The teniposide and cisplatin regimen has been considered as the standard by the EORTC LCCG based on the results of a previous study showing that the combination of teniposide and cisplatin resulted in superior response, progression-free survival and survival when compared to single agent teniposide (see table). Teniposide was preferred over etoposide based upon experimental in vitro results showing higher cellular uptake and concentration of teniposide in tumor cells and an increase in cell cycle perturbation. Teniposide seemed also preferrable with respect to its pharmacokinetic parameters, with a longer half-life, a reduced clearance and a larger volume of distribution.

***Reviewer's comment***: *It was recognized prospectively that the regimen for the control arm of study 103 was going to be severely myelotoxic at the doses given in EORTC 08875, which was 120 mg/m$^2$ on Days 1, 3 and 5. The dose of teniposide in combination with cisplatin was decreased to 100 mg/m$^2$ on Days 1, 3 and 5.*

Three randomized, comparative, multicenter phase III trials using the 3-hour infusion of taxol have been completed, two of which were included in registrational dossier for the NDA application:

**Table No. 3**
**Randomized Trials: 3-Hour Infusion**
(from pre-NDA meeting background document,10/94, sec 4, p. 15)

| Study No. | Study Site | Study Arms | Sample Size | Start Date |
|---|---|---|---|---|
| 103 | EORTC | Cisplatin/Teniposide vs. Cisplatin/Taxol | 332 | 8/93 |
| 208 | European | Cisplatin vs. Cisplatin/Taxol | 414 | 11/94 |
| 224 | UK/ Canada | Taxol vs. Best Supportive Care | 144 | 10/94 |

***Reviewer's comment***: *The sponsor informed the agency that Study 224 was closed in October 1997 after accruing 156 patients. A preliminary analysis of median survival was requested by the agency which the sponsor submitted on February 20, 1998 (summarized below). Although results were submitted,* ***the sponsor cautioned the agency that this analysis was early and limited to the comparison of survival and did not support preparation of a complete study report.***

## Interim Results of Study 224

Between February 27, 1995 and October 3, 1997, a total of 157 patients were randomized from six sites and stratified by stage and ECOG performance status. As of January 1998, 108 (69%) of the 157 patients had died. The median survival for the taxol group was 6.4 months compared to 4.6 months for the best supportive case groups (stratified logrank p=0.074). The hazard ratio estimate (taxol:BSC) based on the Cox model was 0.70 (95% C.I.=0.474 to 1.037), favoring the taxol arm.

***Reviewer's comment**: For the 49 patients remaining who were censored on the last date of follow-up, a more current update of the status is needed.*

The following is a list of ongoing and planned Phase III studies in taxol as of June 1997:

## Regulatory History Of Taxol In Non-small Cell Lung Cancer

In November 1994, the sponsor first met with the agency to discuss a plan to submit an application for approval of taxol in patients with non-small cell lung cancer. Their proposed indication was to "treat advanced non-small cell lung cancer in patients who are not candidates for potentially curative regional therapy or those whose disease has spread to other organs of the body". Data from the following 24-hour infusion schedule studies were proposed for filing:

1. Study 029 : (ECOG Protocol No. EST 1589) Phase II Protocol for Chemotherapy in Metastatic Non-Small Cell Bronchogenic Carcinoma: Merbarone, Proxantrone, Taxol
2. Study 165: (ECOG Protocol No. EST 5592) Phase III Trial Comparing Etoposide/Cisplatin versus Taxol/Cisplatin/G-CSF versus Taxol/Cisplatin in Advanced Non-Small Cell Lung Cancer

On June 6, 1997, the agency held a teleconference with the sponsor to discuss the studies to be included in the supplemental NDA submission. Two randomized phase III trials were identified (165 and 103), supported by four single-agent phase II trials (029, 027, 127, 201). At that time, study 208 (Phase III trial of 3-hour infusion of Taxol/Cisplatin versus Cisplatin) was completed and also identified as an important study that should be included in the submission. It was agreed that the full study report and electronic data on study 208 will be submitted as an amendment. The NDA was submitted on June 30, 1997 and the full study report for study 208 was submitted on January 22, 1998.

## CLINICAL PROTOCOLS

The efficacy supplement was submitted in June 30, 1997 with the proposal to use taxol in patients with advanced non-small cell lung cancer who are not candidates for potentially curative surgery or radiotherapy. It included data from two multicenter, randomized phase III trials (Study CA139-165 and CA139-103) and four supportive studies of single agent taxol, (CA 139-029, CA139-027, CA139-127, and CA 139-201). Data on the Phase III trial (Study 139-208) was provided to the agency as an addendum.

This efficacy supplement is supported by clinical data from three phase III studies summarized as follows:

**Table No. 5**
**Study Design- Taxol Pivotal Studies**

| | Study CA 139-165 | | | Study 139-103 | | Study 139-208 | |
|---|---|---|---|---|---|---|---|
| Treatment Arms | taxol/ cisplatin | HD-taxol/ cisplatin | etoposide/ cisplatin | teniposide/ cisplatin | taxol/ cisplatin | cisplatin | taxol/ cisplatin |
| Initial Dose ($mg/m^2$) | 135/75 | 250/75 | 100/75 | 100/80 | 175/80 | 100 | 175/80 |
| Infusion duration (hr.) | 24/1 | 24/1 | 45 min/1 | 1/1 | 3/1 | 1 | 3/1 |
| Treatment Schedule | Q 3 weeks | | | | | | |

The NDA was submitted in 121 volumes of text divided into 12 sections. The sections of clinical interest are: *Section 1*, which contains the proposed text for the labeling of taxol; *Sections 8,* which contains the Summary of Efficacy and Safety, and Clinical Study Reports on the pivotal and supporting trials, and *Section 11 and 12,* which contains data listings and case report forms of the fatalities and early drop-outs. Electronic data was provided as SAS datasets and MS Access. Annotated CRFs and quality of life questionnaires were provided for reference.

***Reviewer comment**: For the rest of the text in this review, the study sites will be designated as 165(ECOG), 103 (EORTC) and 208. Individual patients will be identified by the subject number prefixed by the study site identifier (eg.165-002 is patient number 2 treated by ECOG in study 165).*

## Study Protocol CA 139-165

### Title:

Phase III Trial Comparing Etoposide/Cisplatin versus Taxol/Cisplatin/G-CSF versus taxol/Cisplatin in Advanced Non-Small Cell Lung Cancer.

### Investigator, Location of Trial: Study Chairman:

Philip Bonomi, M.D., Rush-Presbyterian-St. Luke's Medical Center, Medical Oncology, 1725 W. Harrison, Chicago, IL 60612. This was a multicenter study involving 163 sites in the United States, one site in Canada, two sites in Puerto Rico and one site in the Republic of South Africa.

### Publications:

1) Bonomi P, Kim K, et al: Phase III Trial Comparing Etoposide (E) Cisplatin (C) Versus taxol (T) with Cisplatin-G-CSF (G) versus taxol-cisplatin in Advanced Non-Small Cell Lung Cancer. Proc. ASCO 15:1145, 1996.
2) Bonomi P, Kim K, Chang A, et al: Comparison of Survival for Stage IIIB Versus Stage IV Non-Small Cell Lung Cancer (NSCLC) Patients Treated with Etoposide-Cisplatin Versus taxol ®-Cisplatin: an Eastern Cooperative Group (ECOG) Trial. Proc. ASCO 16:1631, 1997.
3) Cella D, Fairclough DL, et al: Quality of Life (QOL) in Advanced Non-Small Cell Lung Cancer (NSCLC): Results from Eastern Cooperative Oncology Group (ECOG) Study E5592. Proc. ASCO 16:4, 1997.
4) Rowinsky RK, Bonomi P, et al: Pharmacodynamic (PD) Studies of Paclitaxel (T) in ECOG 5592: A Phase III Trial Comparing Etoposide (E) plus Cisplatin (C) Versus Low-Dose Paclitaxel Plus Cisplatin Versus High-Dose Paclitaxel Plus Cisplatin Plus G-CSF in Advanced Non-Small Cell Lung Cancer (NSCLC). Proc. ASCO 16:1618, 1997.

### Study Period:

1 August 1993 - December 1994 (study enrollment period).

### Amendments:

- June 1994: revised the pharmacokinetic procedures, requirements for CBC, FACT-L QOL form and preparation of taxol. It expanded the data monitoring and the toxicity analysis description. Disease stage eligibility was revised.
- September 1994: revised treatment duration and management of cardiovascular toxicity, added dose modifications for neurotoxicity and hypersensitivity, and clarified the criteria

for withholding the cisplatin dosage. Serum electrolytes measurement was required for each cycle and the toxicity list for taxol expanded.

- December 1994: Increase accrual to 585 evaluable patients, randomization procedure was updated.

## Objectives:

The objective of this study was to compare the survival, response and toxicity among the three treatment arms. The secondary objective was to assess quality of life among the treatment arms and correlate the quality of life to toxicity. Serum pharmacokinetics of taxol was to be correlated to response, survival and toxicity.

## Study Design - Methodology:

This was a multicenter, open-label, randomized three arm phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG) in patients with newly diagnosed or recurrent stage IIIB or stage IV NSCLC. Patients were stratified according to a) performance status (0 vs. 1), b) weight loss in the previous six months (<5% vs. > 5%), c) disease stage (IIIB vs. IV), d) disease measurability (bidimensional measurable vs. evaluable)

## Diagnosis and Main Criteria for Entry:

- histologically confirmed non-small cell carcinoma with stage IIIB or stage IV disease.
- bidimensionally measurable or evaluable (unidimensionally measurable or non-measurable) disease.
- newly diagnosed stage IIIB or IV disease. Stage IV patients with brain metastases are ineligible.
- ECOG ≤ 1
- no prior chemotherapy or biologic response modifiers, and no prior radiation to the area of measurable disease. Prior radiation should be completed > 2 weeks prior to registration and the patient should be free of any side effects.
- Laboratory values: (obtained ≤ 2 weeks prior to registration) WBC ≥4000/$mm^3$, platelet≥100,000/$mm^3$; bilirubin ≤ 1.5 mg%; serum creatinine ≤ 1.5 mg/dl.

Patients with brain metastases or those previously treated with chemotherapy or biologic response modifiers were ineligible. No evidence of significant cardiac disease, uncontrolled diabetes mellitus or evidence of neuropathy by history or physical exam.

## Therapy, dose, route of administration:

**Arm 1:** taxol 135 mg/m2 IV over 24 hours day 1 and cisplatin 75 mg/m2 IV over 1 hour day 2

**Arm 2:** taxol 250 mg/m2 IV over 24 hours day 1, and cisplatin 75 mg/m2 IV over 1 hour day 2, given with G-CSF 5 g/kg/day SC, beginning day 3

**Arm 3:** cisplatin 75 mg/m2 IV over 1 hour day 1 and etoposide 100 mg/m2/day over 45 minutes, days 1, 2, 3.

Standard premedication with dexamethasone (po), cimetidine (iv) and diphenhydramine (iv), or their equivalent, was given prior to taxol.

## Treatment Duration:

Patients with a complete or partial response or stable disease were to be treated until evidence of disease progression. Patients were to be removed from the study for progressive disease, excessive toxicity or after six courses if at least one of the following conditions existed: weight loss $\geq$ 5% of starting weight, decrease in ECOG performance status of one level and Grade III nausea.

## Study Parameters

**Table No. 6**

**Patient Evaluation- Study 165**
**(Sec. 3.5, vol. 3, p 694)**

| Parameters | Pretreatment | Weekly | Before each cycle |
|---|---|---|---|
| History and P.E. | x | | x |
| Weight | x | | x |
| Vital Signs | x | | x |
| Performance Status | x | | x |
| Tumor measurement | x | | x |
| Hematology | x | x[1] | x |
| Chemistry | x | | x |
| Creatinine,bilirubin,SGOT | x | x | x |
| Chest X-rays | x | | x[2] |
| Other Imaging | x | | x[2] |
| ECG | x | | x |
| FACT-L | x[3] | | |

[1] required to follow expected toxicity, should be obtained twice weekly beginning on day 7 for all treatment arms and continued until AGC >10,000 for patients on G-CSF or AGC > 1,500 for patients not receiving G-CSF

[2]to be done initially if clinically indicated; if positive, scan to be repeated every 12 weeks if used as indicator for response

[3] FACT_L before start of treatment and before the start of the third and fifth courses of chemotherapy. If they are off treatment, then complete the FACT-L at 6 and 12 weeks after initiation of therapy. The final assessment of all patients is at Week 26, Day1.

## Drug Formulation

Taxol was supplied by Bristol-Myers Squibb (Batch no. D2F37B, C4B00A, K4300B, H2F30B, H3F21D, G4B00, H3F18C, C4BO7B ). Cisplatin and etoposide were obtained through commercial sources.

## Statistical Considerations

Analysis of major efficacy endpoints incorporated the stratification factors at randomization. To account for multiple comparisons among three treatments (e.g. survival and time to progression) , a Bonferroni-type penalty was taken by using 97.5% confidence intervals of the hazard ratios for each of the two pairwise comparisons (one-sided $\alpha$=0.0125): Taxol/cisplatin vs. cisplatin/etoposide and taxol/cisplatin/G-CSF vs. cisplatin/etoposide. Comparisons between the two taxol arms were tested at a two-sided $\alpha$=0.025. For other analyses, a significance level of 95% was used. All tests were two-sided.

***Reviewer's comment:*** *The sample size estimation and statistical analyses that were prospectively defined in the protocol were generally carried out by the sponsor in the study report.*

## Data Collection and Management

All data for CA 139-165 was prospectively transcribed on ECOG flow sheets and ECOG reporting forms by the data managers at the participating ECOG institutions, reviewed and signed by the investigator and submitted to the ECOG Statistical Center at regular intervals. Through a contract research organization (CRO) hired by the sponsor, on-site monitoring was performed and verification of IRB approvals, patient registration and randomization process, transcription of all data from ECOG onto BMS case report forms, and augmentation of the primary ECOG database with key data points were done. The CRO supplemented the ECOG data by collecting all available assessments of any tumor lesion whether or not it was selected by the ECOG as an indicator lesion from radiology reports and patient medical records.
In case of disagreement regarding efficacy assessments, a consensus between BMS and ECOG were reached. The final database for this study was generated from the ECOG dataset supplemented with the BMS data collection.

***Reviewer's comment:*** *According to the NDA summary, study medication administration data were not entered in the ECOG database; and therefore not included in the NDA submission of June 1997. Sample ECOG treatment flow sheets and Bristol-Myers case report forms of recorded the dates, time and doses of chemotherapy given to patients. A request for information was sent to the sponsor on November 1, 1997 stated as follows:*

> *"The annotated case report forms and electronic data for study CA 139-165 do not seem to contain all the information recorded in individual patient forms. Please submit all such data which you have in electronic format. Please submit complete sets of annotated Bristol Myers and ECOG case report forms to enable reviewers to cross*

*reference between the forms and electronic data. Information of special interest include on study medications, doses and dose modifications."*

*The additional electronic data for Study 165 was submitted to the FDA on January 20, 1998.*

## SPONSOR'S STUDY RESULTS

### Patient and Disease Characteristics:

At the start of treatment, the distribution of patient characteristics among treatment arms are summarized in the following table:

**Table No. 7**
**Pretreatment Patient Characteristics, Study 165**
**(summarized from sec. 5.3, vol 86.4, p 721-724)**

| | Number of Patients (%) | | | |
|---|---|---|---|---|
| | Taxol/ Cisplatin (n=198) | HD-Taxol/ Cisplatin (n=201) | Cisplatin/ Etoposide (n=200) | Total (n=599) |
| Stage | | | | |
| IIIB | 45 (23) | 41 (20) | 31 (16) | 117 (20) |
| IV | 153 (77) | 160 (80) | 169 (85) | 482 (80) |
| ECOG PS | | | | |
| 0 | 58 (29) | 67 (33) | 62 (32) | 188 (31) |
| 1 | 140 (71) | 130 (65) | 136 (68) | 406 (68) |
| 2 | -- | 4 (2) | 1 (1) | 5 (1) |
| Weight Loss (prior 6 months) | | | | |
| <5% | 133 (67) | 141 (70) | 142 (71) | 416 (69) |
| >5% | 65 (33) | 60 (30) | 58 (29) | 183 (31) |
| Measurability | | | | |
| Bidimensional | 155 (78) | 158 (79) | 159 (80) | 472 (79) |
| Evaluable | 43 (22) | 43 (21) | 41 (21) | 127 (21) |
| Gender | | | | |
| Male | 122 (62) | 130 (65) | 131 (66) | 38 (64) |
| Female | 76 (38) | 71 (35) | 69 (35) | 216 (36) |

| | Number of Patients (%) | | | |
|---|---|---|---|---|
| | Taxol/ Cisplatin (n=198) | HD-Taxol/ Cisplatin (n=201) | Cisplatin/ Etoposide (n=200) | Total (n=599) |
| Surgery | | | | |
| Diagnostic | 64 (32) | 72 (36) | 70 (35) | 206 (34) |
| Therapeutic± diagnostic | 39 (20) | 37 (18) | 30 (16) | 106 (17) |
| Extent of Disease | | | | |
| Visceral±Intrathoracic | 112 (57) | 117 (58) | 125 (63) | 354 (60) |
| Intrathoracic | 65 (33) | 63 (31) | 54 (27) | 182 (30) |
| Skin/softtissue/node ±intrathoracic | 20 (10) | 21 (10) | 21 (11) | 62 (10) |

[a] Abnormal: >1.25x upper limit of normal of 250u/L

***Reviewer's comment:*** *The FDA reviewer tested the differences with regard to frequency of Stage IIIB and Stage IV disease across treatment groups. Fisher's exact test showed no difference with a p-value: 0.242. Comparing the proportion of Grade IV taxol/cisplatin patients vs. Grade IV cisplatin /etoposide patients ( 77% vs. 85%), the p-value of the probability of assignment was the same for both groups, =0.067.*

## Number of Courses Administered:

Of the 599 patients randomized 11 never received study therapy. Patients in the taxol/cisplatin arm received a median of five treatment courses (range ), in the taxol/cisplatin/G-CSF arm a median of four courses (range ), and in the cisplatin/etoposide arm a median of 4 (range ) for a total of 971, 890 and 799 treatment courses, respectively.

## SPONSOR'S EFFICACY RESULTS

The primary efficacy endpoint was survival. Tumor response, time to response, duration of response, time to progression, and quality of life were secondary endpoints . For all responding patients, the BMS response assessment was compared to the best response assigned by the ECOG study chairman, and in case of discrepancy, a final assignment was obtained by consensus.

## Sponsor's Analysis of Survival

Survival was calculated from the day of randomization to death or to the last day the patient was known to be alive.

**Table No. 8**
**Survival, Study 165**

| | Taxol/ Cisplatin | HD-Taxol/ Cisplatin | Cisplatin/ Etoposide |
|---|---|---|---|
| Median (months)<br>95% C.I. | 9.3<br>8.0 to 10.4 | 10.0<br>8.9 to 11.7 | 7.4<br>6.5 to 8.6 |
| One Year Survival<br>95% C.I. | 36%<br>26 to 39% | 40%<br>34 to 47% | 32%<br>26 to 39% |
| Log Rank (p-value)[a] | 0.1253 | 0.0785 | |
| Hazard Ratio[a]<br>(95% C.I.) | 1.181<br>(0.926-1.507) | 1.207<br>(0.949-1.534) | |

[a] Cisplatin/etoposide versus Taxol-containing arm

At the time the database was closed, a total of 541/599 (90%) randomized patients had died. The hazard ratios in the taxol/cisplatin and HD-taxo/cisplatin arms provide evidence that survival is not likely to be worse than the survival in the cisplatin/etoposide arm.

There was no statistically significant difference in the survival curves for taxol/cisplatin and taxol/cisplatin/G-CSF (logrank p=0.745). Patients from the two taxol-containing treatment groups were pooled and compared with the cisplatin/etoposide group. The median survival was 9.7 months (95% C.I. 8.8 to 10.6 months) for the taxol arms pooled. The sponsor found a statistically significant (logrank p=0.049) difference favoring the pooled taxol-containing arms over the cisplatin/etoposide arm.

***Reviewer's comment**: Pooling of survival data for the taxol containing arms and its comparison to the cisplatin/etoposide arm was not part of the original statistical analysis plan for the study proposed by the sponsor to the agency on November 17, 1994 . At a significance level of $\alpha$=0.0125, the p-value of 0.049 obtained from pooling survival results from the two taxol-containing arms do not reach statistical significance. Similarly, the clinical significance of such an analysis is deserves further discussion since these are two different treatment regimens.*

A stratified Cox regression model was used to examine the impact on survival of pre-defined covariates of potential prognostic value on the primary treatment comparisons of survival. The hazard ratio estimates for cisplatin/etoposide vs. taxol/cisplatin and cisplatin/etoposide vs. taxol/cisplatin/G-CSF were quite consistent with the stratified model with no covariates. Among the covariates examined, only the baseline LDH value was a statistically significant factor in this analysis (hazard ratio= 1.290, p=0.007).

**Table No. 9**
**Survival in Subgroups Based on Baseline Values for Prognostic Factors used in Stratification**
(from sec. 7.3, vol 3, p. 776)

| Variable | Taxol/Cis (I) | HD-Taxol/ Cisplatin (II) | Cis/Etop (III) | I vs. III hazard ratio (97.5% C.I.) | II vs. III hazard ratio (97.5% C.I.) |
|---|---|---|---|---|---|
| **PS** | | | | | |
| 0 | 13.6 (n=58) | 13.0 (n=67) | 10.7 (n=63) | 1.245 (0.992-1.561) | 1.247 (0.816-1.906) |
| 1-2 | 7.7 (n=140) | 9.0 (n=134) | 6.5 (n=137) | 1.043 (0.906-1.200) | 1.188 (0.895-1.577) |
| **Wt. Loss,** previous 6 mos. | | | | | |
| <5% | 9.9 (n=133) | 11.2 (n=141) | 8.2 (n=142) | 1.067 (0.924-1.232) | 1.153 (0.869-1.530) |
| >5% | 8.0 (n=65) | 9.0 (n=60) | 5.9 (n=58) | 1.159 (0.939-1.430) | 1.355 (0.886-2.073) |
| **Disease Stage** | | | | | |
| IIIB | 12.3 (n=45) | 13.3 (n=41) | 7.4 (n=30) | 1.168 (0.878-1.553) | 1.249 (0.699-2.232) |
| IV | 8.3 (n=152) | 9 (n=160) | 7.2 (n=169) | 1.047 (0.918-1.194) | 1.162 (0.897-1.504) |
| **Measurability** bidimensional | 9.5 (n=166) | 11.1 (n=161) | 8.0 (n=161) | 1.071 (0.939-1.220) | 1.222 (0.939-1.590) |
| unidimensional/ non-measurable | 9.0 (n=31) | 8.1 (n=40) | 5.9 (n=39) | 1.141 (0.858-1.519) | 1.137 (0.673-1.920) |

***Reviewer's comment***: *In each of the treatment arms, patients with PS 0, weight loss <5%, disease Stage IIIB and bidimensionally measurable disease showed longer survival compared to the respective worse prognostic factor.*

## Sponsor's Analysis of Time to Progression

Time to progression was defined as follows:

- from the first day of randomization until the date progressive disease was first reported

- date of death for patients who died prior to documentation of progression

Patients who were lost to follow-up were censored on the last known alive date. Patients who were started on another therapy without documentation of progression were censored on the starting date of secondary therapy ; and patients who did not meet histologic criteria or never received study medication were censored on the date of randomization. The distribution of events and censor dates in each of the treatment arms are as follows:

**Table No. 10**
**Time to Progression Analysis- Study 165**
(sec. 7.2, vol.3, p762)

| | Number of Patients (%) | | |
|---|---|---|---|
| | taxol/cisplatin (n=198) | HD-taxol/ cisplatin (n=201) | cisplatin/ etoposide (n=200) |
| **Progression** | 173 (87) | 170 (85) | 174 (87) |
| Documented Progression | 156 | 152 | 162 |
| Death | 17 | 18 | 13 |
| **Censored** | 25 (13) | 31 (15) | 26 (13) |
| **Secondary therapy** | | | |
| Chemotherapy | 7 | 10 | 10 |
| Radiotherapy | 8 | 11 | 7 |
| Surgery | 2 | 1 | - |
| **Not relapsed** | 3 | 5 | 4 |
| **Never treated** | 2 | 4 | 4 |
| **Wrong cell type** | 2 | - | 1 |
| **Lost to Follow-up** | 1 | - | - |

The difference in time to progression between the taxol/cisplatin and cisplatin/etoposide arm was not significant (p=0.0504), $\alpha$=0.0125. The difference favoring time to progression in the taxol/cisplatin/G-CSF treatment compared to the cisplatin/etoposide arm was significant (p=0.004).