | 199 (74) | 198 (69) | 114 (77) | 97 (76) | 76 (67) |
| Vomiting (N) | 148 (57) | 162 (60) | 106 (37) | 77 (52) | 81 (63) | 40 (35) |
| Diarrhea (N) | 111 (43) | 70 (26) | 101 (35) | 81 (55) | 31 (24) | 53 (46) |
| Pain (C) | 180 (73) | 222 (84) | 222 (77) | 106 (72) | 92 (72) | 86 (75) |
| Anorexia (C) | 102 (40) | 103 (38) | 90 (31) | 67 (45) | 55 (43) | 45 (39) |
| Peripheral Edema (C) | 80 (31) | 46 (17) | 61 (21) | 57 (39) | 26 (20) | 35 (31) |
| Infection (N) | 79 (31) | 94 (35) | 117 (41) | 62 (42) | 53 (41) | 57 (50) |
| Fever without infection (N) | 62 (24) | 70 (26) | 93 (32) | 60 (41) | 44 (34) | 41 (36) |
| Stomatitis (N) | 55 (21) | 59 (22) | 75 (25) | 41 (28) | 26 (20) | 31 (27) |
| Weight Loss (N) | 71 (28) | 90 (34) | 71 (25) | 46 (31) | 47 (37) | 31 (27) |
| Dehydration ( C ) | 21 (8) | 18 (7) | 8 (3) | 5 (3) | 10 (8) | 5 (4) |
| Neuro-sensory (N) | 125 (48) | 114 (43) | 81 (28) | 64 (43) | 52 (41) | 36 (32) |
| Neuro-motor (N) | 48 (19) | 43 (16) | 43 (15) | 31 (21) | 26 (20) | 21 (18) |
| Neuro-cortical (N) | 12 (5) | 19 (7) | 11 (4) | 14 (10) | 8 (6) | 7 (6) |
| Neuro-constipation (N) | 46 (18) | 68 (25) | 50 (17) | 27 (18) | 28 (22) | 23 (20) |
| Neuro-mood (N) | 51 (20) | 67 (25) | 67 (23) | 37 (25) | 28 (22) | 29 (25) |
| Neuro-headache (N) | 16 (6) | 28 (10) | 20 (7) | 11 (7) | 5 (4) | 8 (7) |
| Neuro-vision (N) | 8 (3) | 14 (5) | 11 (4) | 9 (6) | 5 (4) | 3 (3) |
| Neuro-hearing (N) | 29 (11) | 59 (22) | 19 (7) | 23 (16) | 24 (19) | 9 (8) |
| Neuro-cerebellar (N) | 5 (2) | 9 (3) | 4 (1) | 6 (4) | 2 (2) | 2 (2) |

**Table 61 : All Grade 3 / 4 or Severe/Life-Threatening AE's by Age < 65 Years or ≥ 65 Years**

| AE (Grade 3 / 4 or Severe/Life-threatening) | Age < 65 Years | | | Age ≥ 65 Years | | |
|---|---|---|---|---|---|---|
| | Doc/Cis N = 258 | Vin/Cis N = 268 | Doc/Car N = 287 | Doc/Cis N = 148 | Vin/Cis N = 128 | Doc/Car N = 114 |
| Vomiting (N) | 21 (8) | 39 (15) | 16 ( 6) | 11 (7) | 25 (20) | 2 (2) |
| Nausea (N) | 25 (10) | 37 (14) | 23 (8) | 15 (10) | 29 (23) | 3 (3) |
| Asthenia (C) | 29 (11) | 35 (13) | 29 (10) | 21 (14) | 22 (17) | 15 (13) |
| Pulmonary (N) | 33 (13) | 30 (11) | 46 (16) | 22 (15) | 19 (15) | 25 (22) |
| Infection (N) | 17 (7) | 18 (7) | 25 (9) | 17 (11) | 14 (11) | 20 (18) |
| Pain (C) | 32 (12) | 31 (12) | 41 (14) | 18 (12) | 18 (14) | 17 (15) |
| Diarrhea (N) | 15 (6) | 7 (3) | 16 (6) | 13 (9) | 4 (3) | 5 (4) |
| Anorexia ( C ) | 12 (5) | 13 (5) | 7 (2) | 10 (7) | 8 (6) | 5 (4) |
| Dehydration ( C ) | 7 (3) | 7 (3) | 2 (1) | 20 (14) | 20 (16) | 9 (8) |
| Peripheral edema ( C ) | 2 (1) | 0 | 3 (1) | 1 | 1 | 0 |
| Fever without infection | 2 (1) | 3 (1) | 2 (1) | 3 (2) | 1 | 0 |
| stomatitis | 5 (2) | 3 (1) | 1 | 3 (2) | 2 | 0 |
| Weight loss | 4 (2) | 5 (2) | 3 (1) | 1 | 0 | 2 |
| Neuro-sensory (N) | 6 (2) | 7 (3) | 4 (1) | 10 (7) | 9 (7) | 0 |
| Neuro-motor (N) | 5 (2) | 8 (3) | 5 (2) | 9 (6) | 9 (7) | 8 (7) |
| Neuro-constipation (N) | 2 (1) | 5 (2) | 1 | 0 | 3 | 1 |
| Neuro-mood (N) | 2 (1) | 9 (3) | 4 (1) | 3 (2) | 1 | 1 |
| Neuro-vision (N) | 0 | 2 | 2 | 3 | 2 | 0 |
| Neuro-hearing (N) | 2 (1) | 5 (2) | 3 (1) | 3 | 2 | 0 |
| Neuro-cerebellar (N) | 1 | 1 | 0 | 1 | 0 | 1 |

2. Race/Ethnicity

The majority of patients enrolled onto the trial 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.

## C. Evaluation of Pediatric Program

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. (9) (10)

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$^2$.

# X. Conclusions and Recommendations

## A. 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 were submitted. Patients were randomized to docetaxel + cisplatin, docetaxel + carboplatin, or an active control of vinorelbine + cisplatin.

The primary endpoint was overall survival. The 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 in analysis of response rates, duration of response, or time to progression. The sponsor's claims and analyses based on QoL data were found to be unreliable by the statistical and medical reviewers due to a number of limitations.

Toxicities encountered were anticipated based on prior experience with docetaxel-based regimens and those containing cisplatin, carboplatin, or vinorelbine. The safety profile of docetaxel + cisplatin was generally 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.

## B. Recommendations

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 who have not previously received chemotherapy for this condition.

The recommended dose of docetaxel when used in combination with cisplatin for the treatment of patients with 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.

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 anticipated in Q1, 2003.
5. TAX.

is

ongoing.

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/s/

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