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CANCER AND LEUKEMIA GROUP B

CALGB 9732/NCCTG C9732/ECOG C9732/SWOG C9732/EPP C9732

A RANDOMIZED PHASE III STUDY COMPARING ETOPOSIDE AND CISPLATIN WITH ETOPOSIDE, CISPLATIN, AND PACLITAXEL IN PATIENTS WITH EXTENSIVE SMALL CELL LUNG CANCER

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A RANDOMIZED PHASE III STUDY COMPARING ETOPOSIDE AND CISPLATIN WITH ETOPOSIDE, CISPLATIN, AND PACLITAXEL IN PATIENTS WITH EXTENSIVE SMALL CELL LUNG CANCER

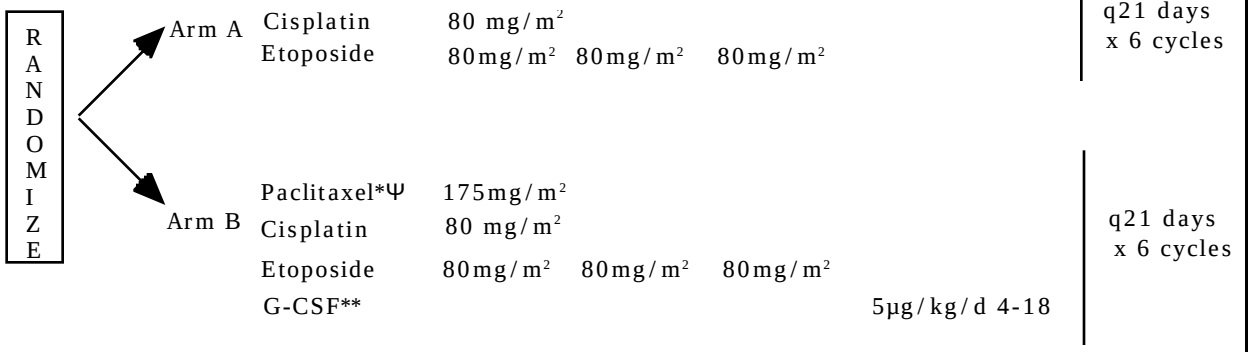
Patient Eligibility

Extensive small cell lung cancer confirmed by biopsy or cytology.
Measurable or evaluable disease.
Age ≥18 years.
Performance Status 0-1.
No prior chemotherapy for SCLC.
No prior pelvic or mediastinal radiotherapy.
No other previous or concomitant malignancy except as per Sec 4.6.

Required Laboratory Values

Granulocytes	≥1,500/µl
Platelets	≥100,000/µl
Serum Creatinine	≤1.5 mg/dl
Bilirubin	<1.5 mg/dl
SGOT (AST)	<2 x normal

SCHEMA



*Paclitaxel is to be administered prior to the cisplatin.
ΨPremedications for paclitaxel include:

1. Dexamethasone: 20 mg PO 12 hours and 6 hours prior to paclitaxel or 20 mg IV 30 min prior to paclitaxel
2. Diphenhydramine: 50 mg IV 30 min. before paclitaxel
3. Cimetidine: 300 mg (or Ranitidine 50 mg or Famotidine 20 mg) IV 30 min. prior to paclitaxel

** G-CSF is to be administered until the ANC ≥10,000 after day 10 or until day 18 (whichever occurs first).

- Patients with rapidly progressive disease after at least one cycle of therapy removed from protocol treatment.
- After completion of above therapy (either Arm A or Arm B), if PR - observation only, if CR - prophylactic cranial irradiation may be done at the discretion of the physician.

Potential Toxicities: Hematologic toxicity, alopecia, nausea, vomiting, nephrotoxicity, hepatotoxicity, neurotoxicity, ototoxicity, skin rash, cardiac toxicity, hypersensitivity reactions, anorexia, and fatigue.

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CALGB DATA COLLECTION FORMS PACKAGE

1.0 INTRODUCTION

Lung cancer is the leading cause of cancer deaths in both males and females in the United States. Approximately 178,100 new cases of lung cancer will be identified in the U. S. in 1997 (1) and approximately 20-25% of these patients will have small cell lung cancer (SCLC) (2). Histologically distinct from other cell types, SCLC displays a unique biological behavior with rapid tumor proliferation, abrupt clinical presentation and a median survival of less than three months if left untreated (3-6). Combination chemotherapy produces high response rates and improved survival in SCLC. Approximately 20% of patients with limited stage disease achieve a five year survival when treated with chemotherapy and irradiation (7-10). In contrast, patients with extensive disease have complete response rates of less than 30% and a median survival duration of 7 to 11 months with almost all patients expiring within two years (9,11). A search for new drug combinations is clearly indicated for patients with extensive SCLC.

1.1 Cisplatin and Etoposide

Over the past decade, cisplatin and etoposide combination chemotherapy has become the most commonly used regimen for patients with SCLC. Cisplatin and etoposide have demonstrated a favorable therapeutic index, ease of administration and compatibility with the simultaneous administration of radiation therapy when compared to older regimens. Doses of cisplatin from 60 to 80 mg/m^2 and etoposide 180 to 390 mg/m^2 have been administered in SCLC patients with acceptable toxicity (12,13). Escalating the dose of cisplatin and etoposide has not resulted in a significant impact on survival in patients with extensive SCLC. Etoposide doses as low as 80 mg/m^2 days 1-3 in combination with cisplatin appear to be highly active in SCLC. A randomized trial by Ihde et al. (14) compared standard dose chemotherapy with high dose chemotherapy in patients with SCLC. Patients received etoposide 80 mg/m^2 days 1-3 and cisplatin 80 mg/m^2 day 1 compared to the higher dose regimen of etoposide 80 mg/m^2 days 1-5 with cisplatin 27 mg/m^2 days 1-5 every 3 weeks. In spite of a 67% escalation in drug received in the high dose arm, complete response rates were identical with 23% versus 22% and similar median survival durations of 10.7 and 11.4 months, respectively. The high dose regimen produced significantly more myelosuppression than the standard regimen. The standard arm produced only 2% grade 4 neutropenia and 2% grade 4 thrombocytopenia.

1.2 Paclitaxel in SCLC

A variety of novel anticancer agents are now available for study in lung cancer. One of the most promising agents is paclitaxel, which was identified as an active anticancer agent produced from the bark of the Pacific Yew, Taxus brevifolia (15). Paclitaxel has been found to bind preferentially to the microtubules, promoting microtubule assembly and stabilization (16). Paclitaxel subsequently interferes with depolymerization of the tubulin molecules, a process which is required for mitosis and cell division. Preclinical studies with paclitaxel revealed a broad range of antitumor activity *in vivo* and *in vitro* (15). Paclitaxel has been shown to have significant activity in SCLC. Kirschling et al. (17) evaluated the single agent activity of paclitaxel using 250 mg/m^2 IV over 24 hours plus G-CSF at 5 µg/kg days 2-15 every 3 weeks in untreated patients with extensive stage SCLC. Of 37 evaluable patients, 25 (68%) experienced a significant response. Ettinger et al. (18) studied 36 previously untreated extensive SCLC patients with paclitaxel at 250 mg/m^2 administered over 24 hours every 3 weeks. Eleven of 32 patients (34%) experienced a partial response (PR). The results of these phase 2 studies established paclitaxel as an active agent in SCLC.

1.3 Three Drug Paclitaxel Combinations

Several phase 1/2 studies have now been published evaluating the optimal dose and schedule for the addition of paclitaxel to standard therapy for SCLC. Glisson et al. (19) treated 26 patients with paclitaxel at 130 mg/m^2 over 3 hours on day 1, cisplatin at 75 mg/m^2 on day 2 and etoposide 80 mg/m^2 on days 2-4 given every 21 days in patients with extensive SCLC. Forty-eight percent of patients experienced grade 4 neutropenia, 6% experienced neutropenic fever and one patient died of sepsis. Five percent of patients experienced grade 2-3 neurotoxicity. Overall, 77% of patients experienced a PR and 19% experienced a complete response (CR) resulting in an overall response rate of 96%.

Levitan et al. (20) treated limited disease SCLC patients with paclitaxel 135 mg/m^2 over 3 hours (11 patients) or 170 mg/m^2 (6 patients) on day 1 with etoposide 80 mg/m^2 on days 1-3 and cisplatin 60 mg/m^2 on day 2. All patients received G-CSF at 5 µg/kg/day days 4-18 of each 21 day cycle. At a paclitaxel dose of 135 mg/m^2, 4 of 11 patients experienced grade 4 neutropenia and 1 of 11 experienced grade 3 neurotoxicity. At a paclitaxel dose of 170 mg/m^2, 3 of 6 patients experienced grade 4 neutropenia and 2 of 6 developed grade 3 neurotoxicity. Overall, 5 of 12 patients obtained a PR and 3 of 12 a CR for an overall response rate of 66%.

Kelley et al. (21) studied 16 patients with extensive SCLC in a phase 1 trial. Patients received paclitaxel 135 mg/m^2 over 3 hours at level 1 and 2 and 175 mg/m^2 at level 3. Cisplatin was given at 80 mg/m^2 at all levels. Etoposide was administered orally at 100 mg/m^2 PO and 50 mg/m^2 IV day 1 at level 1 or 80 mg/m^2 IV day 1 and 160 mg/m^2 PO day 2 at levels 2 and 3. Cycles were repeated every 21 days. Although G-CSF support was not planned, 3 of 5 patients at level 2 and 5 of 6 patients at level 3 required G-CSF support. Febrile neutropenia and thrombocytopenia occurred rarely. All patients responded with 3 of 12 patients obtaining a CR and 9 of 12 obtaining a PR.

Phase 1/2 studies have also been reported using carboplatin based three drug combinations. Niell et al. (22) treated 12 patients with extensive SCLC and stage 4 NSCLC with carboplatin (AUC 6) on day 1, etoposide 80 mg/m^2 on days 1-3 and paclitaxel 200 mg/m^2 over 3 hours on day 3. G-CSF at 5 µg/kg was administered subcutaneously on days 4-18 of each 21 day cycle. Sixty-six percent of patients experienced grade 4 neutropenia during the first 2 courses of therapy but only 2 patients experienced neutropenic fever and there were no deaths. Grade 4 thrombocytopenia occurred in 25% of patients. Neurotoxicity was dose limiting occurring most commonly between cycles 3 and 6 of therapy. Twenty-five percent of patients experienced grade 2 neurotoxicity resulting in a 25% reduction in paclitaxel and 33% developed grade 3 neurotoxicity resulting in discontinuation of paclitaxel. Three subsequent patients with SCLC were treated with etoposide at 100 mg/m^2 plus carboplatin (AUC 6) and paclitaxel 200 mg/m^2 with one grade 4 thrombocytopenia and one grade 2 neurotoxicity. Etoposide doses of 100 mg/m^2 days 1-3 with G-CSF were not found to produce dose limiting neutropenia. It was concluded from this study that 200 mg/m^2 of paclitaxel was associated with excessive dose limiting neurotoxicity and subsequent patients were treated at 175 mg/m^2 of paclitaxel and 100 mg/m^2 days 1-3 of etoposide in this ongoing phase 2 study. Two of nine patients have experienced grade 4 toxicity, one from neutropenic sepsis and one from a CNS bleed secondary to grade 4 thrombocytopenia. All subsequent patients have been treated with 80 mg/m2 of etoposide and 175 mg/m^2 of paclitaxel. No grade 4 neutropenia or thrombocytopenia or grade 2/3 neuropathy has been observed in five patients. Of nineteen evaluable patients with SCLC, 26% have obtained a CR and 46% a PR for an overall resopnse rate of 73%.

Hainsworth et al. (23) treated patients with limited and extensive SCLC with either paclitaxel 135 mg/m^2 over one hour, carboplatin (AUC 5) and etoposide 50 mg PO alternating with 100 mg PO days 1-10 or patients were put on similar doses of

etoposide and carboplatin with 200 mg/m² of paclitaxel. Thirty-eight patients received the low dose paclitaxel arm and 79 patients were treated with the high dose arm. Grade 3/4 neutropenia was higher in the high dose arm (71%/24%), neutropenic fever was lower (32%/39%) and thrombocytopenia was higher (24%/10%). The overall response rate was 84% in the high dose paclitaxel arm compared to 65% in the low dose arm.

A summary of the results of available phase 1/2 studies at or near the dose level to be used in the present proposal for the experimental arm are listed in Table 1 below.

Table 1. Activity of Phase I/II Studies at Dose Level close to the Present Proposal.

Group	Drug Design	Pt. #	CR	PR	Overall
Glisson	Cisplatin 75 mg/m² d 1 Etoposide 80 mg/m² d 1-3 Paclitaxel 130 mg/m² d 1 (3 hr)	26	77%	19%	96%
Levitan	Cisplatin 60 mg/m² d 2 Etoposide 80 mg/m² d 1-3 Paclitaxel 170 mg/m² d 1 (3 hr) G-CSF 5 µg/kg d 4-18	6	0	50%	50%
Kelly	Cisplatin 80 mg/m² d 1 Etoposide 80 mg/m² PO d 1 then 160 mg/m² PO d 2-3 Paclitaxel 175 mg/m² (3 hr) d 1 (G-CSF required in 5 of 6 pts)	6	0	100 %	100%
Niell	Carboplatin (AUC6) d 1 Etoposide 80-100 mg/m² d 1-3 Paclitaxel 200 mg/m² (3 hr) d 3 G-CSF 5 µg/kg d 4-18	19	26%	47%	73%
Hainsworth	Carboplatin (AUC5) d 1 Etoposide 50 mg alt w/100 mg PO d 1-10 Paclitaxel 200 mg/m² (1 hr) d 1	79	21%	63%	84%

The high response rates produced with these paclitaxel based three drug combinations suggest that paclitaxel may enhance the antitumor activity of standard therapy. A randomized trial is needed to determine whether these impressive response rates are associated with improved survival in patients with extensive SCLC.

1.4 Protocol Design

The control arm in the present study will utilize the combination regimen of Ihde et al. (14) with cisplatin 80 mg/m² on day 1 of each 21 day cycle and etoposide 80 mg/m²/day IV days 1-3 of each 21 day cycle.

The experimental arm of the study will utilize doses used in the pilot studies with paclitaxel 175 mg/m² IV over 3 hours on day 1 followed by cisplatin 80 mg/m² IV on day 1 and etoposide 80 mg/m²/day IV days 1-3, with 5µg/kg of G-CSF days 4-18 of each 21 day cycle. The paclitaxel will be given on d1 immediately followed by the administration of cisplatin.

The cisplatin and etoposide two drug regimen will be compared with the three drug combination including paclitaxel for differences in toxicities, response, and

survival.

2.0 OBJECTIVES

2.1 Primary Objective

To determine whether the addition of paclitaxel to standard chemotherapy treatment (etoposide/cisplatin) improves the survival of patients with extensive SCLC.

2.2 Secondary Objectives

2.2.1 To compare the tumor response rate and failure-free survival of patients with extensive SCLC who have received etoposide/cisplatin with or without paclitaxel.

2.2.2 To describe and compare the toxicities associated with etoposide/cisplatin treatment versus etoposide/cisplatin/paclitaxel treatment.

3.0 ON-STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical conditions such as uncontrolled infection, interstitial pneumonia, uncontrolled diabetes mellitus, malabsorption or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients receiving anticonvulsants or chronic steroid therapy, except for steroiods given for adrenal failure or hormones administered for non-disease related conditions (e.g., insulin for diabetes).
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study. Appropriate methods of birth control include oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).
- Pregnant and nursing women, as chemotherapy is thought to present substantial risk to the fetus/infant.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility should be directed to the CALGB Study Chair.

4.1 All patients must have extensive histologically or cytologically documented small cell carcinoma of the bronchus.

The extensive disease classification for this protocol includes all patients with disease sites <u>not defined as limited stage</u>. Limited stage disease category includes patients with disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal, and/or supraclavicular nodes.

4.2 All patients must have measurable or evaluable disease.

4.2.1 Measurable Disease: Any mass reproducibly measurable in two perpendicular diameters, e.g.:

- A solid tumor mass or a hilar lesion surrounded by aerated lung.
- Pleural-based masses.
- Hepatic disease: A clearly defined mass on liver scan, ultrasound, or computerized tomographic (CT) scan considered to represent metastatic disease; or histologically documented hepatic metastasis with an enlarged liver >5 cm below the costal margin on quiet respiration.
- Lymph nodes or subcutaneous skin lesions.

4.2.2 Evaluable Disease: Lesions apparent on chest x-ray which do not fit the criteria for measurability. Patients with both measurable and evaluable disease will be evaluated by criteria for measurable disease.

Evaluable disease includes:

- Ill-defined masses associated with post-obstructive changes.
- Diffuse parenchymal malignant disease.
- Mediastinal or hilar adenopathy measurable in one dimension.

4.2.3 Pleural effusions, bone scan abnormalities, and bone marrow biopsies are neither measurable nor evaluable. Patients with these findings are eligible for this study but they must have an additional site of measurable or evaluable disease.

4.3 Patient Characteristics:

Age ≥18
Performance status 0-1

4.4 Prior Treatment:

No prior chemotherapy for SCLC
No prior pelvic or mediastinal radiotherapy

4.5 Required initial parameters:

Granulocytes	≥1,500/µl
Platelets	≥100,000/µl
Serum Creatinine	≤1.5 mg/dl
Bilirubin	<1.5 mg/dl
SGOT (AST)	<2 x normal

4.6 No previous or concomitant malignancy other than curatively treated carcinoma in situ of cervix or basal cell carcinoma of the skin or other primary cancer completely resected, or treated, more than 5 years ago without recurrence.

5.0 RANDOMIZATION, DATA SUBMISSION AND STRATIFICATION FACTORS

5.1 CALGB Randomization: Randomization will be accepted through the Main Member Institution only. Call the Registrar at the CALGB Data Management Center (919-286-4704, 9 AM - 5 PM, Mon-Fri, Eastern Time) with the following information:

Your name
Study
Institution #
Name of Treating Physician
Patient's Name and Hospital ID #
Patient's Zip Code, Social Security #
Patient's Method of Payment
Date of Signed Informed Consent
Race, Sex, Date of Birth
Diagnosis, Date of Diagnosis
Performance Status
Stratification Factors
List of prior CALGB protocols
Eligibility Criteria met (yes, no)
Date of most recent Institutional Review Board Approval (<1 yr)

The Main Institution will receive a Confirmation of Registration after each registration. Please check for errors. Submit corrections in writing to: CALGB Data Management Center, First Union Plaza, Suite 340, 2200 West Main Street, Durham, NC 27705.

5.2 NCCTG Randomization

NCCTG institutions must fax (507-284-0885) a completed eligibility checklist Monday through Friday, 8:00 AM - 3:30 PM, CT, to register a patient.

A signed HHS 310 form must be on file in the Randomization Center before any institution may register any patients. Patient eligibility and existence of a signed consent form will be checked by NCCTG Randomization Center personnel before a patient will be registered into this study.

Upon confirmation of eligibility, the NCCTG Randomization Center will contact the CALGB Data Management Center to register the patient. The NCCTG Randomization Center will then contact the registering institution with the treatment assignment.

5.3 ECOG Registration

A signed HHS 310 Form, a copy of the institution's IRB-approved informed consent document, and written justification for any changes made to the informed consent for this protocol must be on file at the ECOG Coordinating Center before an ECOG institution may enter patients. These will be submitted to: ECOG Coordinating Center, Frontier Science, Attn: IRB, 303 Boylston St., Brookline, MA, 02445-7648. Patients must not start protocol treatment prior to registration. Treatment should start within three working days of registration.

To register eligible patients on study, the investigator will telephone the Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday-Friday, between the hours of 9:00 AM to 4:30 PM ET to allow time to call the CALGB that same day. ECOG members should not call CALGB directly. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator's name); Patient Identification (including patient's name or initials, chart number, social security

number and demographics [sex, birth date, race, nine-digit zip code and method of payment]); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 4.0. The randomization specialist will verify eligibility by asking questions from the checklist, and will also verify IRB approval. The ECOG Randomization Desk will then contact CALGB to enter the patient, after which the ECOG Coordinating Center will contact the institution to relay the treatment assignment for the patient. The CALGB will forward a confirmation of treatment assignment to the ECOG Coordinating Center for routing to the ECOG participating institution.

If a patient does not receive protocol therapy, the patient may not be canceled.

5.4 SWOG Randomization

Southwest Oncology Group member and CGOP institutions will call the SWOG Statistical Center at 206/667-4623 between the hours of 6:30 am and 1:30 pm (PT) Monday through Friday, excluding holidays. The Statistical Center will obtain all information on the SWOG Registration Form, confirm that the current version of the CALGB Eligibility Checklist has been completed and the patient is eligible (see Section 4.0). In addition, the Statistical Center will request the date of informed consent and IRB approval. The Statistical Center will then contact the CALGB registrar and randomize the patient after which the Statistical Center will contact the institution to confirm registration, as well as relay the SWOG and CALGB patient sequence numbers. The CALGB Registrar will forward a confirmation of treatment assignment to the Statistical Center for routing to the participating institution.

SWOG CCOP institutions will call the SWOG CCOP Office at 206-652-CCOP (206-652-2267), between the hours of 7:00am to 4:00pm, Pacific Time, Monday thru Friday, excluding holidays. The SWOG CCOP Office will obtain all information on the SWOG Registration Form, confirm that the current version of the CALGB Eligibility Checklist has been completed, and the patient is eligible (see Section 4.0). In addition, the CCOP Office will request the date informed consent was obtained and the date of IRB approval for each entry. The CCOP Office will then contact the CALGB registrar to register the patient after which the CCOP Office will contact the isntitution to confirm registration, as well as relay the SWOG and CALGB patient sequence numbers. The CALGB Registrar will forward a confirmation of treatment assignment to the SWOG CCOP Office for routing to the participating institution.

5.5 Stratification Factors

- Performance Status
- Gender

5.6 Data Submission: Please submit data forms on the following schedule to the appropriate office noted in Section 5.8, according to the schedule provided below:

ON-STUDY/TREATMENT DATA	
Eligibility Checklist (page iii) 9732 On-Study Form 9732 Measurement Form 9732 Remarks Addenda *Pages iii, 1-3*	Within 2 weeks of registration.
Dosing Form for Cycle 1 Toxicities Observed from Cycle 1 **(For PS=2 pts, fax to the CALGB DMC following Cycle 1, see Sect. 5.7)** 9732 Remarks Addenda Dosing Form for Cycle 2 Toxicities Observed from Cycle 2 **(For PS=2 pts, fax to the CALGB DMC following Cycle 2, see Sect. 5.7)** Response/Relapse Form for Cycles 1 & 2 9732 Measurement Form *Pages 4-11*	Within 2 weeks of completion of Cycle 2.
Dosing Form for Cycle 3 Toxicities Observed From Cycle 3 9732 Remarks Addenda Dosing Form for Cycle 4 Toxicities Observed From Cycle 4 Response/Relapse Form for Cycles 3 & 4 9732 Measurement Form *Pages 12-19*	Within 2 weeks of completion of Cycle 4.
Dosing Form for Cycle 5 Toxicities Observed From Cycle 5 9732 Remarks Addenda Dosing Form for Cycle 6 Toxicities Observed from Cycle 6 Response/Relapse Form for Cycles 5 & 6 9732 Measurement Form C-300 Off Treatment Notice (once treatment is completed, or if treatment is ended early) *Pages 20-28*	Within 2 weeks of completion of Cycle 6.
C-300 Off Treatment Notice *Page 28*	If patient ends treatment prematurely for any reason, or is taken off treatment prior to assessing response, relapse, or death.
POST TREATMENT: FOLLOW UP EVERY 4 MONTHS FOR 1 YEAR	
Response/Relapse Form for Post Treatment Period Toxicities Observed Post Treatment 9732 Remarks Addenda 9732 Measurement Form *Pages 29-40*	Every 2 months after the completion of treatment for one year.
LONG TERM FOLLOW-UP	
C-400 Long Term Follow-up *Pages 41-42*	Every 6 months for 3 years beginning 18 months after treatment has ended.
Relapse Form For Long Term Follow-Up 9732 Measurement Form *Pages 43-44*	Submit in case of relapse and/or death during the long-term follow-up period.
C-215 Secondary Malignancy *Page 45*	At the discovery of a second malignancy.
Notification of Death *Page 46*	At death.

Follow-up For Survival and Second Malignancy

A patient will be followed only for survival and secondary malignancy after relapse or disease progression has occurred.

If a patient discontinues protocol therapy, and initiates alternative therapy not specified by the protocol, the patient will only be followed for survival and secondary malignancy. If a patient discontinues protocol therapy, but does not initiate alternative therapy, the patient will be followed for relapse, survival, and second malignancy.

5.7 Toxicity Monitoring During Cycles 1 and 2

In order to carefully monitor toxicities occurring during Cycles 1 and 2 **in all patients with a performance status = 2, institutions must FAX the Toxicities Observed From Cycles 1 and 2 Forms following Cycles 1 and 2 to the CALGB Data Management Center (919-286-1142).** ECOG, NCCTG, and SWOG institutions must also mail the forms to their respective group's office, in addition to faxing them to the CALGB. This does not supplant the notification of the CALGB Central Office of adverse events as outlined in Section 14.0.

Patients with a PS = 0-1 will not have the toxicity form faxed to the CALGB DMC. The form is to be mailed to their respective group's office.

5.8 Data forms should be submitted to the following Group offices according to the schedule specified in Section 5.6:

Group	**Office Receiving Forms**
CALGB	CALGB Data Management Center First Union Plaza, Suite 340 2200 West Main Street Durham, NC 27705
NCCTG	NCCTG Operations Office 200 First Street Southwest Rochester, Minnesota 55905
ECOG	ECOG Coordinating Center Frontier Science Attn: DATA 303 Boylston Street Brookline, MA 02445-7648

Do not use ECOG forms, except the ECOG Second Primary Cancer Form (#630), Adverse Reaction (ADR) Form for Investigational Drugs (391RF), NCI/CTEP Secondary AML/MDS Report Form. Include the ECOG and CALGB patient number on the forms.

SWOG

Group Members and CGOPs: Two copies of all data forms as listed in Section 5.6 should be submitted at the required intervals to the Statistical Center in Seattle. CGOPs must submit (# of copies to be determined by Group member) copies of all forms to their Group Member institution for forwarding to the Statistical Center.

CCOP Institutions: Submit 2 copies of all data forms directly to the SWOG CCOP Office at:

Cancer Research Center and Biostatistics (CRAB)
ATTN: SWOG CCOP Office
1100 Oliver Way, Suite 1150
Seattle, Washington 98101-1892

OR CCOP members may submit data via FAX to 206-652-4612. Faxed data must be accompanied by the Data Submission FAX Cover Sheet.

6.0 REQUIRED DATA

To be completed within 16 days before registration:
- All blood work

To be completed within 28 days before registration:
- Any x-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.

To be completed within 42 days before registration:
- Any baseline exams used for screening, i.e., EKG.
- Any x-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

Tests & Observations	Prior to Study	Prior to Each Cycle*	Post-therapy (Restaging) Evaluation***
History	X	X	X
Physical Examination	X	X	X
Performance status	X	X	X
Weight/Body Surface Area	X	X	X
Height	X		
Tumor Measurements	X	A	X
Drug Toxicity Assessment		X$^{\psi}$	X
Laboratory Studies			
CBC, Differential, Plt	X	B	
Serum Creatinine	X	X	
LDH, BUN	X		
Bilirubin, SGOT (AST), Alk. Phos.	X	X	
Tot. Prot., Albumin	X		
Ca^{++}, Mg^{++}	X		
Radiologic Studies			
Chest x-ray, PA & Lateral	X	X	X
CT Scan Chest/Liver/Adrenals	X	C	C
Bone Scan**	X		F
CT or MRI of Brain	X		E
EKG	X		
Fiberoptic Bronchoscopy	D		

* Within 2 days of each cycle. Pre-study tests may be used for day 1 of Cycle 1 tests.

** Abnormal areas on bone scan should also be x-rayed.

*** Within one month of completing chemotherapy and then every two months for 2 years, then every 4 months for 1 year, then every 6 months for 2 years.

ψ Following Cycles 1 and 2, the Toxicities Observed From Cycles 1 and 2 Forms are to be faxed to the CALGB Data Management Center.

A If accessible to physical examination.

B Weekly during the first two cycles of treatment, and then at 2 week intervals for all subsequent cycles (prior to each cycle and at week 2 of each cycle).

C A repeat CT of chest, liver, and adrenals is required for restaging after 2 cycles and upon completion of all chemotherapy. Repeat at suggestion or evidence of disease progression on CXR or other testing.

D If required for the diagnosis only.

E If involved before therapy, repeat at completion of all therapy and then if symptoms suggestive of recurrence develop.

F Repeat bone scan if symptoms suggestive of bony disease appear.

7.0 TREATMENT PLAN

7.1 Overview

This protocol is a two arm study evaluating the efficacy of cisplatin + etoposide versus a paclitaxel + cisplatin + etoposide regimen in SCLC.

7.2 Chemotherapy Schedule And Doses: Patients will be assigned to one of the following therapies:

7.2.1 Cisplatin/Etoposide (Arm A)

Cisplatin 80 mg/m^2 IV day 1

Etoposide 80 mg/m^2/day IV over 1 hour days 1-3

7.2.2 Paclitaxel*/Cisplatin/Etoposide/G-CSF (Arm B)

Paclitaxel 175 mg/m^2 IV over 3 hours day 1

Cisplatin 80 mg/m^2 IV day 1

Etoposide 80 mg/m^2/day IV over 1 hour days 1-3

G-CSF: 5 µg/kg given subcutaneously every day starting on day 4; treatment will continue until the ANC ≥10,000/µl after day 10 or until day 18 (whichever occurs first).

***Premedications for Paclitaxel:**

1. Dexamethasone: 20 mg PO 12 hours and 6 hours prior to paclitaxel or 20 mg IV 30 min prior to paclitaxel
2. Diphenhydramine: 50 mg IV 30 min before paclitaxel
3. Cimetidine 300 mg (or ranitidine 50 mg or famotidine 20 mg) IV 30 min prior to paclitaxel

Treatment will be given every 21 days for a total of 6 cycles in both Arm A and Arm B.

Administration of drugs:

1. **Arm B:** Paclitaxel will be administered before the cisplatin. The cisplatin infusion should immediately follow the paclitaxel infusion.

2. **Arms A and B:** Hydration for cisplatin:

   Aggressive prehydration is recommended for all patients receiving cisplatin but the method is at the discretion of the investigator. One commonly used method is:

   Over 24 hours prior to cisplatin, hydrate with 2 L PO + IV.

   Over 3-4 hours prior to cisplatin, give 1 liter D5 1/2 NS with 8 mEq MgSO4.

   Immediately prior to cisplatin, give 12.5 gm mannitol over 10 minutes.

   Administer cisplatin in 250 ml of D5 1/2 NS.

   Then over 2h, give 500 ml of D5 1/2 NS with 10 mEq KCL, 8 mEq MgSO4, 12.5 gm mannitol.

   Replace urine output with an equal volume of D5 1/2 NS until PO intake adequate.

3. **Arms A and B:** Etoposide will be administered over 1 hour diluted in D5W with

a final volume sufficient to produce an etoposide concentration less than 0.4 mg/ml.

4. **Arm B:** Paclitaxel will be given as a 3 hour continuous IV infusion, diluted in 500-1000 ml of 5% Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP (NSS).

5. **Arm B:** Recombinant rhG-CSF will be given once daily, preferably at the same time each day.

   rhG-CSF will be given subcutaneously daily starting on day 4. Continue rhG-CSF until granulocytes (ANC) ≥10,000/µl after day 10 or until day 18 (whichever occurs first). Cycles of chemotherapy will be administered every 21 days provided that the day of treatment ANC is ≥1,500/µl (>48 hours since last dose of rhG-CSF) and the day of treatment platelet count is at least 100,000/µl.

8.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITIES

All questions regarding treatment or dose modifications should be directed to the CALGB Study Chair.

If different percentages of dose reductions for a given drug are required because of two different types of toxicities, the greater percentage dose reduction should be employed.

8.1 Hematologic Toxicity: based on counts within 2 days of each cycle, give the following:

8.1.1 Granulocyte or Platelet Counts

Granulocytes/µl		Platelets/µl	Chemotherapy Agents
≥1,500	**and**	≥100,000	100%
<1,500	**and/or**	<100,000	0*

* Repeat counts weekly and reinstitute therapy at 100% when granulocytes ≥1,500/µl and platelets ≥100,000/µl. If counts do not reach these levels within 3 weeks notify the Study Chair.

8.1.2 Nadir Blood Counts or Febrile Neutropenia

For nadir neutropenia (ANC ≤500/µl) <5 days in the absence of fever, there will be no dose adjustment. The use of G-CSF in subsequent cycles in ARM A is at the discretion of the treating physician.

For nadir neutropenia (ANC ≤500/µl) ≥5 days or neutropenic fever requiring hospitalization, G-CSF should be added on Day 4 in all subsequent cycles for patients on ARM A. If nadir neutropenia (ANC ≤500/µl) occurs for more than 5 days or neutropenic fever requiring hospitalization occurs despite the use of G-CSF (Arm A or B), the dose of all chemotherapy should be reduced by 25% from the previous dose. There will be no re-escalation.

For grade 4 nadir thrombocytopenia (platelets ≤25,000/µl) the dose of all chemotherapy should be reduced by 25% from the previous dose. There will be no re-escalation.

8.2 Hepatic Dysfunction: Give the following % of full dose for paclitaxel only:

SGOT (AST)		Bilirubin	Paclitaxel
<2.0 x ULN	**and**	<1.5 mg/dl	100%
≥2.0 x ULN	**and/or**	≥1.5 mg/dl	0*

* Hold all treatment for one week. If after one week the liver functions have not normalized, treat with cisplatin and etoposide only (hold paclitaxel). Reinstitute paclitaxel when SGOT <2 x ULN and Bili <1.5 mg/dl.

8.3 Gastrointestinal Toxicity: All patients should receive antiemetics to prevent nausea and vomiting. Specific antiemetic therapy is left to the discretion of the physician treating the patient (steroids may be used). If vomiting is severe, admit and treat with any effective antiemetic regimen. Do not modify dose.

8.4 Nephrotoxicity

Serum Creatinine (mg/dl)	Etoposide	Cisplatin
<1.5	100%	100%
1.5-1.9	100%	50%
2.0-2.9	50%	0
≥3.0	0*	0*

* Hold treatment and repeat labs weekly until creatinine recovers to <2.0 mg/dl. If creatinine does not recover to <2.0 mg/dl after 3 weeks, remove patient from protocol therapy (see Sec. 12.0).

8.5 Hypomagnesemia is not an indication for stopping therapy. Oral or parenteral magnesium supplementation is indicated for serum magnesium levels ≤1.5mEq/l.

8.6 Neurologic Toxicity

Grade	Cisplatin	Paclitaxel
0-1	100%	100%
2	75%*	75%*
3	0	0

* Patients with grade 2 neurotoxicity should recover to grade 1 or better prior to retreatment with this (75%) dose reduction. If grade 2 neurotoxicity recurs with 75%, drug will be given at 50% upon resolution of neurotoxicity to grade 0-1.

8.7 Arthralgia/myalgia: The following dose adjustments are based on the worst grade experienced of arthralgia/myalgia of any preceding treatment course (for paclitaxel only):

Arthralgia/Myalgia	Paclitaxel
Grade 0-1 (Normal to mild)	No change
Grade 2 (Decrease in ability to move)	No change
Grade 3 (Disabled)	0

Steroids may be used as short term treatment for paclitaxel induced myalgias/arthralgias.

8.8 Ototoxicity: Remove patient from therapy if ≥grade 3 ototoxicity.

8.9 Allergic Reactions: Discontinue treatment promptly if ≥grade 3 anaphylaxis develops.

8.10 Grade 3/4 Non-Hematologic Toxicity: If a patient develops grade 3 or 4 non-hematologic toxicity not detailed above (excluding anorexia, fatigue, and alopecia), therapy can be restarted if the toxicity has resolved to ≤grade 1 by the time of the next treatment. Doses of all drugs should then be reduced by 25%.

8.11 Dose Modification for Obese Patients:

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by (1) the patient's body surface area as calculated from actual weight or (2) actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. **Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on CALGB protocols.

9.0 DRUG FORMULATION, AVAILABILITY, PREPARATION, AND ADMINISTRATION

9.1 Paclitaxel (NSC #673089)

Availability

Paclitaxel will be supplied by Bristol-Myers Squibb through the Division of Cancer Treatment, Diagnosis, and Centers, National Cancer Institute (IND #22850). It is supplied as a concentrated sterile solution, 6 mg/ml in 5 ml ampules (30 mg/ampule) in polyoxyethylated castor oil (Chromophore EL) 50% and dehydrated alcohol, USP, 50%.

- Chemical name: (see NIH publication 92-2654, NCI Investigational Drugs-Chemical information (1992)
- Alternative chemical name: None
- Empirical formula: C47H51NO14
- Molecular weight: 853.9

Preparation

The contents of the ampule must be diluted just prior to clinical use. Paclitaxel will be prepared by diluting the total dose in 500-1000 ml of 5% Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP (NSS). The solutions, when prepared at a concentration of 0.3 to 1.2 mg/ml, are stable for 27 hours. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexylphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Chromophore vehicle in which Paclitaxel is solubilized.

> *Note:* Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II and IVEX-HP, Abbott Pharmaceutical) into the IV fluid pathway distal to the infusion pump. Although particulate formation dose not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Storage and Stability

The intact ampules should be stored between 2-25°C. Each bag/bottle should be prepared immediately before administration. The vials will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3 - 1.2 mg/ml) are physically and chemically stable for 27 hours.

Administration

Paclitaxel, at the appropriate dose, will be given as a 3 hour continuous IV infusion, diluted in 500-1000 ml of 5% Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP (NSS). Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered.

Toxicities

Principal toxicities include myelosuppression, hypersensitivity reactions, nausea, vomiting, cardiac arrhythmias, diarrhea, myalgias, mucositis, stomatitis, pharyngitis, typhlitis, ischemic colitis, heart block, ventricular tachycardia, myocardial infarction, bradycardia, hypotension, taste alterations, seizures, mood changes, infiltration (erythema, induration, tenderness, rarely ulceration, radiation recall, rash), fatigue, arthralgia, light-headedness, risk of sensation of flashing lights and blurred vision, myopathy, increases in liver function tests, neuropathies, urticarial reactions, alopecia, hepatic failure, and hepatic necrosis.

9.2 Etoposide

Availability

Intravenous etoposide is commercially available (VePesid Injection from Bristol-Myers Oncology) in ampules containing 1000 mg/50 ml, 500 mg/25 mg, 150 mg/7.5 ml, and 100 mg/5 ml. It is now available from generic sources and is available in a 20 mg/ml, 1 gm vial.

Preparation

The dose of etoposide should be further diluted with D_5W or Normal Saline for Injection to a final concentration of less than 0.4 mg/ml.

Storage and Stability

Unopened vials are stable at room temperature for 24 months. Vials diluted up to a concentration of 0.2 or 0.4 mg/ml are stable for 96 and 24 hours, respectively, at room temperature under normal light.

Administration

Administer the diluted infusion solution at a maximum rate of 500 mg/hr; an administration that is too rapid may be associated with hypotension.

Toxicities

Myelosuppression, anorexia, nausea and vomiting, headaches, alopecia, phlebitis, fever, and peripheral neuropathy may occur. Acute arterial hypotension may result from rapid intravenous infusion. Anaphylaxis, somnolence and fatigue, rash, pigmentation, uticaria and pruritis may also occur.

9.3 Cisplatin

Cisplatin (DDP): Cisplatin (Platinol; cDDP; Platinum, Platinol AQ; cis-DDP; cis-Diamminedichloroplatinum; cis-Platinum II.

Availability

Platinol (Bristol-Myers Oncology Division) is commercially available as an aqueous solution (platinol AQ 1 mg/ml injection in 50 ml and 100 ml vials).

Compatibility

Incompatible with dextrose solutions (or any solution) containing less than 0.2% sodium chloride. Y-site incompatibility: Chlorpromazine, Piperacillin/Tazobactam.

Storage and Stability

Reconstituted vials are stable for 20 hours at room temperature. Vials reconstituted with bacteriostatic solutions are stable for 72 hours. Intact vials of cisplatin for injection and powder for injection should be stored at room temperature and protected from light.

Do not refrigerate.

Aluminum reacts with cisplatin to form black precipitates and loss of potency; do not prepare or administer with aluminum needles or IV sets; stainless steel or plated brass hubs may be used.

Toxicities

Nephrotoxicity (dose related and severe); Electrolyte abnormalities (increased excretion of Mg, K, Ca, PO4, Na); hyperuricemia; ototoxicity (30%, particularly high frequency hearing), nausea/vomiting, anaphylaxis/hypersensitivity; cardiotoxicity (rare: bradycardia, CHF); neurotoxicity (peripheral neuropathies, myasthenic-like syndrome); myelosuppression (moderate and reversible; infrequent at low dose); elevations in liver enzymes; optic neuritis; SIADH; seizures; cortical blindness (rare); loss of taste.

9.4 Recombinant Human Granulocyte-Colony Stimulating Factor (rhG-CSF) (Neupogen@ - AMGEN)

G-CSF is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by E. Coli Bacteria containing the human granulocyte colony stimulating factor gene.

Availability

G-CSF (Neupogen) is commercially available in 300 µg/1ml and 480 µg/1.6ml vials. For patients who do not have insurance or whose insurance coverage does not include reimbursement for G-CSF, the health care provider or patient should contact the AMGEN Reimbursement Hotline at 1-800-272-9376 for assistance. See Appendix III for further information.

Storage and Stability

Intact vials must be stored under refrigeration at 2 to 8° C. Prolonged exposure of G-CSF to temperatures outside this range will inactivate the drug. Do not allow G-CSF injection to freeze; do not use G-CSF injection that has been frozen.

Neupogen vials contain no preservatives. Discard vials 24 hours after entry. Store open vials under refrigeration at 2 to 8° C.

Special Handling: G-CSF injection should not be shaken; transportation in institutional pneumatic tube systems or other high speed mechanical devices is also not advised.

Administration

By subcutaneous injection.

Toxicities

The major clinical toxicity described with G-CSF is medullary bone pain which has been reported to occur in up to 20% of patients. The pain is generally acute in onset during the time period immediately prior to peripheral neutrophil recovery, and involves marrow-containing bone, such as the sternum, spine, and/or pelvis. The intensity is generally mild-moderate, with relief provided by over-the counter analgesics, and persists for 24-48 hours. MORE PROLONGED OR SEVERE PAIN SHOULD PROMPT A CLINICAL EVALUATION FOR OTHER CAUSES OF BONE PAIN.

Other clinical toxicities that have been described rarely include splenomegaly and exacerbation of underlying inflammatory skin disorders, such as psoriasis. Erythema, swelling, or pruritis at the injection site may also occur. Rarely, anaphylactic reactions have occurred.

Biochemical abnormalities that may occur include an increase in alkaline phosphatase, uric acid and lactate dehydrogenate that are reversible and correlate with G-CSF administration, and may relate to increased myeloid activity. These changes were seen in >50% of patients receiving G-CSF in one study; 20% of patients demonstrate a mild increase in transaminase on G-CSF.

CALGB GROUP FILGRASTIM DOSING POLICY

Round the dose to the nearest .1 ml (30 µg) for administration.

Flow sheets should accurately record the dose received by the patient. According to this policy, a 10% deviation from the actual calculated dose is permitted.

NURSING IMPLICATIONS

1. Filgrastim should be kept in the refrigerator until needed and the vials should not be shaken. Vials of filgrastim are single-dose and remaining drug should be discarded.
2. Acetaminophen is the recommended analgesic for mild bone pain.

9.5 Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

9.6 Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water

for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

9.7 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

10.0 ANCILLARY THERAPY

10.1 Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Steroids may be used as antiemetics.

10.2 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure, anti-emesis, treatment of myalgias/arthralgias or hormones administered for non-disease-related conditions (e.g., insulin for diabetes).

10.3 Radiation Therapy

10.3.1 If patients present with brain metastases they must complete radiation therapy prior to randomization and must be off steroids and anticonvulsants. The suggested radiation dose is whole brain radiation delivered to 30 cGy in 10 fractions.

10.3.2 It is recommended that patients who subsequently develop cranial metastases prior to completing protocol therapy receive whole-brain irradiation. These patients will be considered to have progressed and will be removed from protocol treatment and treated at the discretion of the physician.

10.3.3 It is recommended that patients who subsequently develop cranial metastases after completing chemotherapy shall receive whole-brain irradiation. These patients will be considered to have progressed.

10.3.4 Patients achieving a CR from chemotherapy can be considered for prophylactic irradiation of the brain after completion of the 6 cycles of chemotherapy at the discretion of the investigator.

10.4 CALGB Policy Concerning the Use of Growth Factors

10.4.1 Erythropoetin (EPO)

The use of EPO is **permitted** at the discretion of the treating physician.

10.4.2 Filgrastim (G-CSF)

For patients on Arm A, treatment with Filgrastim (G-CSF) will be allowed per Section 8.1.2. Patients on Arm B will receive G-CSF as part of their protocol treatment.

11.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

11.1 Complete response (CR): Disappearance of all measurable and evaluable disease, signs, symptoms, and biochemical changes related to the tumor.

11.2 Partial response (PR) (Measurable Disease only): When compared with pre-treatment measurements, a reduction of ≥50% in the sum of the products of the perpendicular diameters of all measurable lesions with which no new lesions appearing or enlargement of any existing lesion.

11.3 Regression (R) (Evaluable Disease only): Definite decrease in tumor size agreed upon by 2 independent investigators with no new lesions appearing.

11.4 Stable Disease

11.4.1 Measurable: A <50% reduction or <25% increase in the sum of the products of two perpendicular diameters of all measured lesions over the size present at entry on-study, and the appearance of no new lesions.

11.4.2 Evaluable: No clear cut change in tumor size and the appearance of no new lesions.

11.5 Objective Progression or Relapse

11.5.1 Measurable: An increase in the product of two perpendicular diameters of any measured lesion by ≥25% over the size present at entry on-study, or, for patients who respond, the size at the time of maximum regression.

Evaluable: Definite increase in tumor size.

11.5.2 The appearance of new areas of malignant disease.

11.5.3 A 2 step deterioration in performance status, >10% loss of pretreatment weight, or increasing symptoms in and of themselves do not constitute progression; however, their appearance should initiate a new evaluation for extent of disease.

11.5.4 If a patient has received any treatment and criteria 11.5.1 or 11.5.2 is satisfied, this will be considered as disease progression regardless of how much treatment has been received.

11.6 Unevaluable Response

11.6.1 If a follow-up imaging study or a physical examination measurement is not performed at an appropriate interval after initiation of treatment, tumor response is unevaluable.

11.6.2 If criteria 11.1, 11.2, 11.3, 11.4, or 11.5 is satisfied for a patient who has received any treatment, response will be evaluable regardless of how much treatment has been received.

11.6.3 If a patient who has received any treatment has not experienced disease progression nor satisfied the criteria for complete response, partial response, regression, or stable disease, response is unevaluable.

12.0 REMOVAL OF PATIENTS FROM THERAPY

12.1 Duration of Treatment: Continue treatment to a total of 6 cycles at the highest tolerable percentage of prescribed dose until the appearance of progressive disease. Upon the completion of chemotherapy, all patients will undergo complete restaging evaluation, including measurements of all positive indices of disease activity. Patients that have progressive disease will be taken off protocol therapy.

Patients with rapidly progressive disease at any time after at least one cycle will be removed from protocol treatment.

12.2 Complete responders can receive prophylactic cranial irradiation at the discretion of the investigator after 6 cycles of treatment (Section 10.3.4), and will then be observed. Partial responders will be observed only.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Study Design

CALGB 9732 is a 2-arm study in which patients with extensive small cell lung cancer will be randomly assigned to a standard treatment arm consisting of cisplatin/etoposide, or an experimental arm in which cisplatin, etoposide, and paclitaxel are administered with G-CSF support. Patient randomization will be stratified by performance status and gender.

13.2 Sample Size Justification

The median survival of patients with extensive small cell lung cancer who are treated with standard treatment is approximately 8.5 months. CALGB 9732 is designed in order that the comparison between cisplatin/etoposide/paclitaxel has 80% power to detect a difference in the distribution of survival time, where the median has increased by 30%, i.e. an increase in median survival to 11.0 months.

Assuming the survival comparison will be performed using the logrank test at a one-sided significance level of 0.025, 228 deaths on each arm need to be observed for a total of 456 deaths (24). Use of the O'Brien-Fleming boundary (25, 26) for interim monitoring necessitates that the required number of deaths be increased by approximately 3-5 %, i.e. increased to 470 deaths.

The accrual goal for this study is 580 patients. When CALGB 9732 was originally activated, an accrual rate of 40 patients per month was projected; however, an accrual rate of approximately 20 patients per month has actually been seen. Therefore, with approximately 4 months of additional accrual after February 2001, accrual should be complete. Approximately 12 months follow-up are needed in order to observe 470 deaths.

13.3 Interim Monitoring

In accordance with CALGB Policies and Procedures, the status and progress of CALGB 9732 will be reviewed semi-annually by the CALGB Data and Safety Monitoring Board. Reports to the Monitoring Board will regularly summarize reported toxicities. After 50 deaths (i.e. approximately 10% of needed number of deaths) are observed, formal efficacy analyses will be initiated and reported to the DSMB on a semi-annual basis.

Interim monitoring of the study will be conducted in order to allow for early stopping with rejection of the null or alternative hypothesis. Methodology developed by Lan and DeMets (27) and extended by Pampallona, Tsiatis, and Kim (31) will be used to determine boundary significance levels at each of the interim

analyses. Boundaries analogous to those proposed by O'Brien and Fleming (25) truncated at a nominal p-value of 0.001 (32) will be used. The methodology of Lan and DeMets, and Pampallona, Tsiatis, and Kim allow the type I and II error to be used up as a function of the accumulating "information" in order to maintain overall Type I and II errors.

13.4 Analytic Methods

13.4.1 Overall and failure-free survival curves will be calculated using the Kaplan-Meier life-table method (28). Failure-free survival is defined as the time between randomization and disease relapse or death. Survival time is defined as the time between randomization and death. Comparisons of survival will be performed using the logrank test for censored data (29).

13.4.2 Contingency tables will be used to summarize the frequency of toxicity by severity and treatment.

13.5 Minorities and Women

Women and minorities will be eligible for this study without alteration in eligibility criteria. There is currently no evidence to suggest that differences in response to treatment exist between groups on the basis of gender or race. Our data will allow exploratory examination of this question.

The accrual goal for this study is 580 patients. We expect the gender/minority composition of this patient group to be as follows:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	2	2	16	4	144	0	168
Male	0	2	34	10	362	4	412
Unknown	0	0	0	0	0	0	0
Total	2	4	50	14	506	4	580

HHS Racial and Ethnic Categories

American Indian or Alaskan Native: A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.

Asian or Pacific Islander: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes China, India, Japan, Korea, the Philippine Islands and Samoa.

Black, not of Hispanic Origin: A person having origins in any of the black racial groups of Africa.

Hispanic: A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin regardless of race.

White, not of Hispanic Origin: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

14.0 ADVERSE EVENT (AER) REPORTING FOR CALGB, NCCTG, ECOG, AND SWOG INSTITUTIONS

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the Investigational Drug Branch (IDB), the CALGB Central Office, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event (follow guidelines in the tables below). This study will utilize the Common Toxicity Criteria version 2.x to determine the severity of the reaction for adverse event reporting.

Reporting requirements and procedures depend upon: (1) whether agents are suspected of causing the adverse event, (2) whether the possibility of such an adverse event was reported in the protocol, consent form, or manufacturer's literature (expected or unexpected adverse event), (3) the severity or grade of the adverse event, (4) the phase of the study and attribution (the determination of whether an adverse event is related to a medical treatment or procedure). All reactions in a "reportable" category must be reported. Reactions attributable to a regimen that includes an investigational agent must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS). Reactions attributable to a regimen including only commercial agents must be reported on form FDA #3500 (Medwatch) and CALGB Medwatch Addendum Form, C-804.

Investigators are also required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols. Reporting of cases of secondary AML/MDS is to be performed using the NCI/CTEP Secondary AML/MDS Report Form. This form should be used in place of the form FDA #3500 (Medwatch). All other secondary malignancies should be reported using the form FDA #3500 (Medwatch).

CALGB requires investigators to route all adverse event reports (AERs) through the Central Office for CALGB-coordinated studies.

14.1 Reporting Requirements for Arm A (Regimens Containing Only Commercial Agents)

Expedited reporting for adverse events attributable to Arm A (Cisplatin/Etoposide) is required as described in Table 1.

Note: If a commercial agent is combined with an investigational agent supplied by the NCI, the treatment is considered investigational and the guidelines for reporting adverse events for investigational agents (Section 14.2) should be followed.

Table 1: Reporting requirements for Arm A

Phase II and III Commercial	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Expected[1]	Adverse Event Expedited Reporting **NOT** required.	Adverse Event Expedited Reporting **NOT** required.	Adverse Event Expedited Reporting **NOT** required.	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[2,3]	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[2,4]
Unexpected	Adverse Event Expedited Reporting **NOT** required.	Adverse Event Expedited Reporting **NOT** required.	Adverse Event Expedited Reporting **NOT** required.	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[2]	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[2,4]

1 A list of agent specific expected adverse events can be found in Section 9.0. Additional information regarding expected adverse events can be obtained from the package insert and the Physician's Desk Reference®.

2 Expedited reports are to be submitted using form FDA #3500 (Medwatch) and CALGB Medwatch Addendum Form C-804 within 5 working days to the Central Office (fax: 312-345-0117).

3 Grade 4 hematosuppression does not have to be reported for agents known and expected to cause myelosuppression at the dose used.

4 This includes reporting of all deaths within 30 days of the last dose of treatment regardless of attribution.

14.1.1 NCCTG Institutions

AER Reporting is based on the Common Toxicity Criteria version 2.x. Adverse reactions requiring submission to NCCTG Operations Office must also be reported to the local IRB.

Reporting for Commercial Drugs (Arm A):

	Unexpected Grade 4-5	Increased incidence of a known ADR[1]	Secondary AML/MDS[2]
FDA Form 3500 to NCCTG within 5 days[3]	X	X	
NCI/CTEP Secondary AML/MDS Report Form to NCCTG within 15 working days[3]			X

1. Any increased incidence of a known ADR that has been reported in the package insert or the literature, including adverse event resulting from a drug overdose.
2. Reporting for this toxicity required during or after treatment.
3. Fax or mail:

NCCTG Operations Office
200 First Street, SW
Rochester, MN 55905
Fax: 507-284-1902

The NCCTG Operations Office will immediately forward a copy of the ADR form to CALGB and to IDB if deemed a reportable ADR.

14.1.2 ECOG Institutions

AER Reporting should be based on the Common Toxicity Criteria v. 2.x.

Written Adverse Drug Reaction reports for Investigational drugs are to be reported on the Adverse Reaction (ADR) Form for Investigational Drugs (Form 391RF). CALGB will accept this form in lieu of the two page NCI Adverse Drug Reaction (ADR) form. Toxicities occurring on the commercial arm are to be reported on the FDA Form 3500. ECOG will accept this form instead of the ECOG Form #391RF, for commercial toxicities only. ADR reports are to be accompanied by supporting data and your institution's IRB must also be notified.

Reporting for Commercial Drugs (Etoposide, Cisplatin, and G-CSF): Arm A

	Unexpected Grade 3-5	Increased incidence of a known ADR[1]
FDA Form 3500, w/supporting data, to ECOG within 5 days	X	X
Call ECOG within 24 hrs	X	

1. Any increased incidence of Grade 4 or 5 known reactions.

14.1.3 SWOG Institutions

All Southwest Oncology Group (SWOG) investigators are responsible for reporting of adverse drug reactions according to the NCI and Southwest Oncology Group guidelines. SWOG Investigators must:

Call the Southwest Oncology Group Operations Office at 210/677-8808 within 24 hours of any suspected adverse event deemed either drug- or treatment-related, or possibly drug- or treatment-related.

Instructions will be given as to the necessary steps to take depending on whether the reaction was previously reported, the grade (severity) of the reaction, study phase, and whether the patient was receiving investigational and/or commercial agent(s). The SWOG Operations Office will immediately notify the CALGB Central Office.

Within 10 days of the initial telephone report, the investigator must send the completed (original) FDA 3500 Form to the NCI:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824

In addition, within 10 days the investigator must send:

- A copy of the above report,
- Copies of prestudy forms
- Copies of flow sheets from prestudy through event, and
- Documentation of IRB notification, to the following address:

ADR Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217

At the SWOG Operations Office a multilayered review will be performed and pertinent findings, along with supporting documentation, will be forwarded to the CALGB Central Office, NCI, Study Coordinator, and SWOG Statistical Center.

14.2 Reporting Requirements for Regimens Containing Investigational Agents (Arm B)

Expedited reporting for adverse events (including hospitalization defined below) attributable to Arm B (Paclitaxel/Cisplatin/Etoposide) is required as described in Table 1.

Hospitalization occurring in patients treated on regimens containing investigational agents: Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) occurring on a regimen using an investigational agent supplied by the NCI must be reported regardless of attribution or whether the adverse event is expected or unexpected, UNLESS the medical event is excluded from reporting in footnote #2 of the tables below. If the medical event is named in footnote #2, no AdEERS report should be submitted. Instead, the adverse event will be reported on the standard data forms for this study.

Table 1: Reporting requirements for Arm B

Phase II and III	Grade 1	Grade 2	Grade 3 and/or Hospitalization	Grade 4 and/or Hospitalization	Grade 5 and/or Hospitalization
Investigational Expected[1]	Adverse Event Expedited Reporting **NOT** required.	Adverse Event Expedited Reporting **NOT** required.	Adverse Event Expedited Reporting **NOT** required. Hospitalization must be reported. [2,3]	Regardless of Attribution, Adverse Event Expedited Reporting **required**.[2,3]	Regardless of Attribution, Adverse Event Expedited Reporting **required**.[2,3,5]
Unexpected	Adverse Event Expedited Reporting **NOT** required.	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required.**[3]	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required.**[3]	Regardless of Attribution, Adverse Event Expedited Reporting **required**.[3,4]	Regardless of Attribution, Adverse Event Expedited Reporting **required**.[3,4,5]

[1] A list of agent specific expected adverse events can be found in Section 9.0.

[2] Grade 3/4 myelosuppression or hospitalization resulting from grade 3/4 myelosuppression does not require expedited reporting, but should be submitted as part of study results. All other grade 3, 4 or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported (see Section 14.1).

[3] Within 5 working days of the adverse event, expedited reports are to be submitted electronically using AdEERS (**http://ctep.info.nih.gov/AdEERS**) to the CALGB Central Office (calgb@uchicago.edu). Faxed (312-345-0117) copies of the AdEERS paper template (downloadable from the AdEERS webpage) will also be accepted but electronic submission is preferred.

[4] Phone the Study Chair, the Central Office (773-702-9860) and IDB (301-230-2330) within 24 hours.

[5] Includes reporting of all deaths within 30 days of the last dose of treatment regardless of attribution.

14.2.1 NCCTG Institutions

NCCTG Investigators should follow the above guidelines for adverse event reporting. However, if the reaction is clearly a known reaction of the commercially available agent involved, it should be reported according to the commercial agent guidelines (see Section 14.1.1). If further clarification is necessary, call the research-base pharmacist (507/284-2701).

14.3 The reporting of adverse reactions described in the tables above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (see Section 5.6 for required CALGB forms). All reportable serious adverse reactions should also be forwarded to your local Institutional Review Board.

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16.0 MODEL CONSENT FORM FOR: A RANDOMIZED PHASE III STUDY COMPARING ETOPOSIDE AND CISPLATIN WITH ETOPOSIDE, CISPLATIN, AND PACLITAXEL IN PATIENTS WITH EXTENSIVE SMALL CELL LUNG CANCER

We invite you to take part in this research study for patients with extensive small cell lung cancer. It is important that you read and understand general principles that apply to all who take part in this study: 1) taking part in this study is entirely voluntary; 2) personal benefit may not result from taking part in this study, but knowledge may be gained that will benefit others; 3) any significant new findings that relate to your treatment will be discussed with you; and 4) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of this study, the risks, inconveniences, discomforts, and other important information about the study are discussed below. You are urged to discuss any questions you have about this study with your doctor.

The Cancer and Leukemia Group B (CALGB) assures you that your care is our primary concern. Through a variety of opportunities, new knowledge to fight your disease may be gained, both during the course of your treatment and later. Your cooperation now may prove useful in years to come. You may be asked to assist us in future studies of a non-medical nature, an agreement from which you may withdraw at any time. We understand your desire for privacy and will use standard, accepted methods to protect this right. You are urged to discuss any questions you have about this study with the staff members (doctors, nurses, etc.) who explain it to you.

Your physicians have found that you have a lung cancer. It is called small cell carcinoma (cancer) of the lung. This disease cannot be cured by surgery, but it is sometimes sensitive to radiation (x-rays) and to medications called chemotherapeutic drugs. For this reason, small cell carcinoma of the lung that spreads outside the chest (extensive disease) is usually treated by administering chemotherapeutic drugs (chemotherapy), as will be done in your case.

Purpose of the Study

The purpose of this study is to determine whether the addition of a new chemotherapy agent named paclitaxel to two drugs (etoposide and cisplatin) which are standard treatment for small cell lung cancer will improve the effectiveness of treatment. Paclitaxel has been shown to be effective in treating other cancers, but has not been fully tested in lung cancer. The study will attempt: 1) to slow, stop or decrease the growth of your disease; 2) to gain information about your disease; and 3) to evaluate the effectiveness and side effects of the drug treatment plans.

Study Description

Approximately 580 patients will participate in this study. It is not clear at the present time which of the treatments described below would be better for you. For this reason, the plan offered to you will be picked by a method called randomization. Randomization means that your doctor will call a statistical office which will assign one of the two therapies to you. The chances of your receiving either one of the treatments are approximately equal.

You will be randomly assigned to receive one of following treatments:

Treatment 1: Chemotherapy Treatment With Etoposide and Cisplatin:

Etoposide will be given into your vein (by IV) for an hour each day for 3 days. A second drug, cisplatin, will also be given by IV with etoposide on the first day of treatment. This treatment will be repeated every 21 days for a total of six treatment courses (one course equals 21 days).

OR

Treatment 2: Chemotherapy Treatment With Etoposide, Paclitaxel and Cisplatin:

Paclitaxel will be given by IV for three hours on the first day (you will be given several drugs before the paclitaxel to help reduce the side effects of the paclitaxel). Cisplatin will also be given by IV on the first day of treatment, along with treatment with etoposide by IV over 1 hour. Etoposide will then be given for 2 more days (a total of 3 days) by IV for one hour. Because these drugs can cause a lowering of your blood count you will be given a shot of G-CSF under your skin (subcutaneous) on days 4 through 18. You, a family member, or a friend can be taught to give these shots at home. This treatment will be repeated every 21 days for a total of six treatment courses (one course equals 21 days).

If one treatment is found to be less effective than the other, you will be informed and further treatment will be discussed. Depending on your response to treatment, you and your doctor may decide to use further drug therapy or supportive care alone later. You or your doctor may decide to discontinue treatment at any time. Following treatment, you will receive follow-up examinations at least every 2 months for 2 years, every 4 months for 1 year, and then at least every 6 months for 2 years. Your doctor will discuss these with you.

Risks

The treatment of small cell lung cancer requires the use of powerful drugs (chemotherapy) that have side effects, some potentially very serious, but rarely fatal. It may be necessary for you to be admitted to the hospital from time to time. The specific side effects for each drug are listed below. Unless otherwise specified, the side effects mentioned are reversible.

Bone Marrow Suppression (Etoposide, Paclitaxel, Cisplatin): The drugs used to kill cancer cells also kill some normal body cells, especially those that grow rapidly (blood cells, hair, cells that line the mouth, stomach, and intestines). Blood cells are made in the bone marrow and are responsible for fighting infections (white blood cells), carrying oxygen (red blood cells), and causing blood to clot (platelets). A reduction in the number of these blood cells (marrow suppression) can lead to an increased risk of infection, weakness, and bleeding. Should these effects occur, they can be treated with blood products (transfusions) and antibiotics. G-CSF may be used to increase the number of blood cells that are present in your bloodstream

Neurologic Abnormalities (Etoposide, Paclitaxel, Cisplatin): Patients may experience temporary unsteadiness when walking, fatigue, headache, tingling of the fingers and toes, jaw pain, muscle weakness, loss of reflexes, and blurred vision. These side effects occur more commonly in older patients, but are usually temporary and disappear after several days. More serious side effects are rare but have occurred with higher doses: blindness, cranial nerve paralysis, convulsions, and death.

Liver Irritation (Paclitaxel, Cisplatin): High doses may be associated with inflammation of the liver. This is temporary, usually mild, and does not lead to any long term damage. Rarely, liver breakdown or failure have been reported.

Bone and Muscle Pain (Paclitaxel, G-CSF): Temporary pain in bones, joints, or muscles may occur during treatment. Pain medication may be prescribed if necessary.

Kidney Damage (Cisplatin): Kidney function will be monitored with blood tests. Kidney damage is usually reversible. Certain antibiotics (aminoglycosides) can increase kidney damage when given with cisplatin. Additional fluids will be given to you by IV before and after the cisplatin to lower this risk.

Heart Toxicities (Cisplatin and Paclitaxel): Arrhythmias (irregular heart beats), heart attack, seizure and slow heart rates may occur. If you have a history of heart trouble, especially a slow or fast heart rate, or if you are on heart medication, you must tell your doctor before you start treatment.

Hair Loss (Etoposide, Paclitaxel, Cisplatin): Hair will fall out about three weeks after the first dose of chemotherapy but will grow back when chemotherapy is discontinued. Hair color usually will not change, however, hair is sometimes curlier.

Sensitivity to Sunlight: Take care in sunbathing because your skin will be more sensitive and may burn more easily than normal. Use a maximum protection sunscreen lotion, with an SPF of at least 15.

Nausea and Vomiting, Loss of Appetite (Etoposide, Paclitaxel, Cisplatin): Medication to prevent nausea will be prescribed before, during, and after treatment.

Mouth and Throat Sores, Diarrhea, (Paclitaxel, Cisplatin): Temporary irritation to the mouth and the lining of the bowel may lead to mouth ulcers (similar to canker sores), and to watery diarrhea. Numbing medications may ease the mouth discomfort. Medications to prevent diarrhea will reduce the cramping and discomfort associated with frequent bowel movements.

Changes in Blood Pressure (Paclitaxel, Etoposide): This can be corrected by giving the drug more slowly.

Hearing Loss (Cisplatin): Loss of hearing at higher tones (higher than human speech) is possible.

Mild Allergy (Etoposide): Nasal stuffiness, sinus congestion, sneezing, watery eyes, and runny nose may occur during or immediately following injection of the drug.

Radiation Recall (Paclitaxel): Patients that have previously received radiation therapy may experience skin changes in the area that was irradiated.

Skin Ulcer (Paclitaxel): These chemotherapy drugs will usually be administered through a central venous or Hickman catheter and problems with skin irritation are not likely to occur. On rare occasions, however, you may receive therapy through a regular intravenous line in your hand or arm. Paclitaxel can be irritating to the tissue if it leaks out of the vein. You should tell the person administering the drug if you feel any burning, stinging, or pain while the drug is being given. If the area of injection becomes red and swollen after the injection, you should notify your doctor immediately. In the unlikely event of a severe reaction, permanent tissue damage may result and a skin graft may be required.

Severe Allergic Reaction (Paclitaxel, Cisplatin, Etoposide): A fast heart rate, wheezing, low blood pressure, sweating, and skin rash may occur within a few minutes of treatment. These reactions have generally been controlled with medication. These reactions are rarely severe or fatal the first time the drug is given. The drug will not be given again if you become allergic. You will be observed closely while the drug is given, and medication for controlling an allergic reaction will be immediately available.

Irregular Menstrual Cycle: The menstrual cycle may temporarily be irregular or may stop permanently, resulting in an inability to become pregnant.

Impaired Sperm Production: Male patients may be sterile after receiving chemotherapy.

In an attempt to avoid side effects, your doctor will examine you and obtain laboratory tests (blood tests, chest x-rays, scans, etc.) to determine the effects of your treatment and alter the drug dosages if necessary.

Rare side effects of paclitaxel include rapid heart beat, inflammation or irritation of mouth tissues, mood changes, lightheadedness, mild blistering, itching, muscle aches or weakness and inflammation of the colon or cecum.

Secondary malignancies: A number of anti-cancer drugs can cause secondary cancers and/or leukemias. Certain drugs like those being used in this treatment, not currently known to be associated with this risk, may be shown at a later time to result in the development of these secondary cancers and/or leukemias.

Unanticipated side effects may occur which have not been reported. If you have any unusual symptoms, report them immediately to your doctor.

Pregnancy precaution: It is unknown what effects these medications may have on an unborn child (fetus, embryo). For this reason, you will be asked to practice an effective method of birth control while you are participating in this study.

Benefits

It is unknown which of the two treatments being studied in this study will eventually prove to be better. If this treatment is able to shrink your tumor, this may result in a reduction in your symptoms, improvement in your quality of life and you may live longer.

Alternatives

Other treatments for your disease include supportive care only or different drugs or drug combinations similar to those used in this study with similar side effects.

There is no clear evidence that other treatments:

1) are significantly more effective than those used in this study.

2) are curative.

Your doctor feels that these drugs would be appropriate at this time.

Costs

If you are randomized to receive the treatment that includes paclitaxel, paclitaxel will be supplied free of charge to your doctor by Bristol-Myers Squibb through the Division of Cancer Treatment, Diagnosis, and Centers, National Cancer Institute. You or your insurance company will be responsible for the cost of the other drugs used in this study.

Any procedure related solely to research which would not otherwise be necessary will be explained. Some of these procedures may result in added costs and some of these costs may not be covered by insurance. Your doctor will discuss these with you.

In addition, the use of medications to help control side effects could result in added costs.

Circumstances Under Which Your Participation May Be Terminated Without Your Consent

If health conditions occur which would make your participation possibly dangerous, or if other conditions occur that would make participation harmful to you or your health, then your doctor may discontinue this treatment.

Patient Protection

You may contact either the investigator in charge or a member of the human protection committee of _____Hospital whose names and phone numbers are listed at the end of this form, if at any point during the duration of this treatment you feel that you have been:

a. inadequately informed of the risks, benefits, or alternative treatments,

or

b. encouraged to continue in this study beyond your wish to do so.

In the event that complications occur as a result of this treatment, you will be provided with the necessary care. However, you will not automatically be reimbursed for medical care or receive other compensation as a result of any complications.

Participation is voluntary. If you choose not to participate or wish to withdraw your consent to participate in this treatment at any time, it will in no way affect your regular treatments or medical care.

The results of this study may be published, but individual patients will not be identified in these publications.

A record of your progress will be kept in a confidential form at _____ Hospital and also in a computer file at the statistical headquarters of the Cancer and Leukemia Group B (CALGB) and also ECOG (for ECOG patients) or NCCTG (for NCCTG patients) or SWOG (for SWOG patients).

Results of your tests, including blood samples and pathology slides, and confidential information contained in your medical record may not be furnished to anyone unaffiliated with the _____ Hospital or CALGB and also ECOG (for ECOG patients) or NCCTG (for NCCTG patients) or SWOG (for SWOG patients) without your written consent, except as required by Federal regulation. Your medical record including identifying information, may be inspected and/or photocopied by the National Cancer Institute or other sponsors of this study (including Bristol-Myers Squibb), the Food and Drug Administration, or other Federal or state government agencies in the ordinary course of carrying out their governmental functions. If your record is used or disseminated for such purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person: (name)_____ (title)_____ (address)_____ (phone number)_____.

You should understand that research studies of patients may be conducted on other aspects of health care, which may include topics such as the cost and convenience of treatment, and other issues directly affecting patient care. Your signature below indicates your permission to be included in such studies. You should also understand that cancer patients and their family members are sometimes asked to complete voluntary questionnaires to assess their quality of life, the inconvenience or cost of care. Your signature indicates that you would consider participating in additional, related surveys, if they are carried out.

This research project and its treatment procedures have been fully explained to you. All experimental procedures have been identified and no guarantee has been given about possible results. You have had the opportunity to ask questions concerning any and all aspects of the project and any procedures involved.

By signing below, you also grant permission for the use of tissues body fluids and other specimens, which may be obtained during testing, operative procedures or other standard medical practices to which you have or will give your consent during the course of your treatment, for use in scientific research, teaching purposes or development of new tests or products.

Your signature indicates that you have read this form, have received acceptable answers to any questions, and willingly consent to participate. You will receive a copy of this form.

(Patient's Signature)	(Date)
(Physician' s Signature)	(Date)
(Witness's Signature)	(Date)
(Responsible Investigator)	(Phone #)
(IRB Representative)	(Phone #)

APPENDIX I

CALGB EXPANDED COMMON TOXICITY CRITERIA

1. Toxicity grade should reflect the most severe degree or most abnormal lab value occurring during the evaluated period.

2. Toxicity grade = 5 if that toxicity caused or contributed to the death of the patient.

3. If patient at baseline has grade 1 or greater, do not code unless patient worsens due to toxicity. If there is worsening, code the level to which the patient increases - DO NOT adjust for baseline.

4. Note that for some Toxicity certain grades are not defined and may not be coded, e.g. no grade 3 or 4 Alopecia.

5. Granulocytes (mature cells) refers to segmented neutrophils (Segs, Polys, PMN, Polymorphonuclear leukocytes) plus bands (Staff cells, Stabs). To calculate granulocyte count multiply the white count by the % bands + % segmented neutrophils.

6. All coded toxicities must be documented and described on accompanying flowsheets.

September 11, 1989

CALGB EXPANDED COMMON TOXICITY CRITERIA
(Adapted from Common Toxicity Criteria, SWOG Toxicity Criteria, CALGB Toxicity Grading)

	Grade				
TOXICITY	0	1	2	3	4
HEMATOLOGIC					
WBC	≥4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
PLT	WNL	75.0-normal	50.0-74.9	25.0-49.9	< 25.0
Hgb	WNL	10.0-normal	8.0-10.0	6.5-7.9	< 6.5
Granulocytes/ Bands	≥2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
Lymphocytes	≥2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
Hematologic-Other		mild	moderate	severe	life threatening
HEMORRHAGE (clinical)	none	mild, no transfusion	gross, 1-2 units transfusion per episode	gross, 2-4 units transfusion per episode	massive, >4 units transfusion per episode
INFECTION	none	mild no active treatment, (e.g., viral syndromes	moderate requires outpatient PO antibiotic	severe requires IV antibiotic or antifungal or hospitalization	life-threatening (e.g., septic shock)
GASTROINTESTINAL					
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	--
Vomiting	none	1 episode in 24 hrs	2-5 episodes in 24 hrs	6-10 episodes in 24 hrs	>10 episodes in 24 hrs or requiring parenteral support
Diarrhea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	increase of 7-9 stools/day or incontinence, or severe cramping	increase of ≥10 stools/day, or grossly bloody diarrhea, or need for parenteral support
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers, but can eat	painful erythema, edema, ulcers, and cannot eat	requires parenteral or enteral support
Esophagitis/ Dysphagia	none	painless ulcers, erythema, mild soreness, or mild dysphagia	painful erythema, edema, or ulcers or moderate dysphagia but can eat without narcotics	cannot eat solids or requires narcotics to eat	requires parenteral or enteral support or complete obstruction or perforation
Anorexia	none	mild	moderate	severe	life-threatening

CALGB EXPANDED COMMON TOXICITY CRITERIA

TOXICITY	Grade 0	1	2	3	4
Other GI: Gastritis/ Ulcer	no	antacid	requires vigorous medical management or non-surgical treatment	uncontrolled by medical management; requires surgery for GI ulceration	perforation or bleeding
Small Bowel Obstruction	no	--	intermittent, no intervention	requires intervention	requires operation
Intestinal Fistula	no	--	--	yes	--
GI - other	--	mild	moderate	severe	life-threatening
OTHER MUCOSAL	none	erythema, or mild pain not requiring treatment	patchy & produces serosanguinous discharge or requires non-narcotic for pain	confluent fibrinous mucositis or requires narcotic for pain or ulceration	necrosis
LIVER					
Bilirubin	WNL	--	<1.5 x N	1.5 - 3.0 x N	>3.0 x N
Transaminase (SGOT, SGPT)	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Alk Phos or 5' nucleotidase	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Liver - clinical	no change from baseline	--	--	precoma	hepatic coma
Liver - Other	--	mild	moderate	severe	life threatening
KIDNEY, BLADDER					
Creatinine	WNL	<1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	>6.0 x N
Proteinuria	no change	1+ or <0.3 g% or <3 g/l	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or >1.0 g% or >10 g/l	nephrotic syndrome
Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion
BUN mg%	WNL, <20	21-30	31-50	>50	--
Hemorrhagic Cystitis	none	blood on microscopic exam	frank blood no treatment required	bladder irrigation required	requires cystectomy or transfusion
Renal Failure	--	--	--	--	dialysis required

CALGB EXPANDED COMMON TOXICITY CRITERIA

TOXICITY	Grade 0	1	2	3	4
OTHER Kidney/Bladder:					
Incontinence	normal	with coughing sneezing, etc.	spontaneous some control	no control	--
Dysuria	none	mild pain	painful or burning urination, controlled by pyridium	not controlled by pyridium	--
Urinary Retention	none	urinary residual >100cc or occasionally requires catheter or difficulty initiating urinary stream	self catheterization always required for voiding	surgical procedure required (TUR or dilation)	--
Increased Frequency/ Urgency	no change	increase in frequency or nocturia up to 2x normal	increase >2x, but <hourly	with urgency and hourly or more or requires catheter	--
Bladder Cramps	none	--	yes	--	--
Ureteral Obstruction	none	unilateral, no surgery required	bilateral, no surgery required	not complete bilateral, but stents, nephrostomy tubes or surgery required	complete bilateral obstruction
GU Fistula	none	--	--	yes	--
Kidney/Bladder - Other	--	mild	moderate	severe	life-threatening
ALOPECIA	no loss	mild hair loss	pronounced or total hair loss	--	--
PULMONARY					
Dyspnea	none or no change	asymptomatic, with abnormal-ity in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
pO2/pCO2	no change of pO2>85 and pCO2 $\leq$40	pO2>70 and pCO2$\leq$50, but not grade	pO2>60 and pCO2 $\leq$60 but not grade 0-1	pO2>50 and pCO2$\leq$70 but not 0-2	pO2$\leq$50 or pCO2>70
Carbon Monoxide Diffusion Capacity (DLCO)	>90% of pretreatment value	decrease to 76 - 90% of pretreatment	decrease to 51 - 75% pretreatment	decrease to 26 - 50% pretreatment	decrease to $\leq$25% of pretreatment
Pulmonary Fibrosis	normal	radiographic changes, no symptoms	--	changes with symptoms	--

CALGB EXPANDED COMMON TOXICITY CRITERIA

TOXICITY	Grade 0	1	2	3	4
Pulmonary Edema	none	--	--	radiographic changes and diuretics	requires intubation
Pneumonitis (non-infectious)	Normal	Radiographic changes symptoms do not require steroids	steroids required	oxygen required	requires assisted ventilation
Pleural Effusion	none	present	--	--	--
Adult Respiratory Distress Syndrome	none	mild	moderate	severe	life threatening.
Other Pulmonary: Cough	no change	mild, relieved by OTC meds	requires narcotic antitussive	uncontrolled coughing spasms	--
Pulmonary - Other	--	mild	moderate	severe	life-threatening
HEART					
Cardiac Dysrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension, or ventricular tachycardia, or fibrillation
Cardiac Function	none	asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
Cardiac-ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
Cardiac-pericardial	none	asymptomatic, effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Heart-Other		mild	moderate	severe	life-threatening

CALGB EXPANDED COMMON TOXCITY CRITERIA

TOXICITY	Grade 0	1	2	3	4
CIRCULATORY					
Hypertension	none or no change	asymptomatic, transient increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required.	recurrent or persistent increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis
Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospital-ization	requires therapy and hospitalization; resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for >48 hrs after the stopping agent
Phlebitis/ Thrombosis/ Embolism	--	--	superficial phlebitis (not local)	Deep vein thrombosis	major event (cerebral/ hepatic/ pulmonary/ other infarction) or pulmonary embolism
Edema	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca
NEUROLOGIC					
Neuro-sensory	none or no change	mild par-esthesias, loss of deep tendon reflexes	mild or moderate objective sensory loss; moderate paresthesias	severe objective, sensory loss or paresthesias that interfere with function	--
Neuro-motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
Neuro-cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe: somnolence or agitation or confusion or disorientation, or hallucinations or aphasia, or severe difficulty communicating	coma, seizures, toxic psychosis
Neuro-cerebellar	none	slight incoor-dination, dysdiadokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis

CALGB EXPANDED COMMON TOXICITY CRITERIA

	Grade				
TOXICITY	0	1	2	3	4
Neuro-mood	anxiety-none depression-none	mild anxiety mild depression	moderate anxiety moderate depression	severe anxiety severe depression	severe agitation suicidal ideation
Neuro-headache	none	mild	moderate or severe but transient	unrelenting and severe	--
Neuro-constipation	none or no change	mild	moderate	severe	ileus >96 hrs
Neuro-hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neuro-vision	none or no change	--	--	symptomatic subtotal loss of vision	blindness
Pain	none	mild	moderate	severe	intolerable
Other Neuro: Behavioral Change	no change	change, not disruptive to pt. or family	disruptive to pt. or family	harmful to others or self	psychotic behavior
Dizziness/ Vertigo	none	non-disabling	--	disabling	--
Taste	normal	slightly altered taste, metallic taste	markedly altered taste	--	--
Insomnia	normal	occasional difficulty sleeping may require sleeping pills	--	difficulty sleeping despite medication	--
Neurologic Other	--	mild	moderate	severe	life-threatening
DERMATOLOGIC					
Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Local	none	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated
ALLERGY	none	transient rash, drug fever <38C, 100.4F	urticaria, drug fever >38C 100.4F, mild bronchospasm	serum sickness, bronchospasm, req. parenteral meds	anaphylaxis

CALGB EXPANDED COMMON TOXICITY CRITERIA

TOXICITY	Grade 0	1	2	3	4
FLU-LIKE SYMPTOMS					
Fever in absence of infection	none	37.1 - 38.0C 98.7 - 100.4F	38.1C - 40.0C 100.5 - 104.0F	>40.0C >104.0F for less than 24 hrs	>40.0C (104.0F) for more than 24 hrs. or fever accompanied by hypotension
Chills	none	mild or brief	pronounced or prolonged	--	--
Myalgia/ Arthralgia	normal	mild	decrease in ability to move	disabled	--
Sweats	normal	mild and occasional	frequent or drenching	--	--
Malaise/ Fatigue*	none	mild, able to continue normal activities (PS1)	impairment of normal daily activity or bed rest <50% of waking hours (PS2)	in bed or in chair >50% of waking hours (PS3)	bed ridden or unable to care for self (PS4)
Flu-Like Symptoms-Other	--	mild	moderate	severe	life-threatening
WEIGHT GAIN	<5.0%	5.0-9.9%	10.0-19.9%	≥20.%	--
WEIGHT LOSS	<5.0%	5.0-9.9%	10.0-19.9%	≥20.%	--
METABOLIC					
Hyperglycemia	<116	116 - 160	161 - 250	251 - 500	>500 or ketoacidosis
Hypoglycemia	>64	55 - 64	40 - 54	30 - 39	<30
Amylase	WNL	<1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	>5.1 x N
Hypercalcemia	<10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	≥13.5
Hypocalcemia	>8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤6.0
Hypo-magnesemia	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤0.5
Hyponatremia	no change or > 135	131 - 135	126 - 130	121 - 125	≤120
Hypokalemia	no change or > 3.5	3.1 - 3.5	2.6 - 3.0	2.1 - 2.5	≤2.0
Metabolic-Other	--	mild	moderate	severe	life-threatening
COAGULATION					
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤0.24 x N

CALGB EXPANDED COMMON TOXICITY CRITERIA

	Grade				
TOXICITY	0	1	2	3	4
Prothrombin Time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	>2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	>3.00 x N
Coagulation Other	--	mild	moderate	severe	life-threatening
ENDOCRINE					
Impotence/ Libido	normal	decrease in normal function	--	absence of function	--
Sterility	--	--	--	yes	--
Amenorrhea	no	yes	--	--	--
Other Endocrine: Gynecomastia	normal	mild	pronounced or painful	--	--
Hot flashes	none	mild or <1/day	moderate and ≥1/day	frequent and interferes with normal function	--
Cushingoid	normal	mild	pronounced	--	--
Endocrine Other	--	mild	moderate	severe	life-threatening
EYE					
Conjunctivitis/ Keratitis	none	erythema or chemosis not requiring steroids or antibiotics	requires treatment with steroids or antibiotics	corneal ulceration or vivible opacification	--
Dry Eye	normal	--	requires artificial tears	--	requires enucleation
Glaucoma	no change	--	--	yes	--
Eye Other	--	mild	moderate	severe	life-threatening

*PERFORMANCE STATUS

CALGB (ZUBROD)					
Performances Status	PSO Normal	PS1 Fatigue without significant decrease in daily activities	PS2 Fatigue with significant impairment of daily activities or bedrest <50% of waking hours	PS3 Bedrest >50% of waking hours	PS4 Bedridden or unable to care for self
KARNOFSKY					
Performance Status %	100 - 90	80 - 70	60 - 50	40 - 30	20 - 10

CONVERSIONS/FORMULAS

a) Body Temperature F° = C° x 9/5 + 32
C° = F° - 32 x 5/9

b) Metric measures 1 inch = 2.54 cm
2.2 lbs. = 1 kg

c) Granulocyte Count WBC 2.2; Segs 61%;
Bands 4%;
2200 x .65 = 1430

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APPENDIX II

CRADA Language

The agent (hereinafter referred to as "Agent"), Taxol (paclitaxel), used in this protocol is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Bristol-Myers Squibb (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment, Diagnosis and Center. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and should be maintained as such by the investigators.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Date"):

   a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligation which would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit the use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator for review at the appropriate time (see #5). The NCI expects that clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator, and not to other parties.

4. When a collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and propriety data, in addition to Collaborator's intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

   Regulatory Affairs Branch, CTEP, DCTDC, NCI
   Executive Plaza North, Room 718
   Bethesda, Maryland 20892
   Fax 301-402-1584

   The Regulatory Affairs Branch will then distribute them to Collaborator.

APPENDIX III

Reimbursement Support for Neupogen

Reimbursement Support For NEUPOGEN®

Amgen, the manufacturer of NEUPOGEN® (Filgrastim), has agreed to provide NEUPOGEN® reimbursement assistance through its Amgen Reimbursement Hotline for the Phase III trial titled:

A Randomized Phase III Study Comparing Etoposide And Cisplatin With Etoposide, Cisplatin, And Paclitaxel In Patients With Extensive Stage Small Cell Lung Cancer.

NEUPOGEN® should be administered prophylactically to all patients as indicated in the **Treatment Plan** of the protocol. These uses of NEUPOGEN® are within approved FDA labeling. However, it is anticipated that some insurers may be reluctant or unable to cover patients treated with NEUPOGEN® in this trial. Amgen's Reimbursement Hotline is prepared to assist in providing up-to-date claims advice for these situations. The Hotline's services have been expanded specifically for this clinical trial and include:

1. **Reimbursement Support** The Hotline provides assistance relating to claims filing and appeals, and identification of alternative sources of payment (secondary insurer, state programs, and charity programs).

2. **Claims Support** The Hotline provides claims appeal support at several different levels, including investigating claims denials, preparing the claims appeal, assisting with letters of medical necessity, and providing necessary supporting literature.

The schema on the following page outlines the options should reimbursement assistance be required.

SHOULD THE HOTLINE VERIFY THE PATIENT HAS NO INSURANCE OR NEUPOGEN® IS NOT COVERED THEY WILL COORDINATE WITH AMGEN THE REPLACEMENT OF PRODUCT USED, BUT NOT REIMBURSED BY THE INSURER.

NEUPOGEN® REIMBURSEMENT HOTLINE:

Reimbursement Hotline: 1-800-272-9376

Hours: Monday through Friday 9:00 AM - 5:00 PM EST

When calling be prepared with the following information:

1. Identify yourself as being with the Intergroup (Study #). Name and address of the physician

3. Date of service

4. Patient name and study ID number

5. Name and address of the insurer

6. Insurer's reason for rejecting claim

7. Copy of the claim

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APPENDIX IV

Expanded Participation Project (EPP)

APPENDIX IV

1.0 EPP RANDOMIZATION AND REGISTRATION PROCEDURES

I. EPP institutions will register a patient on-line through the Clinical Trials Mangement Unit (CTMU). Questions pertaining to eligibility criteria should be directed to the CTMU; medical questions should be directed to the Study Chair.

II. A signed HHS 310 form documenting the Institutional Review Board (IRB) approval for this study must be on file at the CTMU before the EPP institution can enter a patient. IRB approval date must be less than one year prior to the date of registration.

III. Once eligibility is confirmed, the CTMU will contact CALGB to randomize the patient. The CTMU will notify the institution by an email upon successful enrollment with CALGB. In addition CALGB will forward confirmation of randomization and treatment assignment to the CTMU for routing to the participating institutions. Please check for errors, and submit any corrections in writing to the CTMU.

NOTE: Only performance status 0/1 patients will be enrolled through the EPP.

2.0 EPP DATA SUBMISSION

Data must be submitted electronically directly to the CTMU according to the following schedule:

FORM	TIME OF SUBMISSION
1. CALGB 9732 Eligibility Checklist*	At registration.
2. CALGB 9732 On-Study form*	Within 1 week of registration.
3. EPP Toxicity Form	Months 1, 2, 3, and every three months while on protocol therapy.
4. EPP Follow-up Form*	Every 3 months while on protocol treatment and every 6 months after completion of protocol treatment until death.
5. EPP Response/Progression Form*	Every 3 months while on protocol treatment, every 6 months thereafter until progression/relapse.
6. EPP Tumor Evaluation Forms (Measurable Lesions and Evaluable lesions)	At baseline and every 3 months until progression.
7. EPP Chemotherapy/Immunotherapy/ Hormonal Therapy Form	At the completion of protocol therapy
8. EPP Off-Treatment Form*	At the completion of all protocol therapy.
9. EPP Notice of Secondary Malignancy Form*	Within 10 days of diagnosis.
10. EPP Death Form*	Within 7 days of knowledge of event.

* These forms are to be submitted according to the above schedule for all patients, including those who never started treatment.

APPENDIX IV

3.0 EPP ADVERSE EVENT REPORTING

For EPP Institutions, all AER's are to be reported through the CTMU using the Adverse Event Expedited Reporting System (AdEERS). AER reporting is based on the revised NCI Common Toxicity Criteria (version 2.0):

AGENTS	GRADE				
	1	2	3	4	5
Investigational Agents Expected AE	-----	------	-----	ADR*	ADR
Investigational Agents Unexpected AE	-----	ADR	ADR	24hr/ADR	24hr/ADR
Commercial Agents Expected AE	-----	-----	-----	-----	-----
Commercial Agents Unexpected AE	-----	-----	-----	ADR	ADR

Arm A = Commercial

Arm B = Investigational

ADR = AdEERS (within 7 days)

24 hr = Report to CTMU within 24 hours

* Grade 4 hematosuppression does not have to be reported for agents known and expected to cause hematosuppression at the dose used.

Summaries of adverse events requiring 24-hour reporting are to be faxed or e-mailed to the CTMU within 24 hours and will be forwarded to the NCI and the Coordinating Group. Within 7 working days of the adverse event, expedited reports are to be submitted electronically using AdEERS (**http://ctep.info.nih.gov/AdEERS**) to the CALGB Central Office (calgb@uchicago.edu). Faxed (312-345-0117) copies of the AdEERS paper template (downloadable from the AdEERS webpage) will also be accepted but electronic submission is preferred.

All AERs should be reported to the local IRB.

All toxicities, including those with separate reporting requirements described above, must be reported on the Toxicity Form. Deaths are required to be reported via the Death Form within 7 days of knowledge of the event.

3.1 Secondary Malignancies

All investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols using commercial drugs. Reporting of cases of secondary AML/MDS is to be performed using the NCI/CTEP Secondary AML/MDS Report Form. This form should be used in place of the DCT Adverse Event Form for reporting this toxicity. All other secondary malignancies should be reported using the form DCT Adverse Drug Reaction Report. The EPP Notice of Secondary Malignancy must also be completed for all cases of secondary malignancy.