A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

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Study Participants: Hoosier Oncology Group
US Oncology

Study Activation: January 2002

Version Date: 10/29/2001
11/27/2001
02/08/2002
08/06/2002
03/24/2003
09/02/2003
03/03/2005

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PROTOCOL SIGNATURE PAGE

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VERSION DATE 03MAR2005

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page and **PRINT** your name, title and the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Please fax completed form to Hoosier Oncology Group at 317.921.2053 Return the original, signed copy to Hoosier Oncology Group and keep a copy for your files.

_____ _____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator Title

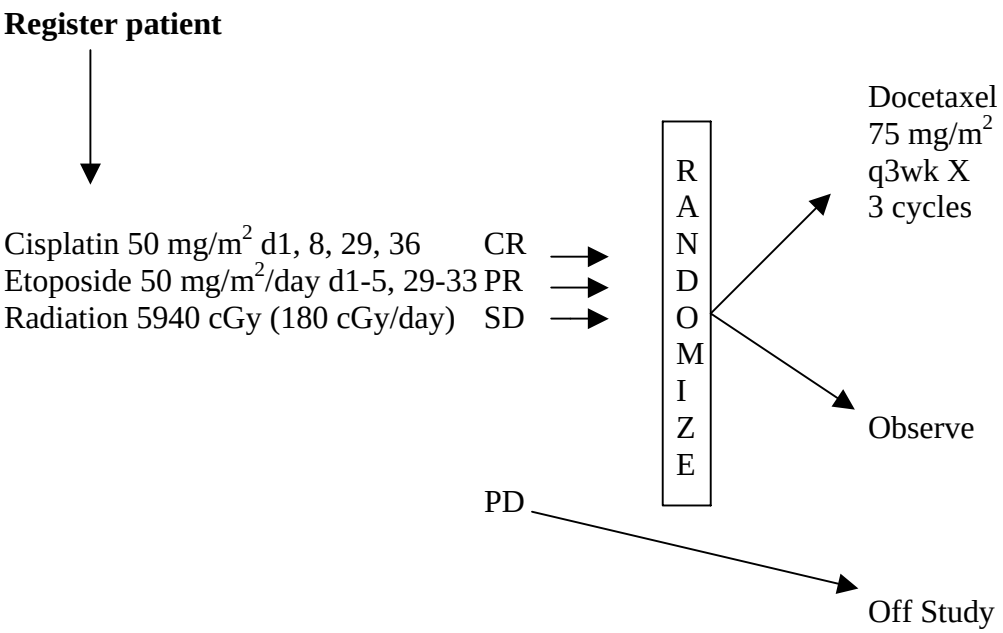
_____
Name of Facility

_____
Location of Facility
(City, State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

PLEASE COMPLETE AND FAX TO THE HOG OFFICE AT 317.921.2053

SCHEMA


Register patient
Cisplatin 50 mg/m2 d1, 8, 29, 36
Etoposide 50 mg/m2/day d1-5, 29-33
Radiation 5940 cGy (180 cGy/day)
CR
PR
SD
RANDOMIZE
Docetaxel
75 mg/m2
q3wk X
3 cycles
Observe
PD
Off Study

1.0 OBJECTIVES

1.1 The primary objective of this study is to assess whether consolidation therapy with docetaxel as compared with observation following cisplatin/etoposide/radiotherapy improves overall survival for patients with unresectable stage III non-small cell lung cancer (NSCLC).

1.2 The secondary objectives of this study are to assess whether consolidation therapy with docetaxel as compared to observation following cisplatin/etoposide/radiotherapy improves progression free survival and to further characterize the toxicity of the addition of docetaxel in this regimen.

2.0 BACKGROUND & RATIONALE

Lung cancer is the leading cause of cancer-death in both men and women in the U.S. with 157,000 projected deaths in the U.S. in 2000 (1). Approximately 80-85% of these patients will have NSCLC, with the majority presenting with locally advanced (stage III) or distant metastatic disease (stage IV). Until the early 1990's, the standard of care for patients with unresectable stage III NSCLC was radiation therapy alone. However, several trials, including a landmark study reported by Dillman et al in 1990 have now established chemoradiotherapy as the new standard (2,3).

In 1990, Dillman et al (CALGB 8433) reported the results of a trial in which patients with unresectable stage III NSCLC treated with cisplatin plus vinblastine followed by radiation therapy had an improved survival over patients receiving radiation alone (2). Median survival time was 13.8 months versus 9.7 months, favoring chemoradiation. A 7-year follow up report indicated that patients treated with chemoradiation continued to demonstrate an improvement in median and long-term survival times (10). These results were confirmed by a larger intergroup trial (RTOG 8808) reported by Sause and colleagues(3). In that trial, 458 eligible patients were randomized to receive either cisplatin plus vinblastine followed by standard radiation versus standard radiation alone versus hyperfractionated radiation alone. An improvement in median survival and long term survival were demonstrated favoring patients treated with chemoradiation.

While chemoradiotherapy has been established as the standard of care for patients with unresectable stage III NSCLC, the current best therapy for these patients remains controversial. These controversies include the sequencing of chemoradiation, choice of chemotherapy drugs, dose and schedule of radiation, and the utility of induction or consolidation chemotherapy to chemoradiotherapy. Two randomized studies comparing concurrent versus sequential chemoradiation seem to favor the use of concurrent chemoradiotherapy for this patient population (4,5); however, two other trials have not demonstrated this same benefit (6,7).

Furuse et al reported the results of a phase III trial comparing the combination of mitomycin, vindesine, and cisplatin given sequentially versus concurrently with radiation in patients with unresectable stage III NSCLC (11). Three hundred and twenty patients were entered onto the study. Median survival time was superior (16.5 months versus 13.3 months, p=0.039) in the concurrently treated patients.

A second trial which seems to confirm the superiority of the concurrent approach is RTOG 9410 (12). In this 3-arm phase III trial, patients with unresectable stage III NSCLC were randomized to receive cisplatin plus vinblastine followed by radiation or cisplatin plus vinblastine given concurrently with radiation, or cisplatin plus oral etoposide given concurrently with hyperfractionated radiation. Patients treated with concurrent, once daily radiation demonstrated a modest survival advantage (17 months versus 14.6 months for the patients treated with sequential therapy).

However, 2 other phase III trials have failed to demonstrate any advantage for the concurrent approach. Early results from one phase II trial indicates that a regimen of carboplatin plus paclitaxel induction followed by the same drugs given concurrently with radiation is no better than historical series of radiation therapy alone (6). In addition, a French trial comparing cisplatin plus vinorelbine followed by radiation versus cisplatin plus etoposide given concurrently with radiation followed by cisplatin plus vinorelbine failed to demonstrate any advantage for the concurrent approach (13).

Regardless of which combined modality approach is used, results with currently available data suggest that a plateau in median survival of 12-18 months may have been reached. The majority of patients with stage III disease will still die from their cancer due to failure of distant control of their disease. As a result, several strategies have been employed to improve upon distant control of stage III NSCLC. These include the use of induction chemotherapy prior to concurrent chemoradiotherapy to treat disseminated disease earlier or the use of consolidation chemotherapy after definitive chemoradiotherapy. The former strategy has thus far failed to improve survival in one recently reported trial (6). However, the latter strategy has demonstrated very encouraging results in a phase II study by the Southwest Oncology Group (SWOG-9504).

In a phase II study (SWOG-9504), 83 patients with pathological stage IIIb (without pleural effusion) NSCLC were treated with concurrent cisplatin and etoposide plus thoracic radiotherapy (61 Gy) followed by 3 cycles of consolidation therapy with docetaxel (8). Docetaxel, a taxane, was selected based upon a survival benefit in patients with recurrent NSCLC (9,10). Its potential molecular mechanism of p53-independent apoptosis also favors “taxane sequencing” prior to the emergence of clinical drug resistance. The median survival time of SWOG 9504 was reported to be 27 months with a 2 and 3 year survival rate of 54% and 40%, respectively. These results are unprecedented in this patient population. Furthermore, the toxicity profile of this therapy compares favorably to that of other new agent-containing chemoradiotherapy regimens. Grade 4 neutropenia occurred in 47% of patients; however, only 1 patient had grade 4 neutropenic fever and 5 had grade 3 neutropenic fever. Updated results of this study at the American Society of Clinical Oncology meeting in May 2000 also revealed grade 3/4

pneumonitis had occurred in 12% of patients, with 3 deaths. Two of these deaths were felt to be due to the radiation-pneumonitis perhaps due to larger radiation fields employed in the phase II studies. This and subsequent studies utilizing chemoradiotherapy will employ the use of 3-D conformal radiotherapy.

Based upon the unprecedented survival results of SWOG 9504, further study of this regimen is warranted in a phase III trial. This trial will evaluate the role of consolidation therapy with docetaxel in patients with unresectable stage III disease. The purpose of the trial is to evaluate survival and toxicities of the regimens employed.

3.0 THERAPEUTIC AGENTS

3.1 Drug Name: Cisplatin (CDDP) (Platinol) (NSC-119875);
Cis-diamminedichloroplatinum

3.1.1 Classification:

Cis-diamminedichloroplatinum is a heavy metal complex and is water soluble. It is a white lyophilized powder with a molecular weight of 300.1.

3.1.2 Mode of Action:

Cisplatin acts as a bifunctional alkylating agent, producing intrastrand and interstrand crosslinks in DNA via covalent bonds with the platinum molecule, leading to DNA strand breakage during replication.

3.1.3 Availability:

Cisplatin (NSC-119875) is commercially available.

3.1.4 Storage & Stability:

The intact vials may be stored at room temperature (15-25 degrees C) for the lot life indicated on the package. Do not refrigerate. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. The reconstituted solution is stable for 20 hours at room temperature, although, due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2NS (precipitate occurs in D5W).

3.1.5 Formulation:

Cisplatin is available as 10 mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of sterile water for injection USP, respectively. Cisplatin is also available as an aqueous solution, 1 mg/ml, in 50 or 100 ml vials.

3.1.6 Side Effects:

1. Hematologic-neutropenia, anemia
2. Nephrotoxicity is dose limiting for an individual dose
3. Neurotoxicity—painful peripheral neuropathy, ototoxicity
4. Gastrointestinal—nausea, vomiting, diarrhea, anorexia
5. Alopecia is rare
6. Cardiac abnormalities are rare
7. Elevated liver enzymes can be seen
8. Chronic renal magnesium and potassium wasting is common and sometimes not reversible.

3.2 Drug Name: etoposide, (VP-16) (VePesid) (Ethylidene-Lignan P.) (NSC-141540)

3.2.1 Classification:

Etoposide is a semi-synthetic podophyllotoxin derivative from the plant posophyllum pletatum, and has antineoplastic properties in experimental animals and in man. The empiric formula C29H32O13 has a molecular weight of 588.

3.2.2 Mode of Action:

The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of thymidine, uridine, and leucine incorporation in human cells in tissue culture suggests effects against DNA, RNA and protein synthesis.

3.2.3 Availability:

Etoposide is commercially available.

3.2.4 Storage & Stability:

The drug is available as a box of 10 vials that are stored at room temperature. Each vial should be kept in the box to protect if from light. Etoposide is poorly soluble in 5% Dextrose or 0.9% sodium chloride and precipitation may occur. A concentration of 0.4 mg/mL or less should always be used to minimize the chance of precipitation.

Etoposide has been administered undiluted at 20 mg/mL for high-dose chemotherapy treatment protocols.

3.2.5 Formulation:

100 mg of etoposide is supplied as 5 ml of solution in Sterile Multiple Dose vials for injection. The pH of the yellow clear solution is 3-4. Each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. Etoposide must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% sodium chloride injection, USP. The time before precipitation occurs depends on concentration, however, when at a concentration of 0.2 mg/ml it is stable for 96 hours at room temperature and at 0.4 mg/ml it is stable for 48 hours.

3.2.6 Side Effects:

1. Hematologic—myelosuppression, primarily leukopenia, is universal and dose limiting.
2. Gastrointestinal—nausea and vomiting are common with oral administration but rare when the drug is given intravenously; stomatitis and diarrhea are rare
3. Alopecia is mild or absent
4. Hepatic toxicity is rare except with high-dose etoposide where a transient increase in SGOT is reported.
5. Neuropathy is rare
6. Hypotension can occur with rapid administration
7. Secondary AML has been reported after etoposide

3.3 Drug Name: Docetaxel (Taxotere) (RP56976) (NSC-628503)

3.3.1 Classification:

A semi-synthetic analog belonging to the taxoid family, using a precursor extracted from the needles of the European yew, *Taxus baccata*, a renewable source.

3.3.2 Mode of Action:

In vitro, docetaxel promotes tubulin assembly in microtubules and inhibits depolymerization thus stabilizing microtubules, which is different from the action of other spindle poisions in clinical use. This can lead to bundles of microtubules in the cell, which by blocking cells in the M phase of the cell cycle, results in the inability of the cells to divide.

3.3.3 Availability:

Docetaxel is commercially available from Aventis Pharmaceuticals.

3.3.4 How Supplied

TAXOTERE (docetaxel) for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, **diluent** (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE 80 MG (NDC 0075-8001-80)
TAXOTERE (docetaxel) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 ml polysorbate 80 and diluent for docetaxel 80 mg, 13% (w/w) ethanol in water for injection. Both items are in a blister pack in one carton.

TAXOTERE 20 MG (NDC 0075-8001-20)
TAXOTERE (docetaxel) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 ml polysorbate 80 and diluent for docetaxel 20 mg, 13% (w/w) ethanol in water for injection. Both items are in a blister pack in one carton.

3.3.5 Storage

Refrigerate between 2 degrees and 25 degrees Celsius (36 degrees and 77 degrees F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

3.3.6 Preparation of the Initial Diluted Solution:

1. Gather the appropriate number of vials of docetaxel for injection concentrate and diluent (13% Ethanol in Water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for injection concentrate. **If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/ml will result.**
3. Gently rotate the initial diluted solution for approximately 15 seconds to assure full mixture of the concentrate and diluent.
4. The initial diluted docetaxel solution (10 mg docetaxel/ml) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process. The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

3.3.7 Preparation of the Final Dilution for Infusion:

Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/ml) with a calibrated syringe and inject into a 250 ml **NON-PVC** infusion

bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of **0.3 to 0.74 mg/ml.**

If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that **maximum concentration of 0.74 mg/ml** docetaxel is not exceeded.

Thoroughly mix the infusion by manual rotation.

As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel initial dilution (in vial) or final dilution for infusion is not clear or appears to have precipitation, it should be discarded.

The final docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Contact of the docetaxel concentration with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or **NON-PVC** plastic bags (polypropylene, polyolefin) and administered through **NON-PVC** polyethylene-lined administration sets, similar to that used with IV nitroglycerin.

3.3.8 Stability

The initial diluted solution in the manufacturers vial may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Fully prepared docetaxel infusion solution (in either NON-PVC 0.9% sodium chloride solution or NON-PVC 5% dextrose solution) stored between 2 degrees and 25 degrees Celsius (36 degrees and 77 degrees F) is stable for 4 hours (which must include the 1 hour IV administration time).

3.3.9 Side Effects:

1. Hematologic—myelosuppression is universal and dose-limiting
2. Alopecia is universal
3. Edema and fluid accumulation, including pleural effusions and ascites are common
4. Mild sensory or sensorimotor neuropathy is common
5. Mucositis and diarrhea are common and usually mild.
6. Hypersensitivity reactions are uncommon and can largely be prevented through premedication with corticosteroids and antihistamines

7. Cutaneous toxicity including rash (generally within 1 week of dosing) and nail changes (including pain or loss) may occur.
8. Elevated liver function is uncommon.
9. Other docetaxel related toxicity such as nausea, vomiting, diarrhea, asthenia, myalgia and arthralgia may occur.

3.3.10 Drug Interactions

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

4.0 ELIGIBILITY CRITERIA

4.1 Eligibility for Chemoradiation

4.1.1 Age $\geq$ 18 years

4.1.2 Histologic or cytologic evidence of NSCLC

4.1.3 Unresectable Stage IIIA (N2) OR Stage IIIB NSCLC.

4.1.3.1 Unresectable Stage IIIA will be defined by the following criteria:

a. N2 mediastinal lymph nodes must be multiple and/or bulky on CT scan such that in the opinion of the treating investigator, the patient is not a candidate for surgical resection
b. N2 disease must be documented by biopsy, FDG-PET scan imaging, or by CT if nodes are > 2 cm on CT scan

4.1.3.2 Stage IIIb patients must have N3 or T4 status. N3 status must be documented by one of the following criteria:

a. Contralateral (to the primary tumor) mediastinal lymph node, supraclavicular or scalene lymph nodes proven by biopsy, FDG-PET scan imaging, or by CT if nodes are > 2 cm on CT scan.

4.1.4 Patients with positive supraclavicular or scalene lymph nodes must not have disease extending up into the cervical region.

4.1.5 Patients with malignant pleural effusions are not eligible. The only exception is a patient with a pleural effusion visible only on CT scan (and not visible on CXR) OR deemed too small to tap.

4.1.6 Patients with pericardial effusions are not eligible.

4.1.7 Patients with superior sulcus (Pancoast tumors) are not eligible for this study.

4.1.8 Patients must have a brain CT or MRI to document no CNS metastases within 28 days prior to study treatment.

4.1.9 All patients must have measurable or evaluable disease documented by CT, MRI, X-ray or physical exam within 28 days prior to study treatment.

4.1.10 Patients must not have received any prior chemotherapy or radiotherapy for lung cancer.

4.1.11 Patients must have a serum creatinine $\leq$ 2 mg/dl or calculated creatinine clearance $\geq$ 50 cc/min using the following formula:

$$\text{Calculated Creatinine Clearance} = \frac{(140\text{-age}) \times \text{body weight (kg)}}{72 \times \text{serum creatinine}}$$

- Multiply this number by 0.85 if the patient is female.

4.1.12 Pre-registration FEV1 > 1 liters by spirometry within 42 days prior to study treatment.

4.1.13 Patients must have ANC $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/ mm^3, and hemoglobin $\geq$ 8 g/dl obtained within 14 days prior to study treatment.
NOTE: PRBC transfusions will be allowed to increase hemoglobin to >8 g/dl

4.1.14 Patients must have adequate hepatic function as defined by a serum bilirubin $\leq$ institutional upper limit of normal (ULN) and an AST $\leq$ 2.5 X the upper limits of normal if alkaline phosphatase is $\leq$ ULN, or alkaline phosphatase may be up to 4 X ULN if AST are $\leq$ ULN, within 14 days prior to study treatment.

4.1.15 All patients must have an ECOG PS 0 or 1 at the time of registration prior to chemoradiation.

4.1.16 Patients with unintended weight loss > 5% body weight in the preceding 3 months prior to study treatment will not be eligible for this trial.

4.1.17 Patients must not have symptomatic peripheral neuropathy prior to entry onto the study. Peripheral neuropathy must be $\leq$ Grade 1 to be eligible.

4.1.18 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for 5 years.

4.1.19 Patients should not have significant history of cardiac disease, i.e. uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the past year, or cardiac ventricular arrhythmias requiring medication.

4.1.20 Patients should not have a history of allergic reactions to drugs utilizing the vehicle polysorbate 80 (docetaxel) and polysorbate 80 + polyethylene glycol (etoposide).

4.1.21 If the patient has hearing loss at pre-study, performance of an audiogram is recommended (not mandatory) to document baseline hearing status in the event of possible further hearing loss due to cisplatin administration.

4.1.22 Pregnant or nursing women are ineligible for entry onto this trial. Women of childbearing potential must have a negative pregnancy test within 14 days prior to receiving any study treatment.

4.1.23 Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for 4 weeks following completion of protocol treatment. (A 6 month period of effective contraception following completion of protocol treatment is recommended, however, not required for participation.)

4.1.24 Patients must give written informed consent and authorization for release of personal health information prior to entry onto this trial.

4.2 Eligibility for Consolidation Therapy

Following completion of induction chemoradiotherapy patients without local progression of disease or distant metastases will then be randomized to receive consolidation therapy with docetaxel or observation. Patients will be stratified and randomized based on stage IIIa vs IIIb disease at baseline, CR vs. non-CR following induction chemoradiation, and ECOG PS 0 or 1 vs. 2.

4.2.1 Patients must have completed chemoradiotherapy per protocol and at least 4 weeks but no more than 8 weeks must have elapsed from the last day of induction therapy (the last day of radiation) to be eligible for randomization to consolidation with docetaxel or observation.

4.2.2 Patients must have undergone re-staging tests according to the study calendar and determined to have no evidence of disease progression to be eligible for randomization to consolidation with docetaxel or observation.

4.2.3 Patients must have an ANC $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/ mm^3, and hemoglobin $\geq$ 8 g/dl obtained within 14 days prior to registration for randomization to consolidation with docetaxel or observation.

4.2.4 Patients must have adequate hepatic function as defined by a serum bilirubin $\leq$ institutional upper limit of normal (ULN) and an AST and/or ALT $\leq$ 2.5 X the upper limits of normal if alkaline phosphatase is $\leq$ ULN, or alkaline phosphatase may be up to 4 X ULN if transaminases are $\leq$ ULN within 14 days prior to registration for randomization to consolidation with docetaxel or observation.

4.2.5 Patients must have an ECOG PS of 0, 1 or 2 prior to randomization to docetaxel or observation.

4.2.6 Patients must not have symptomatic peripheral neuropathy prior to randomization. Peripheral neuropathy must be $\leq$ Grade 1 to be eligible.

5.0 REGISTRATION PROCEDURE

All patients must be registered with the Hoosier Oncology Office Monday through Friday, 8:30 a.m. to 5:00 p.m. prior to beginning induction chemoradiation. See the Confirmation Page #1 (Appendix IV) for information to be supplied at the time of registration. At the time of registration, a copy of the patient's signed and dated informed consent and authorization for release of personal health information along with the Confirmation Page #1 must be faxed to the HOG office, fax number (317) 921-2053. Following induction chemoradiation, patients must be reassessed for disease status within 4-8 weeks. Patients with a complete response, partial response or stable disease will be randomized to receive consolidation docetaxel or observation. Confirmation Page #2 (Appendix VI) must be faxed to the HOG office, fax number (317) 921-2053 for randomization. In the event of a medical emergency, a patient may begin treatment on the non-randomized part of the trial prior to registration. The patient must be registered with the HOG office the next business day. When randomization is required, the patient must wait to be registered by the HOG office.

6.0 STUDY CALENDAR

		Induction Chemo-radiotherapy													Consolidation Therapy or Observation				
Course	Pre-Study														4-8 weeks following induction therapy	1	2	3	Follow-up[6]
Week		1					2	5					6						
Day		1	2	3	4	5	8	29	30	31	32	33	36	49		1	22	43	
TREATMENT																			
Cisplatin 50mg/m^2		X					X	X					X						
Etoposide 50mg/m^2/day		X	X	X	X	X		X	X	X	X	X							
Radiation Therapy		X	X	X	X	X	X	X	X	X	X	X	X	X					
Docetaxel 75mg/m^2																X	X	X	
REQUIRED STUDIES																			
History & Physical	X[1]							X							X[1]		X	X	X
Toxicity Assessment[8]	X[1]						X[8]	X[8]					X[8]	X[8]	X[1]	X	X	X	
Height, Weight, BSA	X[1]							X							X[1]		X	X	
ECOG Performance Status	X[1]							X							X[1]		X	X	
Spirometry (FEV1)	X[2]																		
Audiogram	X[3]																		
LABORATORY STUDIES																			
Blood Chemistries	X[1]						X	X					X		X[1]		X	X	
Serum creatinine or calculated creatinine clearance	X[1]						X	X					X		X[1]		X	X	
CBC, differential, Platelet Ct	X[1]						X[5]	X[5]					X[5]	X[5]	X[1]		X[5]	X[5]	
Urine Pregnancy Test (if pre-menopausal female)	X[4]																X	X	
RADIOLOGICAL STUDIES																			
CT or MRI of the brain	X[1]																		
Chest and upper abdominal CT	X[1]														X[1]				X
Chest X-ray															X[1]		X	X	X
Disease Evaluation	X[1]														X[1]				X
Bone Scan (if clinically indicated)	X[1]																		
Informed Consent Form	X																		
Confirmation Form	X														X				
Radiation Rapid Review	X[7]																		

*1. H & P, height, weight, BSA, Chemistries, serum creatinine or calculated creatinine clearance, CBC, diff, and Plts are to be obtained within 14 days prior to beginning study treatment. Patients must have radiological studies and disease evaluation within 28 days prior to study treatment. Smoking history required at baseline, at time of randomization to consolidation, off-study, and at each follow-up visit.

2. Spirometry test (FEV1) is to be obtained within 42 days prior to beginning study treatment.
3. Performance of an audiogram is recommended (but not required) to document baseline hearing status in the event of possible further hearing loss due to cisplatin administration.
4. Women of childbearing potential must have urine pregnancy test obtained within 14 days prior to beginning study treatment.
5. CBC, diff and Plts to be obtained weekly through the completion of chemoradiation, then prior to each docetaxel for patients randomized to this arm.
6. Patients are to be followed every three months if less than 2 years from study entry; and every six months if 2 – 5 years from study entry; and annually if greater than 5 years from study entry. All patients will be followed until death.
7. See Appendix VIII
8. Weekly toxicity assessments required through the completion of chemoradiation, then every 3 weeks during consolidation docetaxel.

*Chemistries to include: Bilirubin, Alk Phos, AST (SGOT), BUN, Calcium, Glucose, Albumin, Electrolytes (sodium, potassium, bicarbonate and chloride).

7.0 TREATMENT REGIMEN

7.1 Radiation therapy will commence on the first day of the chemotherapy dose schedule. Day 1 radiotherapy must be a Monday, Tuesday, or Wednesday, but no later in the week.

NOTE:
If a patient begins therapy on a Tuesday, then Day 5 etoposide should be given the following Monday, and the Day 8 cisplatin should be given on the following Tuesday. Day 29 of chemotherapy should then be given on a Monday and continued on schedule per protocol.

If a patient begins therapy on a Wednesday, then day 4 and 5 etoposide should be given the following Monday and Tuesday, and the Day 8 cisplatin should be given the following Wednesday. Day 29 of chemotherapy should then be given on a Monday and continued on schedule per protocol.

For unavoidable schedule changes (i.e. holidays), investigator discretion is allowed for treatment schedule variations.

DRUG	DOSE	ROUTE	DAYS	NOTES
Cisplatin*	50 mg/m^2/d	IV	1,8,29,36	In 250 ml NS over 60 min**
Etoposide*	50 mg/m^2/d	IV	1-5, 29-33	In 250 ml NS over 60 min

* Patients may receive cisplatin/etoposide as per institutional standards. It is recommended that the cisplatin be administered first because of its emetic side effects. The etoposide infusion will immediately follow the cisplatin.

**It is recommended that the cisplatin be preceded by appropriate antiemetics with a 5HT3 antagonist and dexamethasone 30 minutes prior to the infusion or as per institutional standards. Patients will receive intravenous pre and post hydration as per institutional standard.

7.2 Radiation Therapy

7.2.1 Special Instructions

Within two weeks of initiation of radiotherapy, copies of the radiation prescription, relevant CT scans and films, treatment plans for each phase of treatment and detailed dose-volume histograms for the complete treatment course to the final prescribed dose will be sent the Indiana Cancer Pavilion as per Appendix VIII.

7.2.2 Radiation Dose

Radiation therapy will commence on the first day of the chemotherapy dose schedule. Total dose to the involved areas will be 5940 cGy. This will be administered at 1.8 Gy daily, 5 days a week for total of 25 fractions (45 Gy) to the primary and mediastinum (primary planning target volume: I^o PTV) followed by a boost to the primary and involved nodes (secondary planning target volume: 2^o PTV) to 1.8 Gy daily in 8 fractions (1440 Gy). The total dose will be 5940 cGy in 33 fractions in 7 weeks.

A volumetric treatment planning CT study will be required to define gross tumor volumes (GTV), and planning target volume (PTV). Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices, 3-5 mm thickness of the regions harboring gross tumor and grossly enlarged nodes and 8-10 mm thickness of the remaining regions, are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the liver. The GTV, CTV, and PTV and normal organs will be outlined on all appropriate CT slices and displayed using beam's eye view. Normal tissues to be contoured include both lungs, skin, heart, spinal cord, esophagus, and liver. A measurement scale for the CT image shall be included.

IV contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessel. If not, IV contrast should be given during the planning CT.

Optimal immobilization will consist of an Alpha cradle or alternate immobilization system

7.2.3 Technical Factors

7.2.3.1 Beam Energy

Megavoltage equipment is required with effective photon energies ≥ 6 MV. 3-D conformal radiotherapy is strongly recommended

7.2.3.2 Treatment Distance

Minimal treatment distance to skin should be ≥ 100 cm for SSD technique and minimum isocenter distance should be 100 cm for SAD techniques.

7.2.3.3 Blocking

Primary collimation and blocking will be required only for shaping of the ports to exclude volume of tissues that are not to be irradiated.

7.2.3.4 Compensating Filters or Wedges

In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may also be used as a two-dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures.

7.2.3.5 Therapy Interruptions

If interruptions of therapy up to one week become necessary, irradiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.

If more than one-week interruption is required, contact the HOG office for consultation with the Principal Investigator. Radiotherapy interruptions or delays will be permitted only for any $\geq$ grade 3 non-hematologic toxicity or any grade 4 hematologic toxicity or as determined to be appropriate by the treating radiation oncologist.

7.2.4 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

7.2.4.1 Gross Tumor Volume (GTV) is defined by the physician as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary tumor (GTV-P) and abnormally enlarged regional lymph nodes > 1.0 cm (short axis measurement) (GTV-N). These volume(s) may be disjoint. Note ICRU Report #50 also defines a clinical target volume (CTV) which includes the area of subclinical involvement around the GTV.

7.2.4.2 Planning Target Volumes (PTV) will be divided into primary planning target volume (I^o PTV) and secondary planning target volume (2^o PTV).

Primary planning target volume (I^o PTV) will provide margin around the CTV to provide subclinical regional nodal RT. A margin around the CTV will define the 1^o PTV. The 1^o PTV volume must include a minimum 2.0 cm margin and a maximum 2.5 cm margin around the CTV.

Secondary planning target volume (2^o PTV) will provide margin around the GTV to compensate for variabilities in treatment setup, breathing, or motion during treatment. A margin around the GTV will define the 2^o PTV. The 2^o PTV volume must include a minimum 2.0 cm margin and a maximum 2.5 cm margin around the GTV.

7.2.4.3 Regional Nodal RT

The following lymph node regions must be included even in the absence of clinical or radiological involvement (to 45 Gy):

Elective treatment of supraclavicular nodes is not allowed.

Ipsilateral hilar lymph nodes - always (2 cm margin)

Superior mediastinal lymph nodes (above carina) - always (ipsilateral 2 cm margin).

Subcarinal lymph nodes (include the contralateral main stem bronchus and extend field at least to 3 cm below the carina) -always.

Inferior mediastinal nodes to the diaphragm (to bottom of T10) for patients with lower lobe lesions or inferior mediastinal involvement.

Contralateral hilar lymph nodes - for patients with contralateral mediastinal, or contralateral hilar involvement - (1 cm margin).

7.2.4.4 The ICRU Reference Point is to be located in the central part of PTV. Typically this point should be located on the

beam axis or at the intersection of the beam axis (isocenter). This is the point at which the doses used in this protocol will be prescribed. Every effort should be made to achieve dose homogeneity across PTV.

7.2.5 3D Planning

Planning Volume (PTV) - The PTV is to be treated with any combination of coplanar or noncoplaner three-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D- planning to produce the optimal conformal plan in accordance with volume definitions.

7.2.6 Normal Tissue Volume and Tolerances

The normal tissues in the table below are to be contoured in their entirety.

The following organs and doses by volume are guidelines for the 3-dimensional treatment plan. Physician/dosimetrist should make every effort not to exceed these tolerance levels. All normal tissues assume treatment at 1.8 Gy/fx (uncorrected).

ORGAN	VOLUME	TOLERANCE DOSE $TD_{5/5}$	END POINT
Lung	Ipsilateral whole lung Contralateral lung (only if necessary)	25 Gy 20 Gy	Clinical Pneumonitis
Esophagus	1/3 2/3 3/3	65 Gy 58 Gy 55 Gy	Clinical Stricture and Perforation
Brachial Plexus	point dose	60 Gy	Clinically Manifested Nerve Damage
Spinal Cord	5 cm 10 cm 20 cm	50 Gy 50 Gy 47 Gy	Myelitis Myelitis Myelitis
Heart	1/3 2/3 3/3	66 Gy 50 Gy 40 Gy	Clinical Pericarditis Clinical Pericarditis Clinical Pericarditis
Liver	1/2 2/2	35 Gy 30 Gy	Clinical Hepatitis Clinical Hepatitis

It is expected that the dose to the lungs will be the primary dose-limiting structure. Every effort to keep the total lung dose to a minimum should

be performed. Since most lung tumors are localized to one lung, efforts to keep the contralateral lung at a minimum should also be performed. The patient's overall lung function is evaluated by the FEV1 and DLCO should also be evaluated in determining an individual's lung function reserve and thus the ability to radiate.

When planning the beam arrangement to the PTV, the heart, esophagus, and spinal cord should be out of the field to the extent possible. The dose per fraction to the lungs, heart, esophagus, and spinal cord should be maintained at 2 Gy or less per fraction to the extent possible. If tolerance dose to any of the normal organs is exceeded, alternate beam arrangements should be used.

Total lung volume is defined as the lung volume of both lungs minus the PTV.

7.2.7 Localization Films

All fields treated require filming on simulator units. Portal verification must be done for all treated fields.

7.3 Consolidation chemotherapy with docetaxel

7.3.1 All eligible patients will have repeat tumor measurements with CT scan imaging within 4-8 weeks of completion of chemoradiotherapy.

7.3.2 Patients with non-progressing disease (CR, PR, or SD), after completion of chemoradiotherapy will then be randomized to receive consolidation chemotherapy with docetaxel or observation.

7.3.3 Chemotherapy with docetaxel will begin approximately 4-8 weeks after completion of chemoradiation.

7.3.4 Dexamethasone 8 mg p.o. bid will be given every 12 hours x 3 days (total of 6 doses) starting 24 hours prior to docetaxel treatment.

7.3.5 Docetaxel will be given at 75 mg/m2 IV over 60 minutes on day 1. Cycles will be repeated every 21 days for a total of 3 cycles.

7.4 Criteria For Removal From Protocol Treatment

7.4.1 Disease progression at any time during therapy.

7.4.2 Unacceptable toxicity

7.4.3 The patient may withdraw from study at any time for any reason.

7.4.4 Development of intercurrent, non-cancer related illnesses that prevent continuation of therapy or regular follow-up.

7.4.5 Any delay > 2 weeks beyond planned administration dates for chemoradiotherapy or consolidation chemotherapy.

8.0 NURSING IMPLICATIONS

8.1 CISPLATIN

8.1.1 Hematologic: Neutropenia can be moderate to severe with nadir occurring at day 14-21 and recovery usually by day 28. Thrombocytopenia and anemia are less frequent but can occur as well. Check CBC and platelet count before administering chemotherapy. Instruct patient on neutropenic precautions.

8.1.2 Nephrotoxicity: Nephrotoxicity is dose limiting for an individual dose. Assure adequate intravenous fluid hydration per protocol and encourage patients to drink plenty of fluids the day they receive the drug. Check serum creatinine level or calculated creatinine clearance before administering cisplatin.

8.1.3 Gastrointestinal: Nausea and vomiting are common but manageable if prophylactic antiemetics are administered prior to chemotherapy. Nausea and vomiting may occur within 6 hours after the drug is given and may last 24 hours. Delayed nausea and vomiting is also common, which may be treated with dexamethasone at 8 mg p.o. bid for 2 days then at 4 mg p.o. for 1-2 days. Standard antiemetics per institutional protocol and antidiarrheal therapy can be given. Instruct patient to increase oral care and inform them of the potential for mucositis. Also inform patients to call for vomiting and diarrhea that last greater than 24 hours. Anorexia and diarrhea are common. Monitor patients for weight loss or appetite changes.

8.1.4 Mild elevation of liver transaminase levels may be seen. Monitor liver function studies while the patient is on study and as directed by physicians.

8.1.5 Ototoxicity: Clinical hearing deficits and tinnitus can occur and are usually transient. Monitor patient for hearing loss and inform patients to report any hearing changes.

8.1.6 Neurotoxicity: Peripheral neuropathy with mild paresthesia may occur. Inform patients to report any numbness, tingling, burning of the hands or feet, or difficulty with gait or fine motor movements.

8.1.7 Electrolytes: Chronic renal magnesium and potassium wasting is common. Monitor levels prior to each dose of cisplatin.

8.2 ETOPOSIDE:

8.2.1 Hematologic: Myelosuppression, primarily leukopenia, is universal and dose limiting. Check CBC and platelet count before administering chemotherapy. Instruct patient on neutropenic precautions

8.2.2 Gastrointestinal: Nausea and vomiting is uncommon when the drug is given intravenously. Patients should call the physician's office for vomiting and diarrhea that last greater than 24 hours.

8.2.3 Stomatitis and diarrhea are also rare. Standard antiemetics and antidiarrheal therapy can be given. Instruct patient to increase oral care and inform them of the potential for mucositis.

8.2.4 Hepatic toxicity is rare. Monitor liver enzymes periodically.

8.2.5 Hypotension can occur with rapid administration of etoposide over < 30 minutes. Halting the infusion and resuming at one-half the previous rate when symptoms resolve is standard practice.

8.3 DOCETAXEL[14]

8.3.1 Hematologic: Myelosuppression is universal and dose limiting. The nadir usually occurs around day 10-14 after administration. CBC and platelet counts should be monitored prior to each treatment. Instruct patients on neutropenic precautions.

8.3.2 Alopecia is universal. Advise patient on use of hair prosthetics.

8.3.3 Fluid accumulation, including pleural effusions and ascites are common. Monitor for fluid accumulation in lower extremities, increase in abdominal girth, and worsening dyspnea. The dexamethasone premedication regimen may decrease the incidence and severity of fluid retention.

8.3.4 Peripheral neuropathy is common. Instruct patients to report any numbness and tingling, burning, in the hands or feet or difficulty with fine motor movements. Sensory symptoms usually improve or resolve within several months of docetaxel being discontinued. Risk factors predisposing patients to peripheral neuropathies include diabetes, alcohol use, renal failure, and prior cisplatin therapy.

8.3.5 Pneumonitis has been reported in patients receiving docetaxel following chemoradiation. Monitor for symptoms of chest pain and/or dyspnea.

8.3.6 Arthralgias/Myalgia: Instruct patients that they may experience mild to moderate pain in the joints of arms and legs 2-3 days after docetaxel and that the pain will resolve within approximately one week. Incidence and

severity of joint pain is dose dependent, and some patients may require analgesia.

8.3.7 Gastrointestinal: Nausea, vomiting, diarrhea, and mucositis can occur. Standard antiemetics and antidiarrheal therapy can be given. Instruct patient to increase oral care and inform them of the potential for mucositis. Also inform patients to call for vomiting and diarrhea that last greater than 24 hours.

8.3.8 Hypersensitivity reactions have been reported in patients who receive docetaxel. Dyspnea, hypotension, chest pains, and arrhythmias can possibly occur during the docetaxel infusion. All patients should be premedicated with dexamethasone to decrease the incidence and severity, according to the protocol. Baseline vital signs should be taken and monitored every 15 minutes during the infusion. Emergency medication should be readily available.

9.0 TOXICITY AND DOSE MODIFICATIONS

No dose escalation will be allowed. Chemotherapy doses may be reduced for hematologic and non-hematologic effects. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicity will be graded using the NCI Common Toxicity Criteria, Version 2.0. Treatment may be delayed no more than two weeks to allow recovery from toxicity. Dose adjustments should be made according to the guidelines which follow.

9.1 Induction Chemotherapy

Dose Level	Cisplatin	Etoposide
Starting dose (0)	50 mg/m^2/d	50 mg/m^2/d X 5 days
-1 Level	25 mg/m^2/d	50 mg/m^2/d X 4 days

9.1.1 Day 8 and 36 cisplatin modifications:

Omit cisplatin on day 8/36 if there is grade 4 neutropenia on day 8/36 or if the patient develops $\geq$ grade 2 renal toxicity, grade 4 esophagitis, or neutropenic fever following day 1 or day 29 for day 8 or 36 respectively. If cisplatin is omitted on day 8, it should not be given again until day 29; if cisplatin is omitted on day 36, it will not be made up.

9.1.2 Day 29 cisplatin and etoposide modifications:

Hematologic adjustments:

1. If on day 29, the ANC $\geq$ 1500/mm^3 and platelets $\geq$ 100,000/ mm^3, give full dose of both drugs.

2. If on day 29, the ANC < 1500/ mm^3 or platelets < 100,000/ mm^3, delay both drugs one week.
3. If, after 1 week delay (day 36), the ANC ≥ 1500/ mm^3 and platelets ≥ 100,000/ mm^3, give full doses of both drugs. Next dose of cisplatin will be on day 43.
4. If, after 1 week delay (day 36), the ANC < 1500/ mm^3 or platelets < 100,000/ mm^3, notify the HOG office for consultation with the Principal Investigator.
5. If febrile neutropenia occurs during the previous course, reduce etoposide to level –1.

Renal Adjustments:

1. If on day 29 the serum creatinine is > 2 mg/dl and/or calculated creatinine clearance < 50 ml/minute, delay cisplatin and etoposide by 1 week.
2. If, after a 1 week delay (day 36) the serum creatinine is < 1.7 mg/dl and/or calculated creatinine clearance ≥ 50 ml/min then give full dose of cisplatin and etoposide but increase pre and post hydration. The next dose of cisplatin will be on day 43.
3. If, after 1 week delay (day 36) the serum creatinine is ≥ 1.7 mg/dl but ≤ 2 mg/dl and calculated creatinine clearance ≥ 45 ml/min, reduce cisplatin and etoposide 1 level and increase pre and post cisplatin hydration. The next dose of cisplatin will be on day 43 at dose level -1.
4. If, after 1 week delay (day 36) the serum creatinine is ≥ 1.7 mg/dl and calculated creatinine clearance < 45 ml/min, omit cisplatin and etoposide and contact the HOG office for consultation with the Principal Investigator.

Non-hematologic adjustments:

If non-hematologic toxicity ≥ grade 3 (except for nausea and vomiting) occurs, both drugs should be held for 1 week then re-instituted at a one level dose reduction if toxicity resolves to ≤ grade 1.

If a delay beyond 1 week is anticipated, please call the HOG office for consultation with Principal Investigator.

9.2 Radiation Interruptions/Delays

If interruptions of therapy up to one week become necessary, irradiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.

If more than one-week interruption is required, contact the HOG office for consultation with the Principal Investigator. Radiotherapy interruptions or delays will be permitted only for any ≥ grade 3 non-hematologic toxicity or any grade 4 hematologic toxicity or as determined to be appropriate by the treating radiation oncologist.

Patients with severe esophagitis may be provided symptomatic treatment such as antacids, sucralfate, viscous lidocaine, and dyclonine as well as dietary supplements.

If treatment for severe esophagitis results in a delay of greater than one week, this may be grounds for treatment removal and should be discussed with the principal investigator.

9.3 Consolidation Docetaxel Dose Modifications:

Drug	Dose Level	Dose
Docetaxel	Full Dose	75 mg/m^2/d
Docetaxel	Dose Level –1	55 mg/m^2/d
Docetaxel	Dose Level –2	35 mg/m^2/d

Hematologic adjustments:

Patients with neutropenic fever or grade 4 neutropenia lasting > 7 days or grade 4 thrombocytopenia or thrombocytopenic bleeding should be retreated after recovery with a one level dose reduction.

Peripheral neuropathy adjustments:

If patients experience a grade 2 toxicity, the subsequent retreatment after recovery should be with a one level dose reduction.

If patients experience a grade 3 or higher peripheral neuropathy toxicity, they should be removed from study.

Hypersensitivity reaction adjustments:

No dose reductions will be made for any hypersensitivity reactions. If, despite proper pretreatment with dexamethasone as outlined in the protocol, the patient experiences a hypersensitivity reaction, treatment should be as indicated below:

Grade 1 symptoms (eg., mild flushing, rash, pruritis)—complete infusion. Supervise at bedside. No treatment required.

Grade 2 symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort)—Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a slower rate, then increased incrementally to the initial planned rate. Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment and the rate of infusion should be decreased initially and then increased back to the recommended 1 hour infusion. Report as an adverse event.

Grade 3 symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria)—Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to

administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The patient will go off study. Report as an adverse event.

Grade 4 symptoms - Anaphylaxis—Off protocol treatment.

Hepatic adjustments:

Patients who develop abnormal liver function tests for any reason while on the study will have the following docetaxel dose reductions:

Abnormal Liver Function Dose Modifications for Docetaxel (Taxotere)

Bilirubin	Alkaline Phosphatase	SGOT (AST)	Action
> ULN	or > 5 X ULN	or > 5 X ULN	Wait ≤2 weeks. If recovered*, reduce docetaxel (Taxotere) dose by –1 dose level. If not, off study.
≤ ULN	and ≤ 5 X ULN	and 1.6-5 X ULN	Reduce docetaxel (Taxotere) dose by –1 dose level.

*Bilirubin ≤ ULN and alkaline phosphatase ≤ 5 X ULN *and* SGOT (AST) ≤ 5 X ULN.
Note: A maximum of two dose reductions per patient are allowed.
ULN= upper limit of normal for institution

Fluid retention adjustments:

If symptomatic, patients developing fluid retention may be treated with diuretics at the investigator's discretion.

If grade 3, drug should be held until resolution to ≤ grade 1, then reinstituted, if medically appropriate, after recovery, with a one level dose reduction.

Stomatitis adjustments:

If grade 3 or 4 stomatitis occurs, retreatment after recovery to grade 1 or less with a one level dose reduction.

Other non-hematologic toxicities:

If toxicities ≥ 3, drug should be held until resolution to grade 1 or less, then reinstituted, if medically appropriate, after recovery, with a one level dose reduction.

Patients requiring a > 2 week delay in starting cycle 2 or 3 consolidation docetaxel due to non-hematologic toxicity will be removed from the treatment protocol.

Use of Growth Factors:

Use of granulocyte colony stimulating factors (i.e. .filgrastim, pegfilgrastim, sargramostim) will not be allowed during induction therapy with cisplatin, etoposide and radiation therapy. Use of granulocyte colony stimulating factors is permitted and encouraged during consolidation therapy with docetaxel. Use of erythropoietic agents (i.e. epoetin alfa, darbepoetin alfa) is allowed at any time during protocol therapy.

10.0 REPORTING ADVERSE DRUG REACTIONS

An adverse event is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy. All adverse events while on study will be recorded on the flow sheet utilizing the Common Toxicity Criteria Version 2.0. Some adverse events require more immediate reporting. Reporting requirements for such adverse events should include only those events, which are both serious and possibly related to the protocol therapy. This includes serious, possibly related, labeled (expected) and serious, possibly related, unlabeled (unexpected) adverse events. **Such events must be reported to the HOG office via fax (317) 921-2053 within 10 working days of discovery of the event.** Reports must also be sent to your local IRB per its guidelines.

10.1 Serious defined:

A serious adverse event is one occurring at any dose level that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of an existing hospitalization, persistent or significant disability/incapacity, cancer (other than cancers diagnosed prior to enrollment), a congenital anomaly/birth defect or significant for other reasons.

The definition of serious adverse event (experience) also includes *important medical event.* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dysrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience.

10.2 Death:
Any death while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended, but which is felt to be treatment related must be reported on the HOG SAE reporting form (Appendix III) **within 24 hours** of the discovery of the event as well as with a telephone call to the Hoosier Oncology Group office locally at (317) 921-2050 or 1-800-732-4HOG. Reports must also be sent to your local IRB per its guidelines.

10.3 When reporting SAEs:
Common toxicities observed for progressive disease and events secondary to progressive disease are generally excluded from adverse event reporting.

Utilize the HOG SAE reporting form and fax to the HOG office at (317) 921-2053. The HOG SAE reporting form is the preferred tool for reporting. It is critical to provide on the fax cover sheet the name and phone number of a contact person at your site. Please also provide the investigators opinion of the relatedness to study drug(s).

The HOG office will send reports to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology by **FAX** or **E-MAIL.**

By **FAX**: (908)-231-4827, within 24 hours of receipt. FAX transmission should include Grant-in-Aid Study Number, Study Title, and name of Principal Investigator.

By **E-MAIL**: GPEmailbox@aventis.com, within 24 hours of receipt. E-MAIL transmission should include Grant-in-Aid Study Number, Study Title, and name of Principal Investigator.

For Comparator Drugs/ Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

11.0 EVALUATION OF RESPONSE

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

Baseline documentation of "Target" and "Non-Target" lesions - all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Responses will be assigned according to the RECIST criteria as follows:

Complete Response (CR): Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms. Normalization of markers and other abnormal lab values. All disease must be assessed using the same technique as baseline.

Partial Response (PR): Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same technique as baseline.

Stable: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same technique as baseline.

Progression: One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same technique as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration.

Symptomatic Deterioration: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

Assessment Inadequate, Objective Status unknown: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

Best Response will be recorded for each patient. This is calculated from the sequence of objective statuses.

CR: Two or more objective statuses of CR a minimum of 4 weeks apart
PR: Two or more objective statuses of PR a minimum of 4 weeks apart
Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration
Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration.
Stable: At least one objective status of stable documented at least 6 weeks after registration and before progression or symptomatic deterioration.

12.0 REPORTING PROCEDURES AND FORMS

Confirmation Form #1 (Appendix IV) will be completed prior to initiation of study treatment and the form along with the signed informed consent should be faxed to the HOG office. The fax number for the HOG office is (317) 921-2053.

Special Instructions
Rapid Review Form: Within two weeks of initiation of radiotherapy, copies of the radiation prescription, relevant CT scans and films, treatment plans for each phase of treatment and detailed dose-volume histograms for the complete treatment course to the final prescribed dose will be sent the Indiana Cancer Pavilion as per Appendix VIII.

Confirmation Form #2 (Appendix VI) will be completed prior to randomization to consolidation therapy with docetaxel or the observation portion of the study. Patients are to have their disease reevaluated and randomization must be done between 4-8 weeks following completion of induction therapy.

Inclusion/Exclusion Exception Form (Appendix IX) An exception granted to any of the eligibility criteria must be noted on the Inclusion/Exclusion Exception Form (See Appendix IX). The investigator or designee will discuss with and fax to the HOG representative all requests for exception. The Hog representative will send each request to the Study Chair for review or discuss with the Study Chair. The Study Chair/HOG

representative will indicate whether an exception is granted on the form. The HOG representative will contact the study center with the Study Chair's decision and fax a signed copy of the Inclusion/Exclusion Exception Form to the study center to document the decision. The study center should place a copy of this form for subject accountability records in the investigator's study files.

Case report forms will be completed for each patient entered on the study utilizing the Hoosier Oncology Group Data Collection and Management System.

13.0 STATISTICAL CONSIDERATIONS

13.1. Statistical Endpoints

13.1.1. Primary endpoint

The primary endpoint of this study is to test the effect of docetaxel following radiotherapy and chemotherapy (with cisplatin and etoposide) for patients with unresectable stage III non-small cell lung cancer (NSCLC). It is projected that the control group (observation after chemoradiation) will achieve a median overall survival of 15 months, while the treatment group (additional treatment with docetaxel) will have an increase in median survival to 25 months. Survival of an individual is defined as the time from treatment initiation with docetaxel or initiation of observation after chemoradiation until death. Subjects that are still alive at the time of study completion will be assumed to survive at least as long as the time of analysis without further assumptions being made about the duration of their survival (censored observations).

13.1.2. Secondary endpoint

The secondary endpoint of this study is to assess the progression-free survival in subjects treated with docetaxel after chemoradiation as compared to observation. Progression-free survival is the time from initiation of therapy with docetaxel or initiation of observation after chemoradiation, until the occurrence of a documented progression (as defined in section 11.0) or death. Subjects that have not experienced either disease progression or death by the time of study completion will be considered as having progression-free survival time that is at least as long as the time of the data analysis. No further assumption of the duration of progression-free survival will be made (censored observations).

13.2. Power and sample size calculations

This study will plan to randomize **180 patients** (90 to each group) over 55 months (3.3 patients per month) based on the power calculation discussed below. We will accrue **259 patients** in total 4.7 per month for 55 months), since it is expected that up to 30% of the patients accrued will not be

randomized due to progressive disease following induction therapy. Patient accrual will occur for approximately **55 months** and patient follow-up will continue for **ten months** after the last patient has been enrolled.

The sample size is calculated by assuming 5% two-sided type-I error (alpha level) and 80% power. About 124 deaths are expected at the time of final data analysis. Uniform patient accrual was assumed along with exponential distribution of (overall) survival times (i.e., constant hazard of failure at any time point).

13.3. Statistical analyses

13.3.1. Baseline characteristics such as age, gender and concomitant disease will be compared between treatment groups using t tests for continuous variables and Fisher's exact test for discrete variables. If the continuous variables are not normally distributed, then the Mann Whitney U test will be used.

13.3.2. The primary outcome of survival will be compared between the two treatment groups using the log rank test stratified for stage (IIIA vs. IIIB) in the context of a Kaplan-Meier survival analysis.

13.3.3. Median survival will be calculated along with 95% confidence intervals (produced by the Kaplan-Meier analysis). Progression-free survival will be analyzed similarly.

13.3.4. If any baseline characteristics, believed to be related to survival, differed between the two groups, Cox Regression Analysis will be done so that the treatment comparisons can be adjusted for any effects of these baseline characteristics.

13.3.5. The rate of occurrence of specific toxicities will be calculated for each treatment group. If numbers are sufficient, then the rates will be compared between the groups using Fisher's exact test. Logistic-regression analyses will be carried out, in order to evaluate the association of the occurrence of a toxicity (a dichotomous – yes/no – outcome) with various baseline and time updated factors (in similar fashion as our regression analyses of survival times).

13.4. Study monitoring

An interim analysis will be performed at approximately half way through the study (when about 62 confirmed deaths have been observed). The analysis will involve an interim "look" at efficacy data comparing the two treatment arms. The primary endpoint of overall survival will drive the analysis results although secondary endpoints (progression-free survival) and safety data (toxicities, adverse events) will be summarized and considered. The O'Brien-Fleming [15] (1979) boundary (for early stopping under both the null hypothesis – no

survival improvement – or the alternative – survival benefit associated with the docetaxel or observation arm) will be defined (see Figure I below).

The exact time of the interim data analysis will depend on scheduling issues, along with the statistical requirements. If the analysis occurs at a time when more or less than half of the expected endpoints have been observed, the Lan-DeMets alpha spending function approach will be used [16]. All calculations were performed with East software version 3.1 (Cytel Corporation, Cambridge, MA). To maintain the power levels, the expected number of events is 124. Under the current scheme, the O'Brien-Fleming boundary is defined as follows:

Table I. O'Brien-Fleming bounds for design

Analysis	Number of events	p-value[1]	
		Under the null (futility)	Under the alternative (early advantage)
1 (interim)	62.1	0.727	0.0031
2 (final)	124.2	0.0509	0.0509

.

The above table suggests that if the test of equality in the overall survival between the two arms results in a two-sided p value of 0.0031 or less, the study will be stopped early as having detected a large enough survival advantage associated either with the docetaxel or observation arm. If, on the other hand, the p value of the same comparison is larger than 0.0727, this would constitute evidence of futility. The current study is unlikely to show a survival advantage between either the docetaxel or observation arm if allowed to be completed. In that case the study will also be stopped during the interim analysis. Pictorially, the above information is summarized in the following figure.

[1] To reject the null hypothesis of no overall survival difference between the two treatment arms; two-sided p value.

[1] To reject the null hypothesis of no overall survival difference between the two treatment arms; two-sided p value.

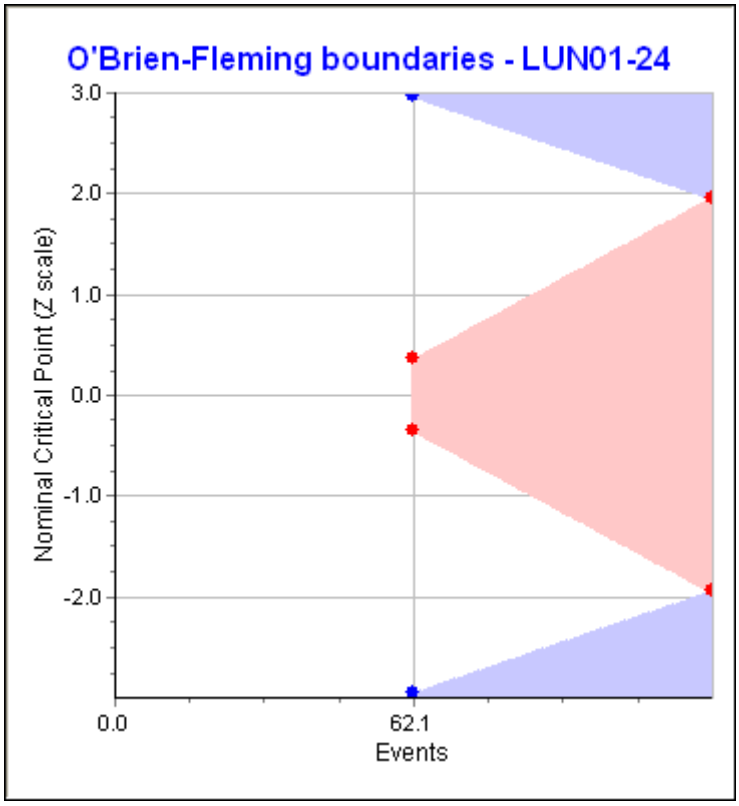


Figure I. O'Brien-Fleming boundaries of LUN01-24. White area, continue study, pink area, interrupt early in favor of the null hypothesis of no difference (futility), upper blue area (interrupt trial in favor of docetaxel), lower blue area (interrupt trial early in favor of observation).

13.5 Data and Safety Monitoring Plan

HOG data safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the Study Chair of recommended action
- Notification of sites coordinated by the HOG of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

Monitoring and Reporting Guidelines
The HOG office will compile data summary reports for this trial and submit these reports monthly to the Study Chair. The report will include: the number of subjects enrolled to date, significant toxicities and responses. Quarterly, the HOG

office will submit data summary reports to the Indiana University Cancer Center Clinical Trial Monitoring Committee (IUCC CTMC) for review. Additional reports will be prepared as per the monitoring plan accompanying this protocol for the interim analysis as described in section 13.4.

Review and Oversight Requirements

a) Serious Adverse Event – Reported by Phone Within 24 Hours
Serious adverse events (SAEs) requiring expedited reporting by phone within 24 hours will be reported to the designated CTMC personnel within one working day by the HOG office. Confirmation that all appropriate parties were notified will be done at this time. Hardcopies or electronic versions of MEDWATCH form (3500) and/or any other documentation available at that time will also be reviewed by the CTMC Committee Chair who will determine if immediate action is required. Within ten working days all subsequent SAE documentation that is available will be submitted to the CTMC Committee Chair who will determine if further action is required. If required, the HOG office will insure that all participating sites are notified of the event and resulting action within one working day of determination.

b) Serious Adverse Event – Reported within 10 days
Adverse events requiring expedited AE reports in writing within 10 working days (as described in the protocol) will be sent to the designated CTMC personnel quarterly, and this information will be tracked in the CTMC database.

c) HOG Internal Review of SAE Rates
When the HOG Administrative Office receives an SAE report that has occurred on a HOG trial, it is assessed for completeness and forwarded to the Study Chair and the manufacturer of the suspected drug (if applicable) for review. Each is requested to comment on relatedness, severity and the need for further information for clarification. If the SAE is determined to meet the reporting requirements as defined in the protocol, the report is forwarded to each investigative site participating in the study. The HOG Administrative Office also reviews the report against previously reported SAEs on the study. The statistical section of the protocol is referenced and the HOG statistician is consulted regarding early stopping rules and other considerations. In consultation with the Study Chair, and the statistician, the HOG will immediately suspend any arm of a trial where subject safety is being compromised. Such suspensions will be done initially via electronic mail or facsimile.

As part of its routine data review, the HOG Administrative Office monitors for SAEs that should have been reported by the institution, but were not. If an unreported SAE is detected, a notice is generated and sent to the institution asking for a complete SAE report form to be submitted within 30 days.

d) Study Progress – Quarterly Review
Study progress assessment of HOG trials to determine whether accrual projections are being met and to determine if the trial should be continued based upon the likelihood

of timely completion are reviewed at quarterly IUCC CTMC meetings. Cumulative reports of adverse events requiring expedited reporting and any new adverse events requiring expedited reporting are also reviewed at the committee's quarterly meetings.

An overall assessment of accrual, toxicities as described in the protocol, and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. The information is provided to the CTMC by the HOG office. The committee may request further information from the Study Chair.

1. The CTMC recommendations for modifications to the trial are forwarded to the Study Chair, and HOG Statistician for consideration of implementation. At this time the Study Chair may submit to the CTMC additional information. The Study Chair may ask the Clinical Research Committee to review the decision. The Study Chair and the HOG office will notify all investigators involved with the study, the IRB, and funding agency and provide written documentation of these notifications to the CTMC. The HOG office will then notify the drug manufacturers. The HOG Chief Medical Officer and Statistician will oversee these activities

14.0 DRUG REQUIREMENTS

Cisplatin is to be supplied by the patient or third party payer. Etoposide is to be supplied by the patient or third party payer. Docetaxel is to be supplied by the patient or third party payer.

15.0 PATIENT CONSENT AND PEER REVIEW

Changes to the protocol, as well as a change of principal investigator, must be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

Written informed consent must be obtained prior to entry of any patient onto study. No patient may be entered on study, until documentation of review and approval by the Institutional Review Board is on file at the Hoosier Oncology Group.

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Appendix I

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

Common Toxicity Criteria Version 2.0
http://ctep.info.nih.gov/CTC3/ctc.htm

APPENDIX II: Performance Status Scale

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

KARNOFSKY ACTIVITY	KARNOFSKY SCORE	ECOG GRADE	ECOG ACTIVITY
Normal, no complaints	100	0	Fully active, able to carry on all predisease activities without restrictions
Normal, only minor signs/symptoms	90		
Normal activity, but requires effort	80	1	Not able to perform physically strenuous activity, but ambulatory and able to carry out light or sedentary work (eg., office work, light house work)
Unable to do active work, but able to care for self	70		
Able to care for most needs, requires occasional help	60	2	Ambulatory/capable of all self-care, unable to perform any work activities Up and about more than 50% of waking hours
Requires frequent medical help and considerable assistance	50		
Disabled, needs special	40	3	Capable of only limited care and assistance self-care, confined to bed or chair more than 50% of waking hours
Severely disabled, needs hospitalization, death not imminent	30		
Very sick, hospitalized, active support needed	20	4	Completely disabled, totally confined to bed or chair. Cannot carry on any self-care.
Moribund	10		
Dead	0	5	Dead

Hoosier Oncology Group

APPENDIX III

1. Protocol Number:	2. Site:	3. Subject Number:	4. Subject Initials:

FAX Immediately to 317.921.2053

5. Date Form Completed (dd/Mmm/YY): _ _ /_ _ _ /_ _

6. Report: ☐ Initial ☐ Follow-up report and number: _____ ☐ Final

7. Country of occurrence:

8. Date of Birth _ _ / _ _ _ / _ _ (dd/mmm/YY)	9. Gender (M/F)	10. Race (Specify)	11. Weight _____ ☐ kgs ☐ lbs	12. Height (cm or in) _____ ☐ cm ☐ in

13. Reason for Serious (✓ all that apply)

☐ **Death**

Primary Cause of Death: _____

Date of Death (dd/Mmm/YY): _ _/_ _ _/_ _

Autopsy Performed? ☐ Yes ☐ No

☐ **Hospitalization:** ☐ Initial ☐ Prolonged

Date of Admission (dd/Mmm/YY):_ _/_ _ _/_ _

Date of Discharge (dd/Mmm/YY): _ _/_ _ _/_ _

☐ **Life-threatening**

☐ **Persistent/significant disability/incapacity**

☐ **Congenital Anomaly**

☐ **Required Intervention to Prevent One of the Above Outcomes**

☐ **Medically Important** (specify) _____

_____

14. List all adverse events considered serious in the context of this SAE

Adverse Event	Grade CTC v 2.0	Date of Onset (dd/Mmm/YY)	Relationship 1=Unrelated 2=Remote 3=Possibly 4=Probably 5=Definitely		Outcome 1=Recovered 2=Recovered with sequelae 3=Not yet recovered 4=Fatal 5=Unknown	Outcome Date (dd/Mmm/YY)
			Sponsor Study Drug	additional Study drug(s)		
1.						
2.						
3.						
4.						
5.						
6.						
7.						

15. Description of the event *Describe the events and their course, treatment administered, and any other relevant information.*

16. Details of Study Drug

Unit dose and units	Frequency	Total Dose	Start Date (dd/Mmm/YY)	Stop Date or Ongoing (dd/Mmm/YY)	Batch Number or Lot Number

17. Indication for Study Drug: _____

18. Details of Additional Study Drugs given

Additional Study Drug Name	Unit dosage and units	Frequency	Start Date (dd/Mmm/YY)	Stop Date or Ongoing (dd/Mmm/YY)

19. Action taken with Study Drugs as a result of the SAE

- ☐ None
- ☐ Drug Therapy Administered
- ☐ Decreased Sponsor study drug Dose
- ☐ Decreased additional study drug Dose
- ☐ Delay Sponsor study drug Treatment
- ☐ Non- drug Therapy Administered
- ☐ Discontinue Sponsor study Drug Dose
- ☐ Discontinue additional study drug
- ☐ Delay additional study drug Treatment

20. Status of subject at time of event

- ☐ Still in trial
- ☐ Withdrawn
- ☐ Lost to Follow-up

21. Concomitant drugs *List only relevant medications. Do not list any drugs used in the treatment of the event.*

Drug	Dose/Frequency	Start Date (dd/Mmm/YY)	Stop Date or Ongoing	Indication

Exclude drugs used for Treatment of Event

22. Relevant Medical History *Describe any "relevant" medical history present at the time of the SAE*

23. Relevant Test/Laboratory Data *Describe any "relevant" information from autopsy report, death certificate, discharge summary, scans, and lab reports.*

24. Investigator's Name *please print*	**Investigator's Signature**
25. Reporter's Name *please print*	**Reporter's Signature**
Reporter's role in the study: _____	**Date (dd/Mmm/YY):** _ _ /_ _ _/_ _
Tel: _____ **Fax:** _____	

For Office Use Only Initial Date of Receipt (dd/Mmm/YY):	For CRO Use Only CRO SAE No.:

APPENDIX IV
CONFIRMATION PAGE # 1

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

Patient Information

Patient Initials	Date of Birth	Age of Pt	Sex of Pt	Race of Pt	SS#
State	**Zip**	**Date of First Treatment**	**Date of Registration**	**Investigator**	**Study Center**

NOTE: Please submit radiation materials as specified in Appendix VIII within two weeks of beginning radiation therapy

	PLEASE CONFIRM THE FOLLOWING:	DATE	VALUE	YES	NO	N/A
1	Does the patient have a confirmed histologic or cytologic evidence of unresectable stage IIIA or stage IIIB (use Appendix VII as a worksheet) non-small cell lung cancer? **NOTE**: 1. Unresectable stage IIIA will be defined by the following criteria: a.N2 mediastinal lymph nodes must be multiple and/or bulky on CT scan such that in the opinion of the treating investigator, the patient is not a candidate for surgical resection. b.N2 disease must be documented by biopsy, FDG-PET scan imaging, or by CT if nodes are > 2 cm on CT scan. 2. Stage IIIB patients must have N3 or T4 status. N3 status must be documented by one of the following criteria: a.Contralateral (to the primary tumor) mediastinal lymph node, supraclavicular or scalene lymph nodes proven by biopsy, FDG-PET scan imaging, or by CT if nodes are > 2 cm on CT scan. b.Patients with positive supraclavicular or scalene lymph nodes must not have disease extending up into the cervical region.	Date of Evaluation	Stage			
2	Does the patient have malignant pleural effusions? **NOTE:** The only exception is a patient with a pleural effusion visible only on CT scan (and not visible on CXR) OR deemed too small to tap.					
3	Does the patient have pericardial effusions?					

	PLEASE CONFIRM THE FOLLOWING:	DATE	VALUE	YES	NO	N/A
4	Does the patient have superior sulcus (Pancoast tumors)?					
5	Does the patient have adequate marrow reserve?					
	Does the patient have an absolute neutrophil count (ANC) $\geq$ 1500/mm^3? **NOTE:** Values must be obtained within 14 days prior to starting therapy.		mm^3			
	Does the patient have platelets $\geq$100,000/mm^3? **NOTE:** Values must be obtained within 14 days prior to starting therapy.		mm^3			
	Does the patient have hemoglobin $\geq$ 8 g/dL? **NOTE:** Values must be obtained within 14 days prior to starting therapy.		g/dL			
6	Does the patient have adequate renal function?					
	Does the patient have serum creatinine $\leq$2 mg/dL? **NOTE:** Values must be obtained within 14 days prior to starting therapy.		mg/dL			
	- OR -					
	Does the patient have calculated creatinine clearance $\geq$ 50 cc/min (see Section 4.1.11)? **NOTE:** Values must be obtained within 14 days prior to starting therapy.		cc/min			
7	Does the patient have adequate hepatic function?					
	Does the patient have bilirubin $\leq$ institutional ULN? **Bilirubin ULN = _____ mg/dL** **NOTE:** Values must be obtained within 14 days prior to starting therapy.		mg/dL			
	Does the patient have AST $\leq$ 2.5 x institutional ULN and alkaline phosphatase $\leq$ ULN? AST ULN = _____ U/L **NOTE:** Values must be obtained within 14 days prior to starting therapy.		U/L			
	- OR -					
	Does the patient have alkaline phosphatase $\leq$ 4 x institutional ULN and AST $\leq$ ULN? Alkaline Phosphatase ULN = _____ U/L **NOTE:** Values must be obtained within 14 days prior to starting therapy.		U/L			
8	Does the patient have pre-registration FEV1 > 1 liters by spirometry? **NOTE:** Must be obtained within 42 days prior to starting therapy.		L			

	PLEASE CONFIRM THE FOLLOWING:	DATE	VALUE	YES	NO	N/A
9	Does the patient have CNS metastases? **NOTE:** Patients must have a brain CT or MRI to document no CNS metastases within 28 days prior to study treatment.	CT/MRI Date				
10	Does the patient have measurable or evaluable disease documented by CT, MRI, X-ray or physical exam? **NOTE:** Must be obtained within 28 days prior to starting therapy.	Date of Evaluation				
11	Has the patient received any prior chemotherapy or radiotherapy for lung cancer?					
12	Does the patient have an ECOG performance status of 0 or 1?		PS			
13	Has the patient had unintended weight loss of > 5% body weight in the preceding 3 months prior to beginning study therapy?					
14	Does the patient have symptomatic peripheral neuropathy > grade 1 prior to beginning study therapy?					
15	Has the patient had a prior history of malignancy in the last 5 years? **NOTE:** With the exception of adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer.					
16	Does the patient have significant history of cardiac disease (i.e. uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the past year, or cardiac ventricular arrhythmias requiring medication)?					
17	Does the patient have a history of allergic reactions to drugs utilizing the vehicle polysorbate 80 (docetaxel) and polysorbate 80 + polyethylene glycol (etoposide)?					
18	Is the patient pregnant or nursing?					
19	If the patient is a female of childbearing potential: Has a negative urine pregnancy test been obtained within 14 days prior to beginning study therapy?					
20	If the patient is of childbearing potential: Has the patient (male or female) agreed to use effective contraception while on treatment and for a four-week period thereafter? **NOTE:** A 6-month period of effective contraception following completion of protocol treatment is recommended, however, not required for participation.					
21	Is the patient as least 18 years of age?					

	PLEASE CONFIRM THE FOLLOWING:	DATE	VALUE	YES	NO	N/A
22	Has the patient given written informed consent and authorization for release of personal health information?					

NOTE: If the patient has hearing loss at baseline, performance of an audiogram is recommended (not required) to document baseline hearing status in the event of possible further hearing loss due to cisplatin administration.

Signature: _____ Date: _____

Printed Name: _____

Complete and fax this form along with the IRB approved, signed informed consent statement to the HOG office @ 317-921-2053.

Following completion of induction chemo-radiotherapy patients without local progression of disease or distant metastases will then be randomized to receive consolidation therapy with docetaxel or observation. Patients will be stratified and randomized based on stage IIIA vs. IIIB disease at baseline, CR vs. non-CR following induction chemo-radiation, and ECOG PS 0 or 1 vs. 2. **CONFIRMATION FORM #2 is to be submitted for randomization to consolidated therapy with docetaxel or observation.**

CONFIRMATION OF REGISTRATION

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

To be completed by registration center and faxed back to site

Your patient _____ (patient's initials) has been registered to LUN01-24

The patient's HOG ID # is _____

REMINDERS:

- Please submit radiation materials as specified in Appendix VIII for review within two weeks of beginning radiation therapy, as per protocol
- Submit confirmation page #2 for randomization to consolidation with docetaxel or observation after completion of induction therapy, if patient is without local progression of disease or distant mets.

Signed (registering agent) _____ Date _____

Appendix V:

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APPENDIX VI
CONFIRMATION PAGE #2

(To be submitted following induction therapy for randomization to consolidation therapy with docetaxel or observation)

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

Date of Randomization (to consolidation therapy OR observation)		**Date of Registration** (for induction therapy)	**Date of Last Treatment** (for induction therapy)
Patient Initials	**HOG ID #**	**Investigator**	**Study Center**

	PLEASE CONFIRM THE FOLLOWING:	**DATE**	**VALUE**	**YES**	**NO**	**N/A**
1	Has the patient completed chemo-radiotherapy per protocol?					
2	Has at least 4 weeks but no more than 8 weeks elapsed from the last day of induction therapy (the last day of radiation)?					
3	Has the patient undergone re-staging tests according to the study calendar and been determined to have no evidence of disease progression?					
4	Does the patient have adequate marrow reserve?					
	Does the patient have an absolute neutrophil count (ANC) $\geq$ 1500/mm^3? **NOTE:** Values must be obtained within 14 days prior to starting consolidated therapy.		mm^3			
	Does the patient have platelets $\geq$100,000/mm^3? **NOTE:** Values must be obtained within 14 days prior to starting consolidated therapy.		mm^3			
	Does the patient have hemoglobin $\geq$ 8 g/dL? **NOTE:** Values must be obtained within 14 days prior to starting consolidated therapy.		g/dL			

	PLEASE CONFIRM THE FOLLOWING:	DATE	VALUE	YES	NO	N/A
5	Does the patient have adequate hepatic function?					
	Does the patient have bilirubin ≤ institutional ULN? **Bilirubin ULN = _____ mg/dL** **NOTE:** Values must be obtained within 14 days prior to starting consolidated therapy.		mg/dL			
	Does the patient have AST ≤ 2.5 x institutional ULN and alkaline phosphatase ≤ ULN? AST ULN = _____ U/L **NOTE:** Values must be obtained within 14 days prior to starting consolidated therapy.		U/L			
	- OR -					
	Does the patient have alkaline phosphatase ≤ 4 x institutional ULN and AST ≤ ULN? Alkaline Phosphatase ULN = _____ U/L **NOTE:** Values must be obtained within 14 days prior to starting consolidated therapy.		U/L			
6	Does the patient have symptomatic peripheral neuropathy > grade 1?					

FOR STRATIFICATION:

Today, the patient's ECOG performance is (circle one): 0 1 2

At baseline, the patient's stage of disease was (circle one): IIIA IIIB

Following induction chemoradiotherapy, the patient's response was (circle one): CR PR Stable

Signature: _____ Date: _____

Printed Name: _____

Complete and fax this form to the HOG office @ 317-921-2053.

Following completion of induction chemo-radiotherapy patients without local progression of disease or distant metastases will then be randomized to receive consolidation therapy with docetaxel or observation. Patients will be stratified and randomized based on stage IIIA vs. IIIB disease at baseline, CR vs. non-CR following induction chemo-radiation, and ECOG PS 0 or 1 vs. 2.

Hoosier Oncology Group

CONFIRMATION OF RANDOMIZATION

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

To be completed by registration center and faxed back to site

HOG Patient ID #: _____

Date of randomization: _____

The patient has been randomized to (circle one):

Consolidated docetaxel **Observation only**

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APPENDIX VII: TNM STAGING CRITERIA
A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

Primary tumor (T)	
TX	Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
T0	No evidence of primary tumor.
Tis	Carcinoma *in situ*.
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than lobar bronchus (i.e., not in main bronchus).
T2	Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves the visceral pleura; or Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, or pericardium; tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; or tumor with a malignant pleural effusion or pericardial effusion, or satellite nodule(s) within the primary bearing lobe.
Lymph node (N):	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including direct extension.
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s).
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
Distant Metastasis (M):	
MX	Presence of distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis.

Stage 0	Tis
Stage IA	T1, N0, M0
Stage IB	T2, N0, M0
Stage IIA	T1, N1, M0
Stage IIB	T2, N1, M0
	T3, N0, M0
Stage IIIA	T1-3, N2, M0
	T3, N1, M0
Stage IIIB	T4, Any N, M0
	Any T, N3, M0
Stage IV	Any T, Any N, M1

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APPENDIX VIII: RAPID REVIEW SUBMISSION FORM
HOOSIER ONCOLOGY GROUP

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Oncology Group LUN01-24

Please submit all data for each patient within two weeks of the patient starting treatment. This is to include: prescription, relevant CT scans and films, treatment plan for each phase of treatment and detailed dose-volume histograms for the complete treatment course to the final prescribed dose. **Please submit data for the initial, boost and composite treatment course together**. Using the table below, please check to verify that all requested information is included.

The following directions are to be used when submitting planning materials for the above referenced study:

1. HOG Patient Initials/ID Number_____

2. Date of Shipment_____

3. The following are requested materials: (please mark appropriately)

MATERIAL:	Is material available (Y/N):	If YES: Date of Study:	Reviewer's Remarks:	Date of Confirmation Per Dr. McGarry:
Prescription				
CT scans/films				
Initial Treatment Plan				
Boost Treatment Plan				
Dose-volume histograms for the complete treatment course to the final prescribed dose.				

4. Name and contact information of sender (please use address, telephone, fax and email address):

_____

_____

_____

Please safely package the materials and ship to the following address with this form and a copy of any applicable reports:

Indiana Cancer Pavilion
Attn: Jill DeLuca or Kathy Tudor
535 Barnhill Dr. RT 041
Indianapolis, IN 46202
(317) 274-1189
(317) 274-0611 (FAX)
jdelucca@iupui.edu or ktudor@iupui.edu

Please call the HOG Office with any questions regarding shipping, and to obtain the account number for billing purposes. 371.921.2050 or 800.732.4464

Hoosier Oncology Group

APPENDIX IX. INCLUSION/EXCLUSION EXCEPTION FORM

Protocol Number: LUN01-24 **Date Exception Requested: _____**

Investigator:	**Site Number:**	**Patient Initials:** ☐☐☐
Phone:	**Fax:**	**Patient Date of Birth:** ☐☐ MM ☐☐ DD ☐☐ YY

Instructions:

1. **Study Center**: Fax completed form to HOG at 317-921-2053. Keep this form with investigator's study files.
2. **Study Chair/HOG Representative**: Complete the form indicating whether exception is granted. A signature or telephone order is required for all requests regardless of whether they are granted.
3. **HOG:** Fax this form back to the site.

EXCEPTION REQUESTED FOR THE FOLLOWING ELIGIBILITY CRITERIA		**For Study Chair:**				
CRITERION (Note specific eligibility criteria and item number)	**COMMENTS**	**Granted**		**COMMENT** (e.g., specific lab value, specific disease, etc.)	**SIGNATURE**	**DATE**
		Yes	**No**			

Patient ID Number:
(To be completed after registration) ☐☐☐☐☐☐☐