

## North Central Cancer Treatment Group

**Phase I/II Study of PS-341 in Combination with Paclitaxel, Carboplatin, and Concurrent Thoracic Radiation Therapy for Non-Small Cell Lung Cancer (NSCLC)**

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**DCTD Supplied Investigational Agents: PS-341 (NSC #681239)**

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**Study Participants**    **Date Activated**  
Entire NCCTG                      September 17, 2004  
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Protocol Resources

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\* No waivers of eligibility per NCI

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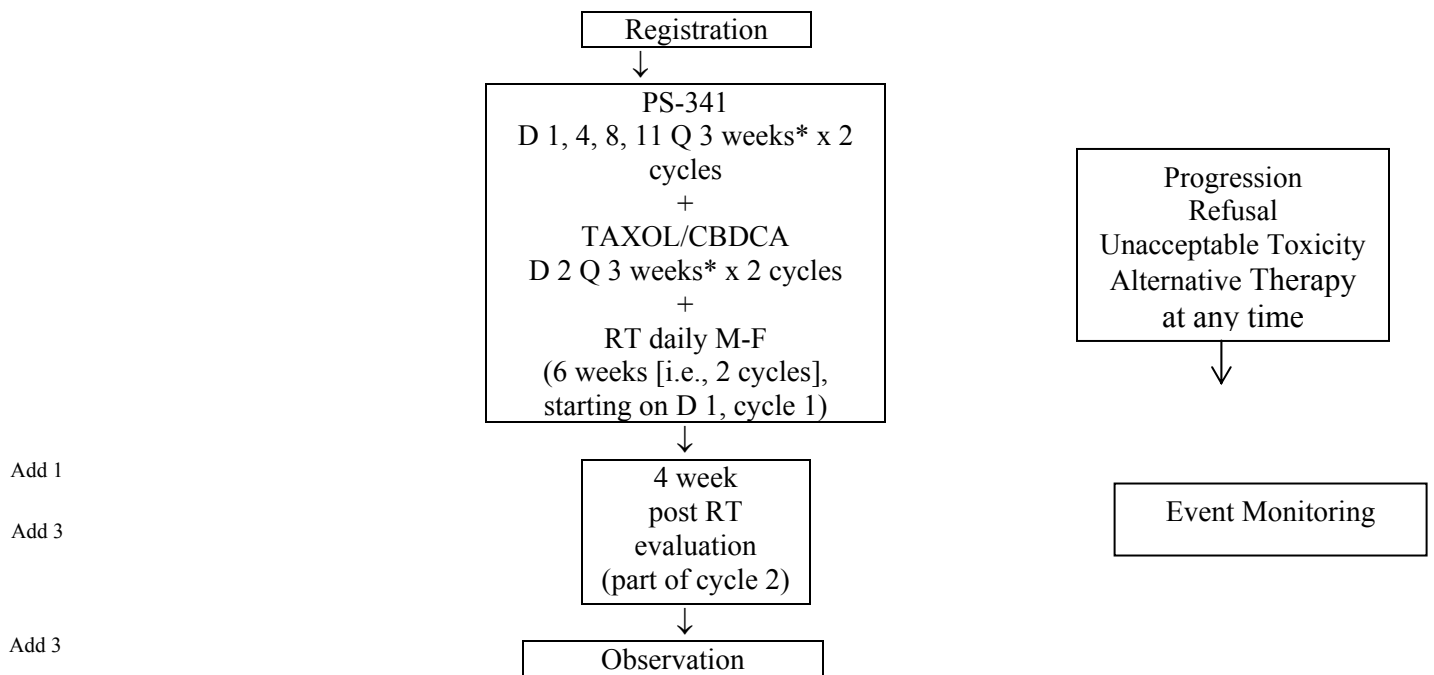
**Schema - Phase I Component**

**Phase I Component- Open to whole NCCTG membership.**

Add 12 **As of Addendum 12, the Phase I portion of the study is complete. The Phase II portion of the study is now open at dose level 6 (see Section 7.0).**

Add 9 **Prior to discussing protocol entry with the patient, call the Registration Office to ensure that a place on the protocol is open to the patient. If an opening is available, a slot may be reserved for no longer than 5 working days.**

**Notification of opening of the Phase II Component will be made via a status update notice.**



Add 1

Add 3

Add 3

Add 3

\*Cycle 1 length = 3 weeks

Cycle 2 length = 7 weeks (last 3 weeks of chemo/RT + 4-week post-RT evaluation)

Dose level	PS-341 mg/m <sup>2</sup>	Paclitaxel mg/m <sup>2</sup>	CBDCA AUC
-1	0.5	120	5
0	0.5	135	5
<b>**1</b>	<b>0.5</b>	<b>150</b>	<b>5</b>
2	0.8	150	5
3	1.0	150	5
4	1.0	175	5
5	1.0	175	6
6	1.2	175	6

**\*\* starting dose level**

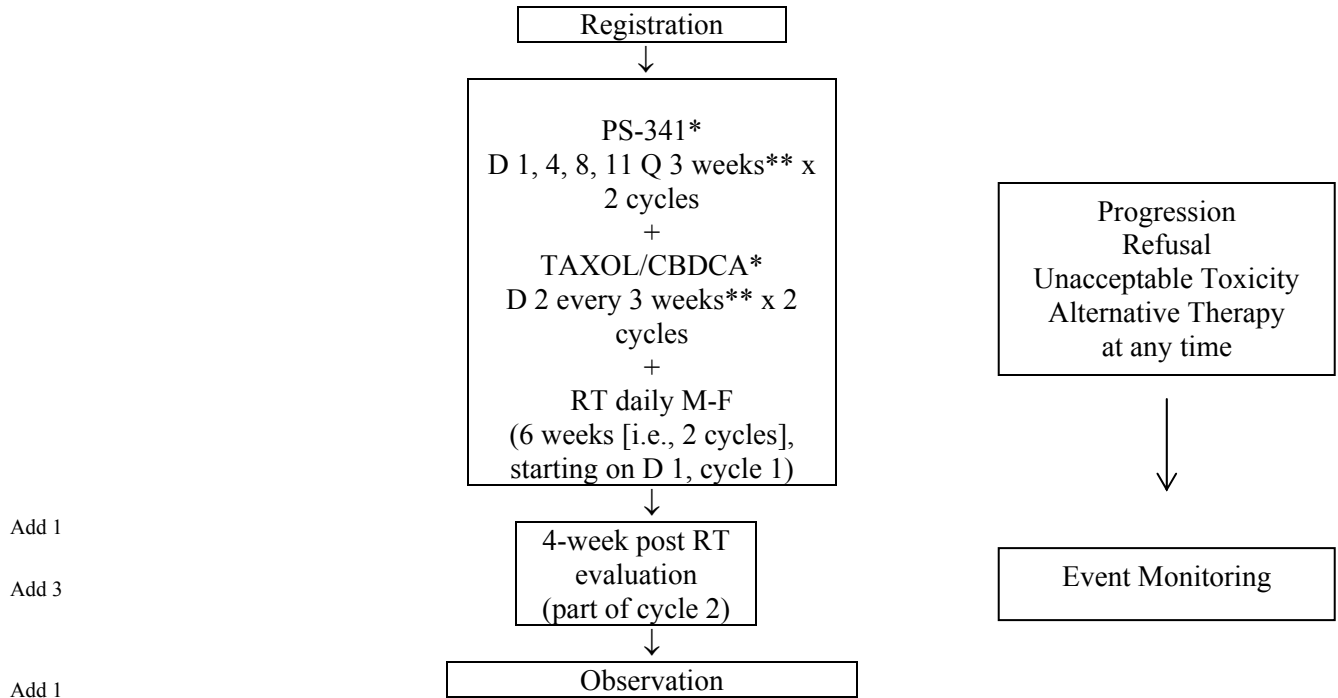
Add 9

Generic name: Bortezomib	Generic name: Paclitaxel	Generic name: Carboplatin
Brand name: Velcade™ (Millenium)	Brand name: Taxol™ (Bristol-Myers-Squibb)	Brand name: Paraplatin™ (Bristol-Myers-Squibb)
Mayo abbreviation: PS341	Mayo abbreviation: TAXOL	Mayo abbreviation: CBDCA
Availability: Provided by NCI	Availability: Commercial	Availability: Commercial

### Schema - Phase II Component

After the recommended maximum tolerated dose (MTD) has been determined in the Phase I Component, patients will continue to be enrolled from the whole NCCTG membership.

Add 12 As of Addendum 12, the Phase II portion of the study is now open.



Add 1

Add 3

Add 1

Add 3

Add 3,  
12

\* **Dose level 6 was selected from the Phase I portion of the trial (see Section 7.0 for dose information).**

\*\* **Cycle 1 length = 3 weeks  
Cycle 2 length = 7 weeks (last 3 weeks of chemo/RT+ 4-week post-RT evaluation)**

Add 1

## 1.0 Background

### 1.1 Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the most common cause of cancer deaths in the United States with an estimated-annual mortality in excess of 160,000 (1). The vast majority of patients with lung cancer are not cured and the overall 5-year survival rate is 11% to 14% (1). Most patients with lung cancer have non-small cell lung cancer (NSCLC) and the mainstay of treatment for these patients is surgical resection. Only 25% to 30% of patients with NSCLC have resectable disease (stage I or II) at the time of diagnosis (2). The 5-year survival rate with surgical treatment in these patients approaches 40% (2). Patients with stage-IIIa disease have been treated with either radiation or, in selected cases, surgical resection. Patients with stage IIIB disease without pleural effusion are treated with radiation therapy. Median survival with radiation alone is only 9 to 13 months, and the 5-year survival rate is only 5% to 10% (3-7). Because of the poor-curative potential of radiation therapy and surgical approaches, combined chemotherapy and radiation therapy are commonly used.

### 1.2 Radiation Therapy in the Treatment of NSCLC

The traditional therapy for locally advanced inoperable lung cancer was RT alone. The RTOG performed a randomized prospective study comparing the use of 40 Gy in 20 fractions with 50 Gy in 25 fractions, and 60 Gy in 30 fractions. The clinically determined local failure rate (determined with serial chest x-rays) was 48% with 40 Gy, 38% with 50 Gy, and 27% with 60Gy. The differences in survival were not significant. This RTOG study defined the standard technique used at most centers in the US to include the delivery of 60 Gy in 30 fractions. Conventional RT (60Gy/30 fractions) alone resulted in a median survival of 10 months and 5-year survival rate of 5%.

### 1.3 Combination of Chemotherapy and Radiation Therapy in the Treatment of NSCLC:

Randomized prospective studies have demonstrated a significant survival advantage for patients who receive chemotherapy in addition to RT for locally advanced NSCLC. The CALGB reported that induction chemotherapy (cisplatin plus vinblastine) followed by conventional RT (60Gy in 30 fractions) yielded significantly better survival than conventional RT alone. The median survival time was 13.7 months for the combination therapy as compared to 9.6 months for RT alone ( $p=0.012$ ). The five-year survival rates were 17% for those who received RT plus chemotherapy as compared to 6% for those who received RT alone (8). A confirmatory RTOG and ECOG trial randomized patients to receive either conventional RT (60Gy/30 fractions) alone, hyperfractionated RT (69.6 Gy in 1.2 Gy fractions BID) alone, or the CALGB program (cisplatin plus vinblastine followed by 60Gy/30 fractions). The 4-year and median survivals were as follows: chemotherapy plus RT 11%, 13.7 months, hyperfractionated RT 9%, 12.2 months, and standard RT 4%, 11.4 months. The survival rates achieved with chemotherapy and RT were significantly better than the RT alone arms, log rank  $p=0.04$  (8).

### 1.4 Concomitant chemo-radiation may be superior but is more toxic than sequential therapy:

Chemotherapy and radiotherapy typically are combined for treatment of NSCLC with the two treatment modalities delivered either sequentially or concurrently. There are two randomized phase III clinical trials that have specifically addressed which method of combining therapy is superior. The RTOG performed a randomized prospective study (RTOG 9410) comparing chemotherapy plus either BID RT or QD RT for locally advanced

NSCLC(9). This trial included patients with inoperable stage II and III NSCLC, good performance status, and little weight loss. Patients were randomized into 3 arms and received either sequential therapy with cisplatin and vinblastine followed by 60 Gy in 30 daily fractions (SEQ QD RT arm), concurrent therapy with cisplatin, vinblastine, and 60 Gy in 30 daily fractions (CON QD RT arm), or concurrent BID RT (69.6 Gy in 1.2 Gy BID fractions) with cisplatin and oral etoposide (CON BID RT arm). The median survival was 17 months in the CON QD RT arm, 14.6 months in the SEQ QD RT arm, and 16 months in the CON BID RT arm. The difference in survival between the CON QD RT arm and the SEQ QD RT arm was significant ( $p=0.038$ ). There was significantly more acute grade  $\geq 3$  non-hematologic toxicity among patients who had CON BID RT (63%) as compared with SEQ QD RT (31%) ( $p = 0.001$ ) and CON-QD RT (50%) ( $p = 0.011$ ).

In a second study, the West Japan Lung Cancer Group randomized 320 patients to receive either concurrent cisplatin, vindesine, and mitomycin with 56 Gy split-course delivered over 7 weeks or the same chemotherapy delivered prior to 56 Gy continuous course RT delivered in 5½ weeks (10). Survival was superior with concomitant chemo/RT with a median survival of 16.8 months versus 13.3 months with sequential therapy ( $p=0.04$ ). The incidence of Grade 3 and 4 esophagitis and stomatitis was similar between the two groups and presumably reflects the split course radiation regimen used with the concurrent chemotherapy group. The toxicity of concurrent chemoradiotherapy was specifically addressed in a combined analysis of 5 RTOG trials (RTOG 88-04, 88-08, 90-15, 91-06, 92-04, 92-04) (11). In this analysis, toxicities were reviewed for patients treated on one of three treatment regimens: 1) sequential CT/standard RT, 2) induction CT followed by concurrent CT/standard RT, and 3) concurrent CT with hyperfractionated RT. The overall incidence of grade 4 or 5 acute toxicity in these studies was approximately 50% for all groups, but the incidence of acute non-hematologic and esophageal toxicities were significantly higher in patients treated with concurrent chemotherapy and hyperfractionated radiation (Table 1). The other salient feature of the toxicity data presented in Table 1, is that aggressive radiotherapy and chemotherapy for lung cancer is associated with significant toxicity and that this level of toxicity is acceptable because of the poor prognosis of unresectable NSCLC.

**TABLE 1:** Toxicity data from RTOG studies with combined chemotherapy/radiation therapy regimens (11).

Toxicity	Sequential CT/RT	Ind./Concur. CT/RT	Concur. CT/hyper. RT
Overall — grade 4	51%	52%	48%
non-hematologic — grade 3	27%	34%	55%
esophageal — grade 3	1.3%	6%	34%

### 1.5 The Ubiquitin-Proteasome System

The ubiquitin-proteasome system degrades proteins involved in cell cycle regulation, cell survival, and metastasis such as p53, p21, p27 and NFkB (12). This fundamental role for the proteasome singles it out as a unique target for anticancer therapy. PS341 is a dipeptidyl boronic acid that inhibits the 20S proteasome with a  $K_i$  of 0.6 nM, and PS-341 is the first proteasome inhibitor to enter human trials. We have performed phase I studies with PS-341

administered in 2 schedules, twice weekly for 2 out of every 3 weeks, or twice weekly for 4 out of every 6 weeks. Based on chronic toxicities, the recommended phase II dose and schedule was 1.5 mg/m<sup>2</sup>, administered twice weekly for 2 out of 3 weeks. The most common and dose-limiting toxicities were fatigue and thrombocytopenia. Other toxicities were fever, myalgia, nausea and vomiting (13). Preliminary evidence of activity has been seen in NSCLC, prostate cancer and multiple myeloma. Broad phase II studies, as well as phase I combination studies with cytotoxic agents are ongoing (14).

In preclinical studies, NFκB activation was demonstrated after ionizing radiation, *in vitro*. PS-341 inhibited NFκB activation and increased radiation-induced apoptosis and enhanced radiosensitivity *in vitro* and *in vivo*. Specifically, treatment with PS-341 resulted in increased apoptosis and decreased cell growth and clonogenic survival. A 7-41% increase in radiosensitivity was observed for cells treated with PS-341. An 84% reduction in initial tumor volume was obtained in LOVO xenografts receiving radiation and PS-341 (15).

We therefore hypothesize that a combination of PS-341 and radiation therapy will show synergistic antitumor killing in patients with locally advanced non-small cell lung cancer.

## 1.6 PS-341

PS-341 (Millennium Pharmaceuticals) is a small, cell-permeable molecule that specifically and selectively inhibits the proteasome by binding in a reversible manner. Chemically, PS-341 is a modified dipeptidyl boronic acid derived from leucine and phenylalanine.

PS-341 has been examined *in vitro* for its effect on cellular functions requiring the ubiquitin-proteasome pathway. It has several mechanisms of action:

- PS-341 is a potent and reversible proteasome inhibitor.
- PS-341 inhibits the growth of cultured tumor cells by blocking cell division in the G<sub>2</sub>-M phase of the cell cycle, leading to cytotoxicity via apoptosis.
- PS-341 inhibits the degradation of the wild-type tumor suppressor protein p53, but not mutated forms of this protein.
- PS-341 stabilizes the CDK inhibitor p21.
- PS-341 inhibits the activation of NF-κB by the stabilization of the inhibitor protein IκBα.
- PS-341 inhibits NF-κB dependent gene expression, as demonstrated by inhibition of cell surface adhesion molecule transcription. As a consequence of the inhibition of CAM expression, PS-341 also inhibits the adhesion of tumor cells to endothelial cells.
- Overexpression of bcl-2, an anti-apoptotic effector protein is inhibited by PS-341, leading to cell death.

The biological activity of PS-341 has been observed *in vitro*, *in vivo* and in xenograft tumor models. PS-341 was a potent cytotoxic agent toward MCF-7 human breast carcinoma cells in culture and demonstrated antitumor activity in the murine Lewis lung carcinoma model (16). According to the Investigator's Brochure (17), activity has been seen in phase I patients with advanced solid tumors, with anti-tumor response in one patient each with cancer of the prostate, kidney, head and neck and lung. 20S proteasome activity (the

catalytic sub-complex of the 26S proteasome complex) can be detected after treatment with PS-341 *in vitro*, *in vivo* and *ex vivo* in cells and tissues.

The pharmacokinetics of PS-341 are well described (17). PS-341 has a short plasma half-life following intravenous administration. Autoradiographic data indicates that PS-341 does not cross the blood-brain or blood-testes barrier. PS-341 is extensively bound to plasma proteins (83% in man). Tissue distribution of PS-341, following intravenous infusion in rats, indicates that the highest levels are found in the adrenal glands, renal cortex, liver, prostate and spleen from 10 minutes to 1, 6 and 24 hours post-infusion. Drug metabolites are excreted in both the bile and the urine.

The adverse events resulting from the administration of PS-341 at various schedules and doses tend to be mild and manageable. The Investigator's Brochure (17) identifies the following adverse events reports in PS-341 clinical studies: fatigue; pruritus; rash and other skin changes; a serum sickness-like event in one patient; fever, rigors and chills; peripheral neuropathy; myalgia; constipation, diarrhea, nausea, vomiting, anorexia, and ileus; hypotension (or hypertension), tachycardia, bradycardia and atrial flutter; anemia, thrombocytopenia and leukopenia (both neutropenia and lymphopenia); and edema and hyponatremia. In addition, instances of various pain, clotting abnormalities, renal dysfunction, abnormal liver function tests and certain central nervous system abnormalities have been reported. Diarrhea has been controlled with loperamide. Neutropenia and anemia are not major toxicities. Several Phase I studies were reported at ASCO 2001. A Memorial Sloan Kettering study reported one grade 3 painful neurosensory toxicity after 4 cycles at the dose level of 1.3 mg/m<sup>2</sup> twice weekly for two weeks. Resolution of painful neuropathy appears to be slow and over weeks. One episode of grade 3 fatigue, 1 episode of grade 3 orthostatic dehydration, 3 episodes of grade 3 diarrhea and 2 episodes of grade 3 painful neurosensory toxicity were seen at the 1.56 mg/m<sup>2</sup> dose level. In an ongoing trial at the Mayo Clinic utilizing a twice-weekly X 4 q 6 week schedule, the major toxicities were grade 3 fatigue and grade 3 thrombocytopenia.

Add 11

RPLS is a clinico-radiological entity associated with capillary leak and vasogenic edema in the brain (27,28). Clinical presentations are nonspecific and may include headache, altered mental status, seizure, and cortical visual disturbance. An MRI is required for diagnosis, typically demonstrating vasogenic edema predominantly involving the white matter of posterior parietal and occipital lobes, although gray matter and abnormalities in the anterior distributions may also be seen. [Vasogenic edema typically presents as hyperintensity in the T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequences, and hypointensity or isointensity on T1-weighted images; new MRI technologies such as diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps may help in differentiating RPLS from ischemic events.] RPLS is often reversible after correction of the underlying conditions, but in more severe cases, permanent neurological deficit may ensue. RPLS has been described in a number of clinical settings such as hypertensive encephalopathy, pregnancy/eclampsia, and renal failure, and has been reported in association with cancer drugs such as interferon- $\alpha$ , G-CSF, cyclosporine, cisplatin, capecitabine, sunitinib, bevacizumab, and others. The mechanism of bortezomib-related RPLS is unknown, but it is possible that bortezomib may induce vasogenic edema/capillary leak in the brain through direct effect on endothelial cells, and/or through indirect mechanisms related to vasospasm and hypertension.

### 1.7 PS-341 in combination with paclitaxel and carboplatin

Preclinical work performed by Teicher *et al* (18) demonstrated additive effects when PS-341 was combined with either cisplatin or paclitaxel in rodent tumor models. The chemotherapy agents were administered 3 days after PS-341 administration commenced. The cytotoxic species generated from both cisplatin and carboplatin are identical (18). Since carboplatin has a more convenient administration schedule and less severe non-hematologic toxicities, it was chosen as the platinum agent for an ongoing phase I study of PS-341, paclitaxel and carboplatin, that has accrued 27 patients to date. Because of conflicting results on the sequence-dependence of the interaction between PS-341 and paclitaxel, two sequences of drug administration, PS-341 on day 1, paclitaxel/carboplatin on day 2 and paclitaxel/carboplatin day 1, PS-341 day 2 are being studied. To date, the day 2 administration of PS-341 appears more toxic. Dose escalation on the day 1 PS-341 cohort is currently at PS-341 1.0 mg/m<sup>2</sup>, paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC = 6. The major toxicity on both arms is thrombocytopenia. Fatigue, low-grade fever and malaise has also been seen.

### 1.8a Paclitaxel/Carboplatin combined with RT:

As discussed above, concurrent chemoradiation therapy appears to be the most efficacious approach to the treatment of locally advanced NSCLC. Based on its low toxicity profile and efficacy in NSCLC, the combination of paclitaxel, carboplatin and radiation therapy has been widely studied. Most trials have examined weekly administration of systemic chemotherapy. Nguyen *et al* have studied induction chemotherapy followed by 3-weekly paclitaxel and carboplatin concomitant with radiation therapy. Following induction chemotherapy, radiation therapy started on day 43 until completion to a tumor dose of at least 5960 cGy. Cycles 3 and 4 of chemotherapy were begun on days 43 and 63, respectively, and consisted of paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours, and carboplatin at AUC 6 following paclitaxel infusion. The response rate to induction carboplatin/paclitaxel was 52%. An overall response rate (complete and partial responders) of 85% was obtained following chemotherapy and radiation. Grade 3-4 acute side effects were recorded in 9 patients (31%) and consisted of esophagitis (8 patients) and anemia (1 patient). One patient died from cachexia 3 months following treatment (3.7%). The median survival and 3-year survival were 15 months and 30%, respectively, for the remaining 27 patients at a median follow-up of 11 months. There was no difference in survival between stages IIIA and IIIB at 2 years (IIIA: 22%, IIIB: 31%). Local or regional recurrences and distant metastases developed in 9 patients (33%) and 13 patients (46%), respectively. These investigators concluded that the combination of paclitaxel, carboplatin and radiation for locally advanced non-small cell carcinoma is feasible with acceptable toxicity (19).

### 1.8b PS-341 in combination with paclitaxel, carboplatin and radiation therapy

Concurrent radiotherapy and chemotherapy appears superior to sequential therapy. Thus while there are sound pre-clinical rationale for evaluating PS-341 in combination with radiation therapy, the addition of standard chemotherapy would potentially improve outcomes. We are already evaluating the combination of PS-341, paclitaxel and carboplatin in the phase I setting, and plan to incorporate radiation therapy into this regimen.

1.8c Prediction of response to PS-341 in combination with paclitaxel, carboplatin and radiation therapy

Many molecular prognostic and predictive factors have been evaluated in lung cancer. Results from such studies have largely been equivocal, and have led to skepticism about such studies. In NSCLC, studies looking at expression of p53, bcl-2, and EGFR have yielded conflicting results. Part of the explanation for conflicting results have been the different methodologies and antibodies used for immunohistochemical staining. Also, there are several instances of a dichotomy between genetic mutations, which can affect protein function, and protein expression itself. Another major drawback in this area of research has been the paucity of available interventions once a poor prognostic marker is found. Despite its potential role as a tumor suppressor, the p27 gene, a member of the Cip/Kip family of cyclin-dependent kinase inhibitor genes, has never been found mutated in human tumors. Esposito and colleagues investigated p27 protein expression in a series of 108 non-small cell lung cancers (57.4% stage 1, 16.7% stage 2, and 25.9% stage 3) and found that tumors expressing low to undetectable levels of p27 contained high p27 degradation activity. When the outcome of the patients was evaluated in relationship to p27 expression, lack of expression of p27 was found to be a prognostic factor correlating with poor overall survival times ( $P = 0.0012$ ) [20]. Further studies have demonstrated the involvement of the proteasome-mediated proteolysis in p27 degradation. Thus, by inhibiting p27 degradation, PS-341 should improve the outcome of this subset of NSCLC patients.

We have previously demonstrated the accumulation of p27 in A549 cells treated with PS-341 (Davis J and Adjei AA, unpublished observations). The following lab correlates will be included: Measurement of p27 in tissue blocks of patients will be done by immunohistochemistry, a procedure for which considerable expertise exists in our group. The expression of p27 will be correlated with response to PS-341. An inverse correlation is hypothesized. We continue to evaluate tumor biopsies obtained from our phase I study of PS-341 in solid tumors. Any proteins that will be found to be potentially involved in the cytotoxicity of PS-341 will be evaluated in the tissue blocks of patients.

1.8d Summary of the Phase I portion of this trial:

Add 12

As of Addendum 12, the Phase I portion of the trial was completed. Dose Level 6 (PS-341 1.2 mg/m<sup>2</sup>; Paclitaxel 175 mg/m<sup>2</sup>; CBDCA AUC = 6) was selected as the dose level to move forward into Phase II testing. At this dose level, we observed 1 dose-limiting toxicity (DLT) in the first 5 patients. The DLT was a grade 4 neutropenia that lasted 8 days and was definitely related to the study treatment. Per protocol, dose level 6 was found to be tolerable, since 0-2 DLT's were allowed in 6 patients enrolled, and a maximum of 2 DLT's in 6 patients was possible for dose level 6. The maximum tolerated dose (MTD) was never actually reached for this study, but we decided to proceed to the Phase II portion at the highest dose level defined in the protocol (dose level 6).

**2.0 Goals**

2.1 Phase I Component

To determine the maximally tolerated dose (MTD) of PS-341/Paclitaxel/Carboplatin, given in conjunction with fractionated daily radiation therapy.

2.2 Phase II Component

2.21 Primary: To assess the 1-year survival of patients treated with this regimen.

2.22 Secondary:

2.221 To assess the tolerability of this regimen

2.222 To assess the response rate, progression-free survival and overall survival of patients treated with this regimen.

2.223 To study the association of p27 expression in tumor with survival, time to progression, and response.

**3.0 Patient Eligibility- (Applies to the Phase I and Phase II portions of the trial.)**Add 9,  
12

## 3.1 Required Characteristics

3.11  $\geq 18$  years of age.

3.12 Histologic or cytologic confirmation of non-small cell lung carcinoma.

Add 4

3.13 Non-metastatic NSCLC requiring definitive radiation therapy.

3.14 ECOG performance score (PS) 0 or 1.

3.15 Life expectancy  $\geq 12$  weeks.3.16 Weight loss  $< 10\%$  in past 3 months.3.17 Forced expiratory volume in 1 second (FEV1)  $\geq 1$  L or  $\geq 35\%$  of predicted.

Add 4

3.18 Locally advanced NSCLC stages IIIA/IIIB not considered resectable. Patients with stage IV disease are not eligible.

3.19a The following laboratory values obtained  $\leq 21$  days prior to registration:

- ANC  $\geq 1500/\text{mL}$
- PLT  $\geq 100,000/\text{mL}$
- Total bilirubin  $\leq 1.5 \times \text{UNL}$  or direct bilirubin  $\leq 1.5 \times \text{UNL}$
- AST  $\leq 3 \times \text{UNL}$
- Creatinine  $\leq 1.5 \times \text{UNL}$

3.19b Negative serum pregnancy test done  $\leq 7$  days prior to registration, for women of childbearing potential only.

## 3.2 Contraindications

3.21 Any of the following:

- Pregnant women
- Nursing women
- Men or women of childbearing potential or their sexual partners who are unwilling to employ adequate contraception (condoms, diaphragm, birth control)

pills, injections, intrauterine device [IUD], or abstinence, etc.) as this regimen may be harmful to a developing fetus or nursing child

*NOTE: This study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.*

- 3.22 Any of the following prior therapies:
- Prior radiation therapy to the chest
  - Prior systemic chemotherapy for NSCLC (phase II portion)
- 3.23 New York Heart Association classification III or IV (see Appendix II).
- 3.24 Any other severe underlying diseases which are, in the judgment of the investigator, inappropriate for entry into this study.
- 3.25 uncontrolled infection.
- 3.26 Major surgery or unhealed wound  $\leq 2$  weeks prior to registration.
- 3.27 Prior history of malignancy  $\leq 5$  years, except for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas (carcinoma in situ), or localized prostate cancer.
- 3.28 Peripheral neuropathy  $\geq$  grade 2.

**4.0 Test Schedule**

Add 1,3

Tests and procedures	≤21 days prior to registration	Wkly during RT	Prior to each cycle	4 wks post RT (part of cycle 2)	Observation 3 months post-RT, q3 months for 1 year post-RT, and then q6 months for a maximum of 5 years from time of registration
History and exam, wt, PS	X	X		X	X
Height	X				
Rad Onc. consultation	X <sup>1</sup>				
Toxicity assessment <sup>2</sup>		X	X	X	X
Hematology group: Hgb, WBC, ANC, PLT	X	X	X	X	X
Chemistry group: (Alk Phos, SGOT, total or direct bilirubin, creatinine, glucose)	X		X		X
FEV1	X				
Tumor measurement	X <sup>3</sup>			X <sup>3</sup>	X <sup>3</sup>
Serum pregnancy test <sup>4</sup>	X				
Tissue blocks (Section 14.3)	X <sup>5</sup>				

1. This is done in order to verify that a radiation oncologist has seen and confirmed that the patient is a suitable candidate for this study.
2. See Section 10.3 for detail.
3. ≤30 days prior to registration. A CT chest to include the liver and adrenals.
4. For women of childbearing potential only. Must be done ≤7 days prior to registration.
5. Submit ≤30 days after registration.

Add 1,3

Add 3

Add 12

**5.0 Grouping Factor:** Component: Phase I patients not receiving MTD vs. Phase I patients receiving MTD +Phase II patients **As of Addendum 12, the Phase I portion of the study is complete.**

**6.0 Registration/Randomization Procedures**

6.1 Phase I Component

**Phase I Component – Open to whole NCCTG membership.**

Add 12

**As of Addendum 12, the Phase I portion of the study is complete.**

Add 9

**Prior to discussing protocol entry with the patient, call the Registration Office to ensure that a place on the protocol is open to the patient. If an opening is available, a slot may be reserved for no longer than 5 working days.**

Add 9

6.11 To register a patient, call (507/284-4130) or fax (507/284-0885) a completed eligibility checklist to the Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

- Add 1,9 6.12 Registration Office will register patients separately to the optional translational research component of this study (see Section 14.0).
- Patient has/has not given permission to give their tissue sample for research testing.
- 6.13 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: [www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp). Guidelines can be found under Quick Fact Sheets.
- Add 1 6.14 At the time of registration, Randomization Center personnel will verify the following:
- IRB approval at the registering institution
  - Patient eligibility
  - Existence of a signed consent form
  - Existence of a signed authorization for use and disclosure of protected health information. (USA institutions only)
- Add 1 At the time of registration, the following will also be recorded:
- Patient has/has not given permission to store sample(s) for future research of cancer.
  - Patient has/has not given permission to store sample(s) for future research to learn, prevent, or treat other health problems.
  - Patient has/has not given NCCTG permission to give their sample(s) to outside researchers.
- 6.15 Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG member physician.
- 6.16 Treatment cannot begin prior to registration and must begin  $\leq 21$  days after registration.
- 6.17 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.
- 6.18 All required baseline symptoms must be documented and graded.
- Add 4 6.19 A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

## 6.2 Phase II Component

**Open to whole NCCTG membership.**

Add 12

**As of Addendum 12, the Phase II portion of the study is now open.**

Add 9

6.21 To register a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the NCCTG Registration Office at (507)-284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a NCCTG subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:

- Contact the NCCTG Registration/Randomization Center (507)-284-4130. If the patient was fully registered, the Registration/Randomization Center staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

Add 1,12

6.22 An optional translational research component is part of this study, there will be an option to select if the patient is to be registered onto this component (Section 14.0).

- Patient has/has not given permission to give their tissue sample for research testing.

6.23 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: [www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp). Guidelines can be found under Quick Fact Sheets.

Add 1

6.24 Prior to accepting the registration, the remote registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information (*USA institutions only*)

Add 1

6.25 At the time of registration, the following will also be recorded:

- Patient has/has not given permission to store samples for future research of lung cancer.

- Patient has/has not given permission to store samples for future research to learn, prevent, or treat other health problems.
- Patient has/has not given NCCTG permission to give their samples to outside researchers.

Add 1	6.26	Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG member physician.
Add 1	6.27	Treatment cannot begin prior to registration and must begin $\leq 21$ days after registration.
Add 1	6.28	Pretreatment tests must be completed within the guidelines specified on the test schedule.
Add 1	6.29	All required baseline symptoms must be documented and graded.

**7.0 Protocol Treatment**

7.1 Phase I Component - Open to whole NCCTG membership.

7.11 Pretreatment medication prior to Taxol

Add 1  
Update 1

Agent	Dose	Route	Day
DXM	10-20 mg	IV or PO	IF PO, begin within 12 hours prior to chemotherapy with route and dosing left to physician's discretion
BEN and RANIT or CIMET or FAMOT	25-50 mg	IV	30 minutes Pretaxol
	50 mg		
	300 mg		
	20 mg		
Bactrim	1 tablet BID twice a week	oral	Continuously during treatment

7.12 Treatment schedule - Use actual weight or estimated dry weight if fluid retention.

Add 1,9

Update 1

Agent <sup>1</sup>	Dose	Route	Day	Chemo ReRx	RT
PS-341	As assigned by NCCTG Registration Office	IV push into the side arm of a running IV of normal saline at 100 mL/hr	Days 1, 4, 8, 11	Q 3 weeks <sup>2</sup>	Total dose of 6,000 cGy given in 30 daily (except weekends) fractions of 200 cGy each, starting on Day 1 (total of 6 weeks or 2 cycles)
TAXOL		IV over 3 hours	Day 2		
CBDCA <sup>3</sup>		IV over 30 minutes after TAXOL			

1. Treatment should begin on a Monday or Tuesday.
2. For a maximum of 2 cycles.
3. CrCl is the creatinine clearance – use Appendix V (Carboplatin Dosing Worksheet) for the dose calculation for each cycle of therapy.

7.13 Dose Escalation

Dose level	PS-341 mg/m <sup>2</sup>	Paclitaxel mg/m <sup>2</sup>	CBDCA AUC
-1	0.5	120	5
0	0.5	135	5
<b>*1</b>	<b>0.5</b>	<b>150</b>	<b>5</b>
2	0.8	150	5
3	1.0	150	5
4	1.0	175	5
5	1.0	175	6
6	1.2	175	6

Add 9

**\*starting dose level**

7.14 Treatment by a local medical doctor is not allowed.

7.15 Three patients will be treated at each dose level and observed for a minimum of 4 weeks, to assess toxicities, before new patients are treated. Doses will not be escalated in any individual patient.

7.16 Dose escalation from one level to the next cannot occur until all patients enrolled on a specific dose level have completed RT.

Add 1

7.17 Investigators are to contact the NCCTG Operations Office (507-538-1079) as soon as any dose-limiting toxicity occurs.

7.2 Definitions of DLT

7.21 For this protocol, dose-limiting toxicity (DLT) will be defined as follows:

Add 15

**Toxicity (CTCAE v3.0\*)**

**Definition**

Add 3

Skin

Grade ≥4 radiation dermatitis

Hematologic (ANC, PLT)\*\*

Grade ≥4 for ≥8 days

Grade ≥4 febrile neutropenia

(ANC <1000/mm<sup>3</sup> & fever ≥38.5°C)

PLT <25,000/ mm<sup>3</sup>

Esophagitis

Grade ≥3 requiring hospitalization

Pneumonitis

Grade ≥3 (requiring O<sub>2</sub>)

Dyspnea

Grade ≥4 (at rest)

Other non-hematologic

Grade ≥4 that is not manageable with medical interventions (IV, narcotic) as per NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0

Add 3

\*Adverse event at least possibly related to the study medication.

\*\*Cycle 1 of chemotherapy only.

7.22 MTD Determination

Aggressive radiotherapy and chemotherapy for lung cancer is associated with significant toxicity. In an analysis of 5 RTOG chemo/RT studies, the incidence of

grade 4 toxicity was 50% (See table in section 1.4). The MTD in this study will be defined as the highest safely tolerated dose where at most 2 patients out of six experience DLT with the next higher dose having at least 3 out of 6 patients experience DLT.

### 7.23 Dose Escalation

7.231 If DLT is not seen in any of the 3 patients at a given dose level, then 3 additional patients will be treated at the next dose level.

7.232 If DLT is seen in 1 or 2 of 3 patients treated at a given dose level, 3 additional patients will be entered at that same dose level.

7.233 If DLT is seen in 3 of 3 patients treated at a given dose level, then the MTD will have been exceeded and defined as the previous dose level unless only 3 patients were treated at the lower dose level. In this case, 3 additional patients will be treated at the next lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

- After enrolling 6 patients on a specific dose level, if DLT is observed in at most 2 of 6 patients, then dose escalation can continue as shown in the dose escalation table of section 7.13.
- After enrolling 6 patients on a specific dose level, if DLT is observed in at least 3 of 6 patients, then the MTD will have been exceeded and defined as the previous dose level unless only 3 patients were treated at the lower dose level. In this case, 3 additional patients will be treated at the next lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

### 7.24 Dose De-Escalation from Dose Level 1

7.241 If DLT is seen in at least 3 patients at Dose Level 1, patients will be enrolled at Dose Level -1. Dose-escalation may then proceed (as discussed in section 7.23) to Dose Level 0. As the study progresses, the dose escalation table may be revised based on the toxicity pattern observed.

## 7.3 Duration of therapy

7.31 Patients will receive 6 weeks of chemotherapy and 6 weeks (30 weekdays) of radiation therapy, concurrently. This will allow the delivery of 60 Gy of radiation therapy (30 fractions).

7.4 Phase II Component - After the recommended maximum tolerated dose (MTD) has been determined, patients will continue to be enrolled from the whole NCCTG membership.

7.41 Pretreatment medication prior to Taxol

Add 1  
Update 1

Agent	Dose	Route	Day
DXM	10-20 mg	IV or PO	IF PO, begin within 12 hours prior to chemotherapy with route and dosing left to physician's discretion
BEN and RANIT or CIMET or FAMOT	25-50 mg	IV	30 minutes Pretaxol
	50 mg		
	300 mg		
	20 mg		
Bactrim	1 tablet BID twice a week	oral	Continuously during treatment

7.42 Treatment schedule - Use actual weight or estimated dry weight if fluid retention.

Add 1, 12

Add 1, 12  
Update 1

Agent <sup>1</sup>	Dose	Route	Day	Chemo ReRx	RT
PS-341	1.2 mg/m <sup>2</sup>	IV push into the side arm of a running IV of normal saline at 100 mL/hr	Days 1, 4, 8, 11	Q 3 weeks <sup>2</sup>	Total dose of 6,000 cGy given in 30 daily (except weekends) fractions of 200 cGy each, starting on Day 1 (total of 6 weeks or 2 cycles)
TAXOL	175 mg/m <sup>2</sup>	IV over 3 hours	Day 2		
CBDCA <sup>3</sup>	AUC=6	IV over 30 minutes after TAXOL			

Add 1

Update 1  
Add 14

1. Treatment should begin on a Monday or Tuesday.
2. For a maximum of 2 cycles.
3. Dosed using Calvert Formula with Cockcroft & Gault Equation Calvert Formula: CBDCA dose (mg) = target AUC x (GFR + 25). Note: The glomerular filtration rate (GFR) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. Therefore, for newly enrolled patients, the maximum carboplatin dose for this study is 900 mg. For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CrCl) and can be measured or calculated (Note: When concerned about patient safety in a given patient, measure GFR. The CrCl is calculated by the method of Cockcroft & Gault (CrCl[mL/min] = [140 – age) x actual body weight [kg] divided by plasma Cr [mg/dL x 72 x [0.85 if female or 1.0 if male]). Note: A correction factor is NOT to be used to calculate carboplatin doses based on the IDMS serum creatinine.

7.43 Treatment by a local medical doctor is not allowed.

- Add 1 7.5 Radiation Therapy (Phase I and II Components) - Use of IMRT is not allowable. Respiratory gating is allowable if conventional or 3D-conformal therapy planning is used.
- 7.51 Conventionally fractionated thoracic irradiation: Radiation therapy is to begin on day 1. If a holiday precludes treatment on one day of the week then that treatment will be made up at the end.
- 7.52 Equipment: The beam energy required will be 6 or 10 MV.
- 7.53 Technique:
- 7.531 All treatments will be isocentrically rotational with minimum source axis distance of 100 cm. Radiation therapy will be initiated with AP-PA opposed fields until 4400 cGy is prescribed to isocenter (see Sections 7.54 and 7.58). At that point, off-cord opposed oblique fields will be used. (The off-cord oblique volumes will begin after a maximum prescribed isocentric dose of 4400 cGy.) Dose to the spinal cord will not exceed 4800 cGy. Radiation therapy will begin on day 1 which will be a Monday or Tuesday.
- 7.532 Shaped fields with customized blocking or multileaf collimation must be used.
- 7.533 A treatment planning CT scan must be obtained, optimally, with IV contrast.
- 7.534 The treatment position is supine with the arms immobilized over the head or located at the side.
- 7.54 Volume
- 7.541 Initial AP:PA volume (Initial Fields):
- 7.5412 Primary tumor: The target volume will include the extent of tumor/nodal disease as identified on CT chest with a 2 cm margin between the block edge and tumor volume defined by CT.
- 7.5413 Hilum: The ipsilateral hilum will be covered with a 2 cm margin to block edge. The contralateral hilum will not be included, all gross disease must be treated with a 2 cm margin in all directions.
- 7.5414 Mediastinum: The minimal mediastinal volume superiorly to inferiorly will extend from the top of T1 superiorly to 5 cm below the carina inferiorly (gross disease must be treated with a minimum of 2 cm margin in all directions – this may necessitate the raising of the superior border above T1, or the lowering of the inferior border

to a point more than 5 cm below the carina). Laterally, the ipsilateral and contralateral mediastinum will be covered with a 2cm margin. The field borders will be placed 2 cm lateral to the edge of the trachea, or 2 cm lateral to the edge of the vertebral body, whichever is more lateral.

7.5415 Supraclavicular fossae: Elective inclusion of the supraclavicular fossa will be at the discretion of the treating physician. If supraclavicular disease is present, then both fossae will be treated. The superior border will be placed 2 cm superior to gross disease, and the lateral supraclavicular borders will be placed at the outermost edges of the most lateral part of the first rib (unless bulky supraclavicular disease is present and wider borders are necessary to include gross disease with a 2 cm margin).

7.542 Off-cord oblique volumes: The initial off-cord oblique volumes will begin after a maximum prescribed isocentric dose of 4400 cGy.

Off-cord oblique boost volumes (oblique fields ): The oblique volume will include gross disease only (defined with a contrast enhanced CT scan), with 2 cm margins. A 1-2 cm margin may be required, so that the posterior border is placed at the anterior edge of the vertebral pedicles (anterior to the spinal cord). Spinal cord dose not to exceed 4800 cGy.

7.55 Normal tissue considerations:

7.551 An AP:PA larynx/throat C/T-spine block may be used at the discretion of the treating physician if the supraclavicular fossa are being treated electively. At no time should a throat block be placed within 2 cm of tumor volume. Ideally, a tissue compensator/wedge will account for change in the slope of the chest wall.

7.552 No part of the spinal cord can receive greater than 4800 cGy from this treatment. For the oblique fields, the field border should be placed on the anterior edge of pedicles anterior to the spinal cord. The cord will receive only scatter dose in the oblique fields.

7.553 Lung dose volume histograms are required. One should strive to treat the patient with a minimal volume of lung receiving >20Gy. No patient shall be treated on this study if the volume of lung receiving >20 Gy exceeds 40%. For those patients who have a total lung volume receiving >20 Gy at between 30 and 40%, one should consider methods to decrease this volume by avoiding treatment of the Supraclavicular volumes, or an alternative choice of oblique angles.

- 7.554 The off-cord treatment will consist of paired opposed oblique fields, or in uncommon situations, multiple oblique fields which are designed to keep the  $V_{20}$  as low as possible.
- 7.56 Dose Prescription
- 7.561 Each individual treatment will deliver 200 cGy to isocenter.
- 7.562 One treatment per day will be given, five days per week. BID treatment is not acceptable.
- 7.563 The total radiation therapy dose will be 6,000 cGy, given in 30 daily fractions of 200 cGy each prescribed to the isocenter. With the exception of weekends, this protocol contains no planned treatment breaks. See Radiation Summary in Section 7.58. Breaks will only be given for the indications described in Section 8.0.
- 7.564 Primary dose-limiting structures are the spinal cord, heart, lungs, and esophagus. The following limitations on dose to these structures must be observed:
- 7.5641 Spinal Cord: The maximum dose to the spinal cord must be  $\leq 4800$  cGy.
- 7.5642 Lung: Lung dose volume histograms are required. The maximum dose to the lungs will be based on lung dose volume histograms. If the  $V_{20}$  is  $>40\%$  then the patient should not be treated on this study. See Section 7.57221 for more details.
- 7.5643 Heart: 1/3 of the heart cannot receive greater than 60 Gy, 2/3 cannot receive more than 50 Gy and the entire heart can not receive more than 40 Gy. This may disqualify some patients with tumors behind the heart from participating in this study.
- 7.57 Other considerations
- 7.571 Portal (verification) films should be checked as soon as possible, preferably on day one of each new field and weekly thereafter.
- 7.572 Dosimetry
- 7.5721 Transverse isodose plots will be required at the central axis, 2 cm inferior to the superior edge of the field, and 2cm superior to the inferior edge of the field. The spinal cord dose at 2 cm below the upper field edge should be specified. An isodose plot through the

center of the primary tumor should also be submitted if this is different than the isocenter.

7.5722 No inhomogeneity corrections will be made. DVH for the esophagus should be calculated and recorded in the radiotherapy data collection sheet.

7.57221 Lung dose volume histograms (DVH) must be obtained. See Sections 7.5642 for details. (This will include both lungs as a single total lung volume.)

7.57222 DVH for heart, and spinal cord should be obtained. The entire length of the esophagus should be included for the DVH calculation. See Sections 7.5643 and 7.5641.

7.5723 Treatment interruptions: Radiation shall be held according to Section 8.0. During treatment breaks, patients should be monitored. Interruptions that are required because of toxicity due to RT, or major holidays shall not result in protocol violation. See Appendix III.

7.5724 Quality control will be done utilizing the guidelines in Appendix III.

7.58 Radiation Summary:

	Energy	Total dose (cGy)	Fraction (cGy) size	# of fractions	Total cumulative dose after this field complete
Initial Fields	6 or 10 MV	Approx. 4400*	200	Approx. 22*	4400 cGy*
Oblique fields	6 or 10 MV	Approx. 1600- **	200	Approx. 8**	6000 cGy**

\* Total number of AP:PA fractions determined by maximum spinal cord dose of 4800 cGy.

\*\* Total number of fractions to be given to oblique fields to be determined by the number of fractions given to initial AP PA fields.

**8.0 Dosage Modification Based on Adverse Events** – Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

**ALERT:** ADR reporting may be required for some adverse events (See Section 10)

→→ Use Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0 unless otherwise specified ←←

CTCAE V3.0 Category	Adverse Event	Agent(s)	Action
<i>Blood/Bone Marrow</i>	ANC <sup>1</sup> <500 or PLT <20,000	RT PS-341 CBDCA TAXOL	Hold RT, PS-341, CBDCA and TAXOL until ANC ≥ 1000 and PLT ≥ 50,000 and fever absent and/or dysphagia ≤ grade 2. Resume treatment with PS-341, CBDCA and TAXOL doses reduced by 50%. If toxicity recurs, hold all treatment modalities as above. Resume treatment without PS-341, CBDCA and TAXOL <sup>3</sup> .
<i>Infection</i>	Febrile neutropenia <sup>2</sup>		
<i>Gastrointestinal</i>	Dysphagia, grade 4		
	Dysphagia, grade 3		
<i>Other non-hematologic</i>	Nausea/vomiting grade 3 or 4, not controlled with optimal medication	Discontinue PS-341, CBDCA and TAXOL, continue RT.	
	Grade 3 or greater	Hold RT, PS-341, CBDCA and TAXOL until toxicity ≤ grade 2. Resume treatment with PS-341, CBDCA and TAXOL doses reduced by 50%. If toxicity recurs, hold all treatment modalities as above. Resume treatment without PS-341, CBDCA and TAXOL.	
<i>Neurology</i>	Neuropathy: motor Grade 2	PS-341 CBDCA TAXOL	Decrease dose by 30%. If persists, continue to decrease by 30%.
	Neuropathy: sensory Grade 3 or 4		Discontinue PS-341, CBDCA and TAXOL, continue RT.

1. ANC - Absolute neutrophil count
2. Temperature ≥38.5°C with ANC <1000 or severe infection
3. If RT or chemotherapy is suspended for toxicity, patient evaluation should continue at least weekly and hematologic parameter should continue weekly. Patient should go off study if treatment is held for more than 2 weeks, except as clarified in item 4, below.
4. In a patient who is responding to therapy, this dose modification table should be viewed as guidelines. Adjustments can be made to chemotherapy doses in consultation with the PI, so that the patient can remain on study and derive full benefit from treatment.

Add 5

## 9.0 Ancillary Treatment

- 9.1 Patients should receive full supportive care while on this study. This includes blood-product support, antibiotic treatment, nutritional evaluation and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, antiemetics, and medications used for the prevention and treatment of radiation esophagitis from the beginning of treatment until 28 days after the final radiation therapy dose should be recorded in the medical records.
- 9.2 Anti-emetics: Anti-emetics should be prescribed by the treating physician as clinically indicated, if a patient develops nausea and/or vomiting. A suggested anti-emetic regimen is as follows: For severe nausea/and or vomiting, patients could receive granisetron 1mg po pretreatment, together with dexamethasone 20 mg po followed by granisetron 1 mg po BID x 24 hours with dexamethasone 4 mg bid x 48 hours. Prochlorperazine 10 mg po every six hours as needed and lorazepam 1 mg every 4 hours as needed may be prescribed as well.
- 9.3 Diarrhea: A suggested antidiarrheal regimen is as follows: Loperamide (Imodium®): 4 mg, followed by 2 mg every 2 hours until patients are free of diarrhea for at least 12 hours. At night, 4 mg of loperamide should be taken every 4 hours. Diphenoxylate/atropine (Lomotil™) (doses per physician discretion) may be substituted for loperamide.
- 9.4 Growth Factors: Routine use of a colony-stimulating factor (G-CSF or GM-CSF) is not recommended. Prophylactic use of colony stimulating factors during the study is not allowed. Therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc. may be considered at the investigator's discretion. Recombinant erythropoietin to maintain adequate hemoglobin levels and avoid packed red blood cell transfusions is allowed.

## 10.0 Adverse Event (AE) Reporting and Monitoring

- Add 2,15 10.1 CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE v4.0 will be utilized for expedited adverse event reporting only, beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE v4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).
- Add 2 10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (see Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether the event must be reported as an expedited report (see Section 10.2). Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3 and 18.0).
- Add 2 Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited and routine reports are to be completed within the timeframes and via the mechanisms specified in Section 10.2. All expedited AE reports must also be submitted to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

- Add 15 Effective with Addendum 15, and beginning January 1, 2011, expedited AdEERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. Therefore;
- 1) Events requiring expedited reporting through AdEERS must be reported through the AdEERS system in CTCAE v4.0.
  - 2) The events reported via AdEERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTCAE v3.0.
  - 3) Routine data collection via Case Report Forms, including the “Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form,” will remain using CTCAE v3.0 for this study.
- Add 2 10.12 Expected vs. Unexpected Events
- Agent(s) under a CTEP IND:
- Add 3 • Expected AEs for expedited reporting purposes are listed on the CTEP Agent Specific Adverse Event List (ASAEL), a component of the Comprehensive Adverse Events and Potential Risks List (CAEPR). Refer to Section 15.0 to locate the CAEPR for the CTEP IND agent(s).
  - Unexpected AEs are those not listed in the ASAEL.
- Add 2 10.13 Assessment of Attribution
- When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
- Definite - The adverse event *is clearly related* to the agent(s).
- Probable - The adverse event *is likely related* to the agent(s).
- Possible - The adverse event *may be related* to the agent(s).
- Unlikely - The adverse event *is doubtfully related* to the agent(s).
- Unrelated - The adverse event *is clearly NOT related* to the agent(s).
- Add 2 10.14 Additional instructions for trials that include both investigational agent(s) (those under an IND) and a commercial agent(s):
- When an investigational agent (an agent under an IND) is used in combination with a commercial agent(s) on the same treatment arm, the combination is considered investigational. Expedited reporting will follow the requirements for investigational agents.

Add 2

10.21 Phase 1 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected and Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days
<b>Possible Probable Definite</b>	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	24-Hour; 3 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under an IND require reporting as follows:  
 AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

<sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see additional instructions and/or exceptions below under section entitled "Additional Instructions or Exceptions."  
 March 2005

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.**

Add 15

Add 14

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE v4.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- SECONDARY MALIGNANCIES (defined as "cancer caused by treatment for a previous malignancy," e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS, as noted in Section 10.23. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Note: Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase I Trials Utilizing an Agent Under a CTEP IND:**

Add 14,15

- In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.
- Refer to Section 10.23 of this protocol for additional expedited reporting requirements.

Add 2

10.22 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
<b>Possible Probable Definite</b>	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	7 Calendar Days
<p><sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:                      AdEERS 24-hour notification followed by complete report within 3 calendar days for:                      • Grade 4 and Grade 5 unexpected events                      AdEERS 7 calendar day report:                      • Grade 3 unexpected events with hospitalization or prolongation of hospitalization                      • Grade 5 expected events</p> <p><sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.</p> <p>Please see additional instructions and/or exceptions below under section entitled "Additional Instructions or Exceptions."                      March 2005</p>									

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Add 15 • Any medical event equivalent to CTCAE v4.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
  - Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
  - Add 14 • SECONDARY MALIGNANCIES (defined as “cancer caused by treatment for a previous malignancy,” e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS, as noted in Section 10.23. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.
- Note: Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND:**

- Add 15 • In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.
- Refer to Section 10.23 of this protocol for additional expedited reporting requirements.

Add 2 10.23 Other Required Expedited Reporting

<u>EVENT TYPE</u>	<u>REPORTING PROCEDURE</u>
Add 14 Secondary AML/MDS	Reporting for this event required during and after completion of study treatment via AdEERS.  Through December 31, 2010, continue using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow – Other (Specify, _____).”  Beginning January 1, 2011, AdEERS will only accept CTCAE v4.0 for this study. Report these events using “Neoplasms benign, malignant and unspecified (including cysts and polyps)” <i>and including the appropriate adverse event:</i> - Leukemia secondary or oncology chemotherapy OR - Myelodysplastic syndrome OR - Treatment related secondary malignancy
Add 4,15 Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	If an AdEERS report has been submitted, this form does not need to be submitted.  Enter into the remote data entry system within 5 working days of notification.  You must use CTCAE v3.0 for data submission with this form. The events reported on this form must also appear on the Case Report Forms (i.e., routine data) for this study.

- 10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated in the table below:

Add  
15

CTCAE v3.0 Category	Adverse Event/symptoms	Baseline	Each evaluation
<i>Allergy/Immunology</i>	Allergic reaction/hypersensitivity (including drug fever)		X
<i>Constitutional Symptoms</i>	Fatigue (lethargy, malaise, asthenia)	X	X
	Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10 <sup>9</sup> /L)		X
<i>Dermatology/Skin</i>	Rash: dermatitis associated with radiation -Chemoradiation		X
<i>Gastrointestinal</i>	# stools/day	X	
	Diarrhea		X
	Dysphagia (difficulty swallowing)	X	X
	Mucositis/stomatitis (clinical exam) -Oral Cavity or pharynx		X
	Mucositis/stomatitis (functional symptomatic) -Esophagus -Oral Cavity		X
	Nausea	X	X
	Vomiting	X	X
<i>Infection</i>	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10 <sup>9</sup> /L, fever ≥ 38.5°C)		X
<i>Neurology</i>	Neuropathy: motor	X	X
	Neuropathy: sensory	X	X
	Somnolence/depressed level of consciousness	X	X
<i>Pain</i>	Musculoskeletal -muscle	X	X
<i>Pulmonary/Upper Respiratory</i>	Dyspnea (shortness of breath)	X	X
	Pneumonitis/Pulmonary infiltrates	X	X

- Add 15 10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs using CTCAE v3.0 experienced by a patient and not specified in Section 10.3:
- 10.311 Grade 1 & 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- Add 2 10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.
- Add 2 10.313 Grade 5 AEs (Deaths)
- Add 2 10.3131 Any death within 30 days after the patient's last treatment, regardless of relationship to study treatment or procedure.
- Add 2 10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.
- 10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

## 11.0 Treatment Evaluation Using RECIST Criteria<sup>20</sup>

- Add 3 11.1 Schedule of Evaluations: Patients should ideally be reevaluated at 4 weeks post-RT, 3 months post-RT, every 3 months for 1 year post-RT, and every 6 months thereafter for a maximum of 5 years from time of registration (see below).
- 11.2 Definitions of Measurable and Non-Measurable Disease
- 11.21 Measurable disease is defined as at least one lesion whose longest diameter can be accurately measured as  $\geq 2.0$  cm with conventional techniques or as  $\geq 1.0$  cm with spiral CT. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- 11.22 All other lesions (or sites of disease), including small lesions (longest diameter  $< 2.0$  cm with conventional techniques or as  $< 1.0$  cm with spiral CT) are considered non-measurable disease. Bone lesions leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CR or MRI), and cystic lesions are all non-measurable.
- 11.3 Guidelines for Evaluation of Measurable Disease
- 11.31 Measurement Methods:
- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
  - The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use spiral CT imaging for both pre- and post-treatment tumor assessments.
- Add 4

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable imaging modalities for measurable disease: CT scan (conventional and spiral), MRI, chest x-ray, and physical examination.

Add 4

- Conventional CT and MRI must be performed with cuts of 1.0 cm or less in slice thickness contiguously.

Add 4

- Spiral CT must be performed using a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities require specific procedures.

Add 4

- Ultrasound (US) may be used to measure tumor lesions that are clinically not easily accessible.

- Color Photography: In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

11.33 Measurement at Follow-up Evaluation:

Add 4

- A subsequent scan must be obtained 4 weeks following initial documentation of an objective status of either CR or PR.
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions

All measurable lesions (as defined in Section 11.21) up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and recorded and measured at baseline. If the protocol specified studies are performed, and there are fewer than 10 lesions identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions. For any one organ, no more than 5 lesions need to be measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive 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 to further characterize the objective tumor response of the measurable dimension of the disease.

#### 11.42 Non-Target Lesions

Add 4

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed in accordance with Section 11.433.

#### 11.43 Response Criteria

11.431 All identified sites of disease must be followed on re-evaluation. Specifically, a change in objective status to either a PR or CR cannot be done without rechecking all identified sites (i.e., target and non-target lesions) of pre-existing disease.

#### 11.432 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD.
- Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

#### 11.433 Evaluation of Non-Target Lesions

Add 4

- Complete Response (CR): Disappearance of all non-target lesions.
- Stable Disease (SD): Persistence of one or more non-target lesions.
- Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of “non-target” lesions only is exceptional, in such circumstances, the opinion of the treating physician will prevail, and the progression status will be confirmed at a later time by the study chair or a review panel.

#### 11.44 Overall objective status

The overall objective status for an evaluation is determined by combining the patient’s status on target lesions, non-target lesions, and new disease as defined in the following table.

Add 4

Target Lesions	Non-Target Lesions	New Lesions	Overall Objective Status
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

11.45 Residual Disease: In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

11.46 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration:

Add 4

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

11.5 Formal statistical definitions of analysis variables involving response and disease progression are contained in Section 16.0.

**12.0 Descriptive Factors**

12.1 Pretreatment supraclavicular involvement: Yes vs. no.

12.2 Maximum pre-treatment tumor size (cm): < 3 vs. 3-6 vs. > 6.

12.3 Weight loss in past 3 months: <5% vs. 5-<10%.

12.4 Diabetes: No vs. Type I vs. Type II.

Add 1

12.5 Stage IIIA vs. IIIB vs. IIIB with pleural effusion.

Add 9,12

12.6 Dose level: -1 vs. 0 vs. 1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6.

**13.0 Treatment/Follow-up Decision at Evaluation of Patient**

13.1 If a patient does not receive treatment and is classified as a cancel, it is not necessary to provide follow-up information. On-study material is to be submitted.

Add 1,3

13.2 At follow-up evaluations

Add 1,3

13.21 If patient goes off study due to refusal to continue participation or unacceptable toxicity, the patient will then go to event monitoring.

- Add 1,3 13.22 Patients who develop proven progression or metastasis after completion of therapy will go to event monitoring per Section 18.0. Treatment off protocol should be continued at the discretion of the attending physician.
- Add 1,3 13.23 After the completion of the study treatment, all patients will be evaluated at four weeks post radiation therapy unless the patient has progressed, refused further treatment, or had unacceptable toxicity.
- Add 1,3 13.24 Observation: If the patient has achieved CR, PR, or SD, at the 4 week post-RT evaluation, the patient will be observed at 3 months post-RT, every 3 months for 1 year post-RT, and then every 6 months for up to 5 years from time of registration.
- Add 1,3 13.25 Adjuvant chemotherapy following RT may not begin until a minimum of 4 weeks have elapsed since the completion of RT and the acute toxicities of radiation have resolved to the satisfaction of both the treating Medical and Radiation Oncologist. Patients who go on to receive alternative therapy will go to event monitoring per Section 18.0.
- Add 1,3 13.26 Phase I component only: If a patient fails to complete the initial course of therapy (defined as PS341/TAXOL/CBDCA/RT and 4 weeks of observation) for reasons other than toxicity attributable to RT or chemotherapy, they will be regarded as inevaluable. A patient found to have a  $V_{20} > 40\%$  (see Section 7.553) will not be treated on this protocol and the patient will be regarded as ineligible and will be replaced.

#### **14.0 Translational/Pharmacologic Studies (Optional):**

- 14.1 We continue to evaluate tumor biopsies obtained from the Mayo Clinic Cancer Center phase I study of PS-341 in solid tumors. Any proteins that will be found to be potentially involved in the cytotoxicity of PS-341 will be evaluated in the tissue blocks of patients.
- 14.2 Measurement of p27 in tissue blocks of patients will be performed by immunohistochemistry, a procedure for which considerable expertise exists in our group. The immunohistochemistry studies will be performed in collaboration with our colleague at Mayo Clinic-Rochester, Dr. Ricardo Lloyd, who has extensive expertise in p27 expression

and biology in a number of tumor types (21,22). The expression of p27 will be correlated with response to PS-341. An inverse correlation is hypothesized.

14.3 Within 30 days of registration submit the following material to:

Add 3,5,8

NCCTG Operations Office  
ATTN: NCCTG PC Office  
RO FF 03 24-CC/NW Clinic  
200 First Street SW  
Rochester, MN 55905

Add 1

Add 1

- One paraffin embedded tumor tissue block. If the institution is unable to provide a block, submit 5 unstained charged slides cut at 5 microns.

- Surgical pathology report

Add 1

- Specimen submission form

The blocks should be placed in individual plastic bags and each bag labeled with the protocol number, study patient number, and patient initials.

Add 1,3,5,9

The blocks/slides will be forwarded by the NCCTG Pathology Coordinator to the TACMA Biospecimen Laboratory, Stable 13-10, Mayo Clinic Rochester, for immunohistochemistry staining.

Add 10

The institutional pathologist must be notified that a block may be depleted. Remaining material will be stored by NCCTG for future research, according to patient consent (see Section 6.14), although the blocks will be promptly returned to the institutional pathologist upon request at any time.

## 15.0 Drug Information

15.1 PS-341 (PS341, NSC # 681239) Investigational  
Other Names: MLN341, LDP-341, Velcade, Bortezomib

Add 1,3

- Investigator brochure contact information
  - Phone: 301-594-2079
  - [ibcoordinator@mail.nih.gov](mailto:ibcoordinator@mail.nih.gov)

Update 1

15.11 Formulation and Storage:

15.111 PS-341 is supplied by the DCTD, NCI as a 3.5 mg vial for injection. Each sterile single use 10 mL vial contains 3.5 mg PS-341 as a lyophilized powder with 35 mg mannitol, USP.

15.112 The chemical name for the proteasome inhibitor, PS-341, is N-Pyrazinacarbonyl-L-phenylalanine-L-leucine boronic acid.

15.113 The intact vials should be refrigerated (2° to 8° C) and protected from light.

15.12 Preparation:

15.121 When the 3.5 mg vial is reconstituted with 3.5 ml normal saline, USP, each milliliter of solution will contain 1 mg of PS-341. The drug is to be given without further dilution as an intravenous bolus (over 3-5 seconds).

15.13 Stability:

15.131 Shelf life surveillance of the intact vials is ongoing. The solution as reconstituted is stable for 43 hours at room temperature.

15.132 Caution: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.

15.14 Incompatibilities: No information available.

15.15 Administration: Intravenously without further dilution as a bolus (over 3-5 seconds).

Add 3,4,11,13

15.16 **Comprehensive Adverse Events and Potential Risks List (CAEPR) for PS-341 (NSC #681239)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

[http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse\\_events\\_adeers](http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers) for further clarification.

Frequency is provided based on 2042 patients. Below is the CAEPR for bortezomib (PS-341).

Version 2.2, March 25, 2010<sup>1</sup>

Adverse Events with Possible Relationship to Bortezomib (PS-341) (CTCAE 4.0 Term) [n= 2042]			EXPECTED AEs FOR ADEERS REPORTING
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Agent Specific Adverse Event List (ASAEL)
			<i>Expected</i>
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>			
Anemia			<b><i>Anemia</i></b>
	Febrile neutropenia		
<b>EYE DISORDERS</b>			
	Blurred vision		
<b>GASTROINTESTINAL DISORDERS</b>			
	Abdominal pain		<b><i>Abdominal pain</i></b>
Constipation			<b><i>Constipation</i></b>
Diarrhea			<b><i>Diarrhea</i></b>
	Dyspepsia		<b><i>Dyspepsia</i></b>
	Gastrointestinal hemorrhage <sup>2</sup>		
		Gastrointestinal perforation <sup>3</sup>	
	Ileus		<b><i>Ileus</i></b>
Nausea			<b><i>Nausea</i></b>
Vomiting			<b><i>Vomiting</i></b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
	Chills		<b><i>Chills</i></b>
Edema limbs			<b><i>Edema limbs</i></b>
Fatigue			<b><i>Fatigue</i></b>
Fever			<b><i>Fever</i></b>
<b>INFECTIONS AND INFESTATIONS</b>			
Infection <sup>4</sup>			<b><i>Infection<sup>4</sup></i></b>
	Infections and infestations - Other (Opportunistic infection associated with >= Grade 2 Lymphopenia))		
<b>INVESTIGATIONS</b>			
	Lymphocyte count decreased		
	Neutrophil count decreased		<b><i>Neutrophil count decreased</i></b>

Platelet count decreased			<b>Platelet count decreased</b>
	White blood cell decreased		
<b>METABOLISM AND NUTRITION DISORDERS</b>			
Anorexia			<b>Anorexia</b>
	Dehydration		
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
	Arthralgia		<b>Arthralgia</b>
	Back pain		<b>Back pain</b>
	Bone pain		<b>Bone pain</b>
	Generalized muscle weakness		
	Myalgia		<b>Myalgia</b>
	Pain in extremity		<b>Pain in extremity</b>
<b>NERVOUS SYSTEM DISORDERS</b>			
	Dizziness		<b>Dizziness</b>
	Headache		<b>Headache</b>
		Leukoencephalopathy	
	Neuralgia		<b>Neuralgia</b>
Peripheral motor neuropathy			<b>Peripheral motor neuropathy</b>
Peripheral sensory neuropathy			<b>Peripheral sensory neuropathy</b>
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
<b>PSYCHIATRIC DISORDERS</b>			
	Anxiety		
	Insomnia		<b>Insomnia</b>
<b>RENAL AND URINARY DISORDERS</b>			
		Acute kidney injury	
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
	Cough		<b>Cough</b>
	Dyspnea		
	Epistaxis		
	Pharyngeal mucositis		<b>Pharyngeal mucositis</b>
	Pleural effusion		
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>			
	Rash maculo-papular		<b>Rash maculo-papular</b>
<b>VASCULAR DISORDERS</b>			
	Hypotension		<b>Hypotension</b>

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

<sup>3</sup>Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

<sup>4</sup>Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

**Also reported on bortezomib (PS-341) trials but with the relationship to bortezomib (PS-341) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (lymphadenopathy); Disseminated intravascular coagulation

**CARDIAC DISORDERS** - Asystole; Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cardiac amyloidosis); Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Right ventricular dysfunction; Sinus bradycardia; Ventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - Hearing impaired

**EYE DISORDERS** - Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (conjunctival hemorrhage); Watering eyes

**GASTROINTESTINAL DISORDERS** - Abdominal distension; Ascites; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (eructation); Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Gait disturbance; General disorders and administration site conditions - Other (hepato-renal syndrome); Injection site reaction; Non-cardiac chest pain; Sudden death NOS

**HEPATOBIILIARY DISORDERS** - Hepatobiliary disorders - Other (portal vein thrombosis)

**IMMUNE SYSTEM DISORDERS** - Allergic reaction

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Fracture

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Creatinine increased; GGT increased; INR increased; Serum amylase increased; Weight gain; Weight loss

**METABOLISM AND NUTRITION DISORDERS** - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Buttock pain

**NERVOUS SYSTEM DISORDERS** - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Seizure

**PSYCHIATRIC DISORDERS** - Agitation; Confusion; Depression; Psychosis

**RENAL AND URINARY DISORDERS** - Bladder spasm; Hematuria; Proteinuria; Renal and urinary disorders - Other (calculus renal); Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (glomerular nephritis proliferative); Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Hiccups; Hypoxia; Pharyngolaryngeal pain; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Voice alteration

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin and subcutaneous tissue disorders - Other (leukoclastic vasculitis); Urticaria

**VASCULAR DISORDERS** - Capillary leak syndrome; Flushing; Hematoma; Thromboembolic event

**Note:** Bortezomib (PS-341) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Add 6,7

## 15.17 Availability

PS-341 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. PS-341 is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Millennium Pharmaceuticals and the NCI, DCTD. See Appendix IVI.

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 7149, Bethesda, MD 20892.

Drug Accountability: The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCTD using the NCI Drug Accountability Record Form. (See the *NCI Investigators Handbook for Procedures for Drug Accountability and Storage* at <http://ctep.cancer.gov/handbook/index.html>)

## 15.18 Nursing Guidelines

15.181 Monitor CBC.

15.182 Counsel patient in weight maintenance dietary regime. Small frequent meals with an increased protein and carbohydrate content may work best.

15.183 Provide symptomatic relief of nausea/vomiting/diarrhea.

15.184 Instruct patient to report any cardiac palpitations, increased pulse, lightheadedness, visual changes, and feelings of weakness or dizziness. Periodically assess vital signs.

15.185 Instruct patient to report any evidence of infection, i.e., redness or soreness, fever, and cough.

15.186 PS-341 has been known to cause both diarrhea and constipation in patients. Instruct patient on appropriate bowel protocol depending on symptoms. Instruct patient to report any diarrhea or constipation that is not relieved, as both of these may lead to more serious problems.

15.187 Instruct patients to report any unusual bruising and/or bleeding

15.2 Paclitaxel (TAXOL)- Please refer to the approved prescribing information or package insert for additional information on this drug.

15.21 Preparation and storage: Supplied as a concentrated sterile solution, 6 mg/mL in 5 mL vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. The intact vials should be stored under refrigeration (2-8°C). All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of the drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/mL) are physically and chemically stable for 27 hours.

Paclitaxel will be prepared by diluting the total dose in 500 mL of 5% dextrose. Paclitaxel must be prepared in glass or polyolefin containers and non-PVC tubing due to leaching of diethylhexylphthalate (DEHP) plasticizer from poly vinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter or pore size not >0.22 microns into the IV fluid pathway distal to the infusion pump. Solutions exhibiting excessive particulate matter formation should not be used.

15.22 Known potential toxicities: Myelosuppression; nausea and vomiting; stomatitis; mucositis; increased SGOT, SGPT, bilirubin, and alkaline phosphatase; pharyngitis; typhlitis; ischemic colitis; neutropenic colitis; arrhythmia; heart block; ventricular tachycardia; myocardial infarction; bradycardia; atrial arrhythmia; pneumonitis; hypotension; hypertension (possibly related to concomitant medication dexamethasone); sensory (taste); peripheral neuropathy; seizures; mood changes; hepatic encephalopathy; encephalopathy; erythema multiforme (Stevens-Johnson Syndrome, toxic epidermal necrolysis), induration, tenderness, and rarely, ulceration, radiation recall, and rash associated with infiltration; acute anaphylactoid and urticarial reactions; flushing, rash and pruritus; hepatic failure; hepatic necrosis; alopecia; fatigue; arthralgia; myalgia; light-headedness; myopathy; visual abnormalities (blurred vision and a sensation of flashing lights), erythema multiforme.

Additional adverse events included in the package insert of paclitaxel: anorexia, dehydration, confusion, pancreatitis, and bowel perforation.

15.23 Nursing guidelines:

15.231 Premedicate with dexamethasone, diphenhydramine, and H2 receptor antagonists as per protocol.

15.232 Assess the patient frequently for the first 30 minutes. Paclitaxel hypersensitivity reactions usually occur early in the infusion. Have anaphylaxis tray available.

- 15.233 Instruct the patient about the importance of taking their premedications at home.
- 15.234 If a reaction occurs, stop the infusion. Epinephrine, IV fluids, diphenhydramine, and methylprednisolone may be used as per MD's order.
- 15.235 Most cardiac disturbances occur during the later hours of the infusion, are self-limiting, and abate quickly after discontinuing the infusion.
- 15.236 Mucositis can usually be managed with a salt and soda mouthwash (1 tsp salt, 1 tsp baking soda, and 1 qt boiled water).
- 15.237 Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.
- 15.238 Monitor CBC. Instruct patient to report signs/symptoms of infection, unusual bruising or bleeding.
- 15.239 Monitor liver function tests.
- 15.240 Assess for peripheral neuropathy. Instruct patient to report any numbness or tingling in hands or feet.
- 15.241 Taxol is an irritant. Monitor IV site closely
- 15.242 Advise patient of probable alopecia.
- 15.243 Use of 0.22 micron final filter is mandatory
- 15.24 Drug procurement: Commercially available.
- 15.3 Carboplatin (CBDCA)- Please refer to the approved prescribing information or package insert for additional information on this drug.
  - 15.31 Preparation and storage: Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 500 mcg/mL, solutions have the following stability: in normal saline, 8 hours at 25° C, 24 hours at 5° C; in 5% dextrose (when reconstituted in sterile water), 24 hours at 5° or 25° C. Add 5, 15, or 45 mL sterile water, normal saline, or 5% dextrose to the 50, 150, or 450 mg vial, respectively. The resulting solution contains 10 mg/mL. The desired dose is further diluted, usually in 5% dextrose.
  - 15.32 Known potential toxicities: Myelosuppression, nausea, vomiting, and electrolyte loss are most common. Hypocalcemia, hypokalemia, hypomagnesemia, and hyponatremia may occur, although these are rarely associated with symptoms. Peripheral neuropathies, diarrhea, constipation, mucositis, hypotension, hypertension, visual disturbances, ototoxicity, changes in taste, CNS symptoms, rare bronchospasms, abnormal kidney and liver tests, pain, alopecia, fever, change in appetite and weight, and secondary leukemia and/or myelodysplastic syndrome are less common. Dermatologic reactions have also been reported. Allergic reactions with congestion, nausea, vomiting, rash, chills, tingling of the extremities, dyspnea, or anaphylactic-like symptoms can rarely develop after repeated treatments.

15.33 Nursing guidelines:

- 15.331 Monitor CBC and PLTs. Watch for profound neutropenia and give low count precautions and instructions as necessary. Nadir occurs at approximately day 21 with recovery at day 28-30. Thrombo-neutro-leukopenia may be cumulative. Thrombocytopenia can be dose-limiting and is more pronounced than with cisplatin. It can be more severe in patients with previous chemotherapy, concurrent radiation therapy, or patients with impaired renal function. Instruct patient to immediately report any unusual bruising or bleeding. Anemia (70-90% of patients) may be symptomatic with asthenia being the most common complaint. Instruct patient in energy saving lifestyle.
- 15.332 Assess baseline renal function (creatinine clearance). Reduced renal function can contribute to an increased risk of thrombocytopenia.
- 15.333 Monitor fluid status - encourage hydration.
- 15.334 Advise patient of probable taste alterations. Frequent oral hygiene is helpful. Instruct patient in appropriate interventions to achieve and maintain optimal nutritional status.
- 15.335 Older patients (>65) may experience some peripheral neuropathy with paresthesias. Instruct patients to report any tingling, burning, loss of sensation.
- 15.336 Mild nausea and vomiting occur in up to 94% of patients, 6-12 hours after treatment and may persist for 24 hours or longer. Diarrhea/cramping/constipation has been experienced by approximately 17%. Premedicate with antiemetics/antidiarrheals—evaluate effectiveness.
- 15.337 Administer following Taxol (in regimens that contain both drugs) to maximize cell kill.
- 15.338 Patients have experienced allergic reactions while receiving carboplatin. Watch for signs and symptoms of hypersensitivity reactions. If these occur, stop drug immediately, notify MD, and treat appropriately.

15.34 Drug procurement: Commercially available.

## 16.0 Statistical considerations and Methodology

- 16.1 Overview: This is a phase-I/II trial designed to (a) determine the MTD of the study treatment regimen of PS-341 in combination with Paclitaxel and Carboplatin with concurrent TRT, in the phase I component, and in the phase II component to b) assess 12-month survival of lung cancer patients receiving the regimen, (c) assess the toxicities associated with this regimen, (d) assess QOL of lung cancer patients receiving the study treatment regimen, and (e) assess associations between clinical variables and p27 expression.

## 16.2 Phase I Component

16.21 The MTD will be defined as the highest safely tolerated dose where at most two out of six patients experience DLT with the next higher dose level having at least 3 out of 6 patients experience DLT. See Sections 7.22-7.23 for the algorithm on how the MTD will be determined.

### 16.22 Accrual and study duration

Patients will be accrued in cohorts of 3. The phase I component may require as many as 30 patients (6 for each of the 5 dose levels) but is more likely to require 21 patients (3 at the first 3 dose levels, 6 for the dose level prior to the MTD, and 6 at the MTD). We anticipate accruing patients from the NCCTG sites for the phase I component and hence the accrual rate for this study is expected to be 6 patients per month, based on the accrual for NCCTG 94-24-52. The study regimen will take 10 weeks (6 weeks of chemotherapy/TRT and a 4-week observation). Thus, each cohort of 3 is expected to take about 3 months for accrual, treatment, and evaluation. Therefore, the accrual and evaluation period for the phase 1 component is expected to be between 1.75 and 2.5 years. The patients treated at the MTD will continue on into the phase II portion of the study.

### 16.23 Operating Characteristics for Phase I

The following table shows the probability of dose escalating for any dose level. The probability of DLT is given by P(DLT) and the only DLT events given are the ones that would lead to a dose escalation:

<b>DLT Events</b>	<b>P(DLT) = .15</b>	<b>P(DLT) = .25</b>
0 of 3 (0 DLT's in cohort of 3)	.614	.422
1 of 6 (1 DLT in cohort of 6)	.200	.178
2 of 6 (2 DLT's in cohort of 6)	.141	.237
Total Probability	.955	.837

### 16.24 Phase I Analyses

The number and severity of all adverse events (overall, and by dose-level) will be tabulated and summarized. The grade 3+ adverse events will also be described and summarized in a similar fashion. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

Although tumor measurements, tissue blocks, etc. will be collected for all patients (Phase I and II), only the phase I patients treated at the MTD will stay on-study for the Phase II portion and be included in the efficacy and translational analyses.

## 16.3 Phase II Component

### 16.31 Overview

16.311 Primary Endpoint: The primary endpoint of this trial is the proportion of patients alive at 1 year (i.e., 365 days) after study registration. Throughout the remainder of Section 16.0, being alive at 1 year will be considered synonymous with “success.” All patients meeting the eligibility criteria who have signed a consent form, begun treatment in the phase II component of the trial, and are not lost to follow-up before 1 year will be considered evaluable.

Note: To obtain realistic estimates of the proportion of patients alive at 12-months under the null hypothesis, we examined patients who were enrolled in NCCTG 94-24-52, a recent NCCTG phase III study of chemotherapy with concurrent TRT Stage IIIA/IIIB NSCLC patients. Of the 230 evaluable patients for survival, 136 (59%) were alive 1 year after going on study.

16.312 Sample Size: A total of 66 patients (60 evaluable + 6 additional patients to compensate for losses due to ineligibility, cancellation, major protocol violations, or lost to follow-up), including all patients treated at the MTD during the Phase I portion of the trial, will be enrolled onto the phase II component unless undue toxicity is encountered. Of the 66 patients, we will actively seek to accrue at least 7 minority patients (10% of full accrual). To accomplish this goal, an amendment will be immediately sent out at the 90% target accrual point requiring the remaining accrual to only be allowed for minority patients, unless 7+ minority patients have already been accrued to the study (see section 16.63 for more details).

16.313 Accrual Rate: In a recent NCCTG study (94-24-52) in the study population, the NCCTG accrual rate was 6 patients per month.

16.314 Study Duration: If the accrual rate is 6/month, it will take about 11 months to enroll 66 patients, and the final analysis can be completed about 23 months after the study opens (11 months to accrue 66 patients + 12 month follow-up after full accrual). The interim analysis will take place approximately 10 months after the phase II portion opens (about 4 months to accrue 26 patients + 6 months to follow them; see sections 16.323-16.324 for more details).

### 16.32 Study Design

16.321 Definition of Success: For design purposes, an eligible patient who signs the consent form and begins study therapy will be considered evaluable for assessment of treatment efficacy. To be classified as a success, a patient must be evaluable and be alive at least 12 months (i.e., 365 days or more)

after registering to the study. If the patient is lost to follow-up prior to being on-study for 12 months, they will be considered unevaluable and will be replaced for these analyses.

16.322 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 60%, and the smallest that would warrant further subsequent studies is 75%. This decision rule is based on Simon's optimum 2-stage design (23), which uses a maximum of 60 patients to test the null hypothesis that the true success proportion in the given patient population is at most 60%.

16.323 Interim Analysis: After the first 26 evaluable patients have been followed for at least 6 months, an interim analysis will be performed. If 20 or fewer of these 26 patients live longer than 6 months, we will terminate accrual and conclude that the regimen is insufficiently active in this population. If 21 or more of these 26 patients live longer than 6 months, we will continue accrual to the full 66 patients (ie. 60 per study design + 6 over accrual). It was decided not to suspend accrual for a couple reasons. First and foremost, this regimen should be at least as effective as the standard regimen and we have a toxicity stopping rule in place to stop the trial for an overly toxic therapy. Second, we can still terminate the trail for an ineffective regimen prior to full accrual (i.e., Assuming accrual is < 6 patients per month, 26 + <36 <62, which means the study would be terminated at least 3 weeks prior to full accrual).

16.324 Interim Analysis Cutpoint Determination: In an effort to conduct the interim analysis sufficiently early in this study to allow action prior to full enrollment (especially if accrual is lower than expected), an interim analysis will be conducted using 6-month survival as the endpoint. The following steps were used to calculate the interim analysis cutpoint of 20:

- The appropriate 1-year survival cutpoint for the interim analysis was determined using a Simon's optimum 2-stage design (23). This design yielded the following decision rule for the interim analysis: 16 or fewer of 26 patients alive at 1 year would close the study for an insufficiently active treatment regimen.
- Based on the 1-year survival cutpoint shown above, a conservative 6-month survival cutpoint was determined by assuming the survival function follows an exponential model (i.e.  $S(t) = \exp(-\lambda t)$ , where  $\lambda$  is the hazard rate and  $t$  is the time variable). This 6-month survival cutpoint was determined as follows:
  - $\lambda$  was calculated by solving this equation:  $16/26 = .615 = \exp(-\lambda t)$ , where  $t=1$  (in yrs)

- After determining  $\lambda = -\ln(.615)$ , then  $S(.5)$  was calculated using  $S(t) = \exp(\ln(.615)*t)$ .
- $S(.5)$  was found to equal .784 which led to a value of 20 of 26 patients alive at 6-months as a decision cutpoint for 6-month survival (being slightly conservative).

16.325 Stage 2: Enter an additional 40 patients (ie. 34 per study design + 6 over accrual) into the study. If 40 or fewer successes are observed in the first 60 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. If 41 or more successes are observed in the first 60 evaluable patients, we will conclude that this treatment regimen has adequate evidence of efficacy and may be recommended for further testing in subsequent studies.

16.326 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule at the interim analyses or the final decision rule. However, they will be included in the final analyses, which is described in section 16.35.

16.327 Toxicity Stopping Rule for Phase II portion: Based on our experience with previous regimens (i.e., 942452, 982452, 982453, N0026) in this patient population, we expect approximately 20% of patients to experience Grade 4 or 5 toxicities (treatment related AEs). If at any time, 7 of the initial 20 patients or 35% of all patients (i.e., when accrual is greater than 20 patients), have experienced any Grade 4+ non-hematologic toxicities or Grade 4+ thrombocytopenia, or, Grade 4+ complications from neutropenia (fever or infection), accrual to the study will be suspended to allow for a full review of the data. After consideration by the study team [ie, Study Chair(s), Statistician, Operations Office, etc] and consultation with representatives at the primary Internal Review Board (IRB) affiliated with the Operations Office, a decision will be made as to whether and how the study will proceed. CTCAE v3.0 will be used to determine grading for these stopping rules.

Add 15

16.33 Power and Significance Level: The probability values shown in the table below were calculated by using the following simulation: A sample of size 60 survival times were randomly selected 20,000 times from an exponential survival model ( $S(t) = \exp(-\lambda t)$ ), where  $\lambda = -\ln(\text{true success proportion})$  and  $t = \text{time}$ . Based on the sampled survival times and the 6-month interim analysis cutpoint determined in section 16.324; the power and the probability of stopping at the interim analysis (using just the first 26 patients from each trial) were calculated. The simulation resulted in a significance level of .09 and a power of .81 (assuming the true success proportion was .75).

If the true success proportion is . . . . .	0.60	0.65	0.70	0.75
then the probability of declaring that the regimen warrants further studies is . . . . .	0.09	0.28	0.56	0.81
and the probability of stopping at the interim analysis is . . . . .	0.55	0.39	0.24	0.13

16.331 Impact of performing the interim analysis on 6-month survival as opposed to 1-year survival.

- Has minor impact on  $\alpha$ ,  $\beta$  (~4% maximum)
  - $\alpha$  dropped by 1% (from .10 to .09)
  - Power (1-  $\beta$ ) dropped by 4% (from .857 to .814) when  $p=.75$
- Changes the probability of stopping at the interim analysis anywhere from 1-8%
  - Decreased by 8% when  $p=.60$
  - Increased by 3% when  $p=.75$
- The expected sample size is slightly lower (from .79% to 3.33% lower)

16.34 Other Considerations: Overall survival, time to progression, toxicity, and QOL measurements observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.35 Analysis Plans: All evaluable patients will be used for these analyses.

16.351 Primary Endpoint: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (24). These confidence intervals were calculated using a 2-stage Simon optimum design (23), using the 1-year survival cutpoint (for interim analysis) rather than the 6-month survival cutpoint because 1-year survival is what we're ultimately interested in estimating. Several pertinent examples follow:

Stopping Stage	Number of Successes	95% Confidence Interval for the True Success Proportion
1	13	(.324, .697)
1	14	(.358, .724)
1	15	(.397, .759)
1	16	(.451, .796)
2	38	(.518, .797)
2	39	(.537, .797)
2	40	(.545, .797)
2	41	(.554, .801)
2	42	(.583, .821)

16.352 Secondary Efficacy Analyses:

16.3521 A confirmed tumor response is defined to be a CR or PR noted as the objective status on 2 consecutive evaluations at least 4 weeks apart. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.3522 Time to progression is defined to be the length of time from study registration to a date of disease progression (defined in Section 11.0) or b) last follow-up. If a patient dies without documentation of disease progression, the patient will be considered to have had tumor progression at the time of death unless there is sufficient documented evidence to conclude no progression occurred prior to death. The distribution of time to progression will be estimated using the method of Kaplan-Meier (25).

16.3523 Progression-free survival is defined to be the length of time from study registration to the first of either death due to any cause or progression. Patients that have not died or progressed will be censored on their last follow-up date. If a patient dies without documentation of disease progression, the patient will be considered to have had tumor progression at the time of death unless there is sufficient documented evidence to conclude no progression occurred prior to death. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier (25).

16.3524 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (25).

16.3525 Kaplan-Meier survival curves (25) and logrank tests will be used to estimate the survival and progression-time distributions of (a) the study patients, (b) comparable patients from recent NCCTG studies, and (c) study patient subsets defined by disease and/or p27 expression. These analyses are intended to be hypothesis-generating and descriptive in manner.

16.3526 Toxicity: All eligible patients that have initiated treatment will be considered evaluable for toxicity analyses. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

- 16.4 Translational Research Endpoints: All analyses with respect to the translational component of this study are intended to be hypothesis-generating and descriptive in manner. Laboratory correlates such as p27 expression will be correlated with survival, time to progression, and response. Cox proportional hazards regression (26) will be used to model the relationship between survival (and time to progression) with p27 expression, while frequency tables (i.e., Chi-square analysis) or ANOVA will be combined with graphical techniques (i.e., scatterplots) to correlate p27 expression with response.
- 16.5 Routine Monitoring: This study will be monitored by the Mayo Clinic Cancer Center Data Safety Monitoring Board. In addition, efficacy, toxicity, and administrative information for this trial will be reviewed by the study team twice per year in conjunction with production of the semiannual NCCTG Group Meeting reports. The study team will monitor the trial for evidence of severe adverse effects and feasibility problems.
- 16.6 Inclusion of Women and Minorities
- 16.61 This study will be available to all eligible patients regardless of race, gender, or ethnic group.
- 16.62 There is no information currently available regarding differential agent effects of either regimen in subsets defined by gender, race, or ethnicity, and there is no reason to expect such differences exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on gender and racial groupings, the samples sizes are not increased in order to provide additional power for such subset analyses.
- 16.63 Based on prior NCCTG Lung Cancer program involving similar disease sites, we expect about 7% patients will be classified as minorities by race and about 40% of patients will be women. In this study we will actively seek to accrue at least 7 minority patients (10% of full accrual), where a minority patient is defined as any non-white patient. To achieve this goal, an amendment (that will modify the eligibility criteria) will immediately be sent out at the 90% target accrual stage requiring the remaining accrual to only be allowed for minority patients, unless 7+ minority patients have already been accrued to the study. Once 7+ minorities have been accrued after the 90% target accrual point, we'll re-open accrual to all patients. The expected accrual by gender and racial/ethnic group is summarized in the following table (based on goal of 10% minority accrual and 40% accrual of women):

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	1	2	0	3
Not Hispanic or Latino	25	38	0	63
Unknown	0	0	0	0
<b>Ethnic Category: Total of all subjects*</b>	26	40	0	66
Racial Category				
American Indian or Alaskan Native	1	1	0	2
Asian	0	0	0	0
Black or African American	2	3	0	5
Native Hawaiian or other Pacific Islander	0	0	0	0
White	23	36	0	59
More than one race	0	0	0	0
Unknown	0	0	0	0
<b>Racial Category: Total of all subjects*</b>	26	40	0	66
<b>Ethnic Categories:</b>	<p><b>Hispanic or Latino</b> – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”</p> <p>Not Hispanic or Latino</p>			
<b>Racial Categories:</b>	<p><b>American Indian or Alaskan Native</b> – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.</p> <p><b>Asian</b> – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)</p> <p><b>Black or African American</b> – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”</p> <p><b>Native Hawaiian or other Pacific Islander</b> – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.</p> <p><b>White</b> – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.</p>			

17.0 Pathology Considerations for Quality Control

- Add 1                      17.1      Central pathology review is required for confirmation of diagnosis. Within 30 days, submit the following material:
- Lung Pathology Reporting Form
  - Surgical Pathology and Operative report
  - Representative diagnostic slides

Slides should be placed in appropriate slide container and labeled with protocol number, study patient number, and patient initials.

- Add 1,3,8                      17.2      Central Review will be performed by Dr. Marie-Christine Aubry and Dr. Mitchel Bauman. The NCCTG memberships (excluding Mayo and affiliates) are to forward their materials specified in section 17.1 to Thomas Hoopingartner, primary clinical research associate at Siouxland Regional Cancer Center, 230 Nebraska Street, Sioux City, IA 51101-1733. The Mayo Clinic is to forward their material to Dr. Marie-Christine Aubry in Mayo Rochester. Submit Pathology Submission Forms to the NCCTG Operations Office.

Add 3

**18.0 Records and Data Collection Procedures**

18.1 Submission Timetable

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Forms	Active-Monitoring Phase (Compliance with Test Schedule)					Event-Monitoring Phase <sup>2</sup> (Completion of Active-Monitoring Phase)				At Each Occurrence			
	Initial Material	Pathology Review	Follow-up material			q. 3 months until PD <sup>2</sup>	At PD <sup>2</sup>	After PD <sup>5</sup>	Death	ADR/AER	New Primary	Grade 4 or 5 Non-AER Reportable Events/Hospitalization	Late Adverse Event
	≤2 weeks after registration	≤30 days after registration	At cycle 1 Evaluation (Cycle 1 = first 3 weeks)	At cycle 2 evaluation (Cycle 2 = last 3 weeks of chemo-RT + 4-week post-RT eval)	Observation								
On-Study Form	X												
Baseline Adverse Events/Symptoms Form	X												
OP and Path Reports	X												
Measurement Form	X		X	X	X <sup>4</sup>								
Pathology Materials (See Section 17.0)		X											
Specimen Submission (See Section 14.0)		X											
RT Material <sup>1</sup>				X									
Event-Monitoring Form						X	X	X	X	X		X	
Evaluation/Treatment Form			X	X	X <sup>4</sup>								
Dose-Limiting Toxicity Reporting Form			X <sup>3</sup>	X <sup>3</sup>									
Nadir/Adverse Event Form			X	X	X <sup>4</sup>								
End of Active Treatment Form				X									
ADR/AER (See Section 10.0)									X				
Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form											X		
CTEP Report Variables Form	X												
<p>1. For patients who do not receive any scheduled radiation therapy, submit a radiation therapy reporting form with the reason radiation was not given. For patients who receive partial or complete radiation therapy, submit the following within two weeks after the last day of radiation:</p> <p>a. RT reporting form. b. Daily treatment records. c. Dosimetry calculations, monitor unit calculations, and isodose curves.</p> <p>d. Copies of representative simulation films of all treated fields. e. Copies of representative port films of all treated fields.</p> <p>NOTE: All materials will be forwarded to the NCCTG Operations Office, Attn: Kathryn Scherger, RT Coordinator, NW Clinic 3-24, 200 First Street SW, Rochester, MN 55905.</p> <p>2. If a patient is still alive after 5 years after registration, no further follow-up is required.</p>						<p>3. Required if ≥ grade 4 hematologic, ≥ grade 3 esophagitis, ≥ grade 3 pneumonitis, or ≥ grade 4 nonhematologic other than esophagitis, pneumonitis, dyspnea, or radiation dermatitis.</p> <p>4. During observation, patients will be followed at 3 months post-RT, q 3 months for 1 year post-RT, and then q 6 months for a maximum of 5 years post-registration. After the observation phase, patients will go to event monitoring for a maximum follow-up time of 5 years from their registration date.</p> <p>5. After PD, q3 months for 1 year post-registration and then q6 months for a maximum of 5 years post-registration.</p>							

**19.0 Budget**

Costs charged to patient: All charges related to use of carboplatin, paclitaxel and RT will be charged to the patient. PS-341 will be supplied by CTEP. All supportive medical care will be charged to the patient, including hospital admission required for the management of side-effects secondary to RT, paclitaxel, CBDCA and PS-341.

## 20.0 References

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## Appendix IA

**TITLE:** N0321, Phase I/II Study of PS-341 in Combination with Paclitaxel, Carboplatin, and Concurrent Thoracic Radiation Therapy for Non-small Cell Lung Cancer (NSCLC) (Phase I Component)

**PARTICIPANTS:**

**This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.**

**Why is this research study being done?**

This study is being done to find the highest dose of the investigational drug PS-341 that can be given in combination with carboplatin, paclitaxel, and radiation therapy without causing bad side effects.

**How many people will take part in the research study?**

The plan is to have about 21-30 people take part in this study.

**What will happen in this research study?**

You will have a full medical history and physical exam taken along with chest x-ray, CT scan, and other tests that the researcher might feel are needed to fully learn about your disease and see if you can be on this study.

Add 1  
Add 1,3  
You will be given PS-341 into a vein in your arm over a very short period of time on days 1, 4, 8, 11, 22, 25, 29, 32; paclitaxel will be given into a vein in your arm over 3 hours on days 2 and 23; and following the paclitaxel infusion, carboplatin will be given into a vein in your arm over 30 minutes on days 2 and 23. Radiation therapy will begin on day 1 and continue Monday-Friday for 6 weeks. Four weeks after the radiation therapy is done, you will have routine blood tests and scans to see how your disease has responded to the treatment. If your disease has not gotten worse at the 4-week post radiation therapy evaluation, you will also have routine blood tests done 3 months after radiation therapy is done, then every 3 months for 1 year after radiation therapy, and then every 6 months for up to 5 years from the time you went on study.

Add 1

<b>Before Study Entry</b>											
Add 1	<table border="1" style="width: 100%;"> <tr> <td style="width: 30%;">Before Study entry</td> <td> <ul style="list-style-type: none"> <li>• Tissue blocks from surgery submitted for research</li> <li>• Routine blood tests</li> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Pregnancy test for women of child bearing potential</li> <li>• Discuss radiation therapy with your doctor</li> </ul> </td> </tr> </table>	Before Study entry	<ul style="list-style-type: none"> <li>• Tissue blocks from surgery submitted for research</li> <li>• Routine blood tests</li> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Pregnancy test for women of child bearing potential</li> <li>• Discuss radiation therapy with your doctor</li> </ul>								
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<b>During Treatment-</b>											
Add 1	<table border="1" style="width: 100%;"> <tr> <td style="width: 30%;">Days M-F x 6 weeks</td> <td> <ul style="list-style-type: none"> <li>• Radiation therapy</li> </ul> </td> </tr> <tr> <td>Days 1, 4, 8, 11, 22, 25, 29, 32</td> <td> <ul style="list-style-type: none"> <li>• PS-341</li> </ul> </td> </tr> <tr> <td>Day 2</td> <td> <ul style="list-style-type: none"> <li>• Paclitaxel given into the vein over 3 hours followed by</li> <li>• Carboplatin given over 30 minutes</li> </ul> </td> </tr> <tr> <td>Day 23</td> <td> <ul style="list-style-type: none"> <li>• Routine blood tests</li> <li>• Paclitaxel given into the vein over 3 hours followed by</li> <li>• Carboplatin given over 30 minutes</li> </ul> </td> </tr> <tr> <td>Weekly</td> <td> <ul style="list-style-type: none"> <li>• Routine blood tests</li> <li>• History and exam</li> </ul> </td> </tr> </table>	Days M-F x 6 weeks	<ul style="list-style-type: none"> <li>• Radiation therapy</li> </ul>	Days 1, 4, 8, 11, 22, 25, 29, 32	<ul style="list-style-type: none"> <li>• PS-341</li> </ul>	Day 2	<ul style="list-style-type: none"> <li>• Paclitaxel given into the vein over 3 hours followed by</li> <li>• Carboplatin given over 30 minutes</li> </ul>	Day 23	<ul style="list-style-type: none"> <li>• Routine blood tests</li> <li>• Paclitaxel given into the vein over 3 hours followed by</li> <li>• Carboplatin given over 30 minutes</li> </ul>	Weekly	<ul style="list-style-type: none"> <li>• Routine blood tests</li> <li>• History and exam</li> </ul>
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<b>4 Weeks Post Radiation Therapy</b>											
Add 1	<table border="1" style="width: 100%;"> <tr> <td style="width: 30%;"></td> <td> <ul style="list-style-type: none"> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Routine blood tests</li> </ul> </td> </tr> </table>		<ul style="list-style-type: none"> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Routine blood tests</li> </ul>								
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<b>After Treatment is Done and Disease is the Same or Better</b>											
Add 3	<table border="1" style="width: 100%;"> <tr> <td style="width: 30%;">3 months after radiation therapy, then every 3 months for 1 year after radiation therapy, and then every 6 months for up to five years from time of registration</td> <td> <ul style="list-style-type: none"> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Routine blood tests</li> </ul> </td> </tr> </table>	3 months after radiation therapy, then every 3 months for 1 year after radiation therapy, and then every 6 months for up to five years from time of registration	<ul style="list-style-type: none"> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Routine blood tests</li> </ul>								
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Add 1 The researchers in this study will also use part of your left over tissue from the biopsy that was done to diagnose your cancer. The researchers will be looking to see if a certain mutation in the tumor tissue relates to how you might respond to treatment. The results of these tests will not be sent to you or your doctor and will not be used in planning your care.

Add 1 You can take part in the treatment part of this study without taking part in submission of tissue for research purposes.

***Please read the following statements and mark your choice:***

1. I agree to tissue samples being given to laboratories associated with NCCTG for research testing.

Yes     No    Please initial here: \_\_\_\_\_    Date: \_\_\_\_\_

**How long will I be in the research study?**

You will get treatment for six weeks. You will be followed for up to five years from the time you started treatment on this study so that the researchers can watch your health status.

**Are there reasons I might leave the research study early?**

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the researcher if you decide to stop and you will be informed if any additional tests may need to be done for your safety.

In addition, the researchers may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped.

**Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG)?**

Add 1

Another part of this research study is taking a small sample of your left over tissue to be stored for future research studies of cancer. The sample may be stored indefinitely. You have a say in how your stored sample is used in future research. You can still take part in the treatment study without giving your sample.

Your sample will be stored safely at NCCTG and will be given a code (rather than your name) when it is used in research. This code will allow your sample to be used without anyone knowing that it is your sample just by looking at the label.

Your samples will be used only for research and will not be sold. You will not be paid for allowing your sample to be used in research even though the research done on this sample may help to develop new products in the future.

Sometimes tissue is used for genetic research (research about diseases that are passed on in families). Even if your sample is used for genetic research, the findings will not be linked with your medical records and they will not be given to people outside of the research process.

***Please read the following statements and mark your choice:***

1. I permit my sample to be stored and used for future research of cancer:

Yes     No    Please initial here: \_\_\_\_\_    Date: \_\_\_\_\_

2. I permit my sample to be stored and used in future research to learn, prevent, or treat other health problems:

Yes     No    Please initial here: \_\_\_\_\_    Date: \_\_\_\_\_

If you want your sample destroyed at any time, write to the Secretary of the \_\_\_\_\_ Institutional Review Board \_\_\_\_\_. NCCTG has the right to end storage of the sample without telling you.

The sample will be the property of NCCTG. Outside researchers may one day ask for a part of your sample for studies now or future studies.

**How do outside researchers get the sample?**

Researchers from universities, hospitals, and other health organizations do research using tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the tissue samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample for future research, they will decide if you will be contacted and, if so, they would have to contact you through the researchers at NCCTG.

I permit NCCTG to give my sample to outside researchers:

***Please mark one box:***

Yes  No    Please initial here: \_\_\_\_\_    Date: \_\_\_\_\_

## What are the risks of the study?

While you are taking part in this study, you are at risk for these side effects. You should talk to the researcher and/or your medical doctor about these side effects. There also may be other side effects that are not known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the PS-341, carboplatin, and paclitaxel are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death.

### **Paclitaxel** (Taxol®)

#### **Likely risks of Paclitaxel** (Taxol®) *(events occurring greater than 20% of the time)*

- Add 1,8
- Loss of appetite
  - Nausea (feeling of being sick to the stomach)
  - Vomiting (throwing up)
  - Diarrhea
  - Loss of body fluids
  - Redness, soreness, and/or irritation of the linings of the mouth, throat, and digestive system
  - Fall in white blood cell counts leading to an increased risk of infection.
  - Hair loss
  - Nerve damage with numbness and tingling, usually of the hands and feet. This usually goes away when the drug is stopped.

#### **Less likely risks of Paclitaxel** (Taxol®) *(events occurring less than or equal to 20% of the time)*

- Add 8
- Muscle and/or joint aching
  - Low blood pressure
  - Lightheadedness
  - Blurred vision
  - Sensation of seeing flashing lights
  - Skin rash
  - Increase in tests of liver function
  - Fall in platelet count leading to an increased risk of bleeding
  - Fall in red blood cell count causing anemia

#### **Rare but serious risks of Paclitaxel** (Taxol®) *(events occurring less than 2-3% of the time)*

- Add 8
- Damage to liver function, which may lead to skin yellowing
  - Inflammation of the lungs that may cause shortness of breath
  - Escape of the drug from the vein injection site may cause local mild swelling, tenderness, and/or chronic skin sores
  - Severe skin reaction which may require hospitalization
  - Loss of bearings and confusion
  - Swelling and soreness of the pancreas
  - Seizures
  - Abnormal heart rhythms that may be serious. You will be carefully watched for any heart problems.
  - Allergic reactions with hives, itching, wheezing, or a severe drop in blood pressure with difficult breathing (rare). This allergic reaction is thought to be caused by Cremophor®, a necessary part of the paclitaxel drug mixture, rather than by the paclitaxel itself. This goes away with medication. Before treatment begins, you will be given a drug so that this reaction will be less likely and you will be closely watched for such a reaction.
- Add 1
- Development of a hole in the wall of the bowel that may be life-threatening

Carboplatin:

Likely side effects:

Add  
1,10

- Change in appetite or weight
- Nausea (feeling sick to the stomach)
- Vomiting (throwing up)
- Low white blood cell counts leading to an increased risk of infections with or without fever
- Low red blood cell count causing anemia
- Low platelet count leading to an increased risk of bleeding
- Abnormal mineral levels in the blood
- Change in blood tests, particularly loss of magnesium

Less likely side effects:

- Difficult bowel movements (constipation)
- Mouth sores
- Change in taste
- Hearing problems
- Fever
- Numbness and/or tingling of the hands and feet, usually this goes away after the drug is stopped, however, for some patients this may not ever go away
- Hair loss or thinning
- Loose stools (diarrhea)
- Abnormal kidney tests
- Abnormal liver tests
- Low or high blood pressure
- Vision problems
- Allergic reactions (rash, hives, redness, itching, swelling, and difficulty in breathing with wheezing)
- Other skin rashes

Rare but serious side effects:

- Secondary leukemia and/or myelodysplastic syndrome (damage to the bone marrow that affects the making of normal blood cells)

As with any medication, allergic reactions are a possibility.

PS-341:

Likely related side effects of PS-341 (events occurring greater than 20% of the time):

Add  
1,3,4,5,6,7,  
11,13

- Fatigue or tiredness
- Loss of appetite
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Swelling and fluid buildup in the arms or legs
- Diarrhea (loose stools)
- Constipation (difficulty passing stool)
- Fever
- Decreased number of blood cells that help to clot the blood

- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Lack of enough red blood cells (anemia)
- Infection
- Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)

Add  
4,5,6,7,9,  
11,13

Less likely related side effects of PS-341 (events occurring greater than 3% but less than 20% of the time):

- Chills, shivering
- Heartburn
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel
- Irritation or sores in the lining of the throat
- Fever with dangerously low white blood cell count
- Double or blurred vision
- Back pain
- Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs
- Infection which occurs due to a decreased number of a type of white blood cell (lymphocyte)
- Dehydration (loss of body fluids)
- Nerve damage causing numbness, tingling, burning (sensory neuropathy)
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Anxiety, feelings of dread or danger
- Cough
- Shortness of breath
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Low blood pressure
- Pneumonia
- Difficulty sleeping or falling asleep
- Decreased total number of white blood cells (lymphocyte)
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decrease in the total number of white blood cells (leukocytes)
- Bleeding of the digestive tract
- Nosebleed
- Blood infection
- Muscle weakness of the whole body
- Fainting
- Belly pain
- Bone pain
- Leg and/or arm pain
- Headache or head pain
- Joint pain
- Muscle pain
- Nerve pain

Add  
1,3,4,6,7,  
11,13

Rare but serious side effects of PS-341 (events occurring less than 3% of the time):

- A hole in the digestive tract
- Syndrome associated with high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings
- Sudden or traumatic injury to the kidney
- Progressive necrosis (tissue death) of a part (the white matter) of the brain without inflammation (swelling and redness)

### Chest radiation

#### More common side effects

- Tiredness
- Hard time swallowing due to injury to the esophagus
- Damage to the skin
- Scarring of the lung, which can be life threatening
- Any organ in the chest (heart, esophagus, skin, muscle, bone, spinal cord or lung) can be injured.

#### Rare side effects

- Life-threatening injury due to severe injury to the chest organs

It is possible that these side effects may be more severe when PS-341, taxol, and carboplatin are combined with radiation therapy.

The study drugs carboplatin and paclitaxel may be harmful to an unborn or breast-fed child. No studies have been performed to determine if there are any harmful effects of PS-341 on an unborn or breast-fed child. There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child in a woman who takes part in this study. One of the following birth control measures must be used by all women who can become pregnant and are sexually active or by their sexual partners while in this study: condoms, diaphragm, birth control pills, injections, intrauterine device (IUD), surgical sterilization, subcutaneous implants, or abstinence. Breast-feeding mothers must stop breast-feeding. Women who can still become pregnant must have a pregnancy test before taking part in this study. Blood will be taken from a vein in your arm with a needle 7 days before you enter the study. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study. During this study if you are female and miss a period or think you may be pregnant, you must notify the Investigator immediately. If you are male and your partner misses her period or thinks she may be pregnant, you must notify the Investigator immediately.

Whether you are male or female, you are strongly urged to use an effective birth control method for 6 months during and after the last treatment you received on this study.

### **Are there benefits to taking part in this research study?**

This study may not make your health better. However, your tumor may shrink, and your life may be prolonged.

### **What other choices do I have if I don't take part in this research study?**

You do not have to be in this study to receive treatment for your condition. Your other choices may include radiation therapy alone, a combination of radiation therapy and chemotherapy, or another type of research study. You could also decide to take no treatment. You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

### **Will I need to pay for the tests and procedures?**

The drugs paclitaxel and carboplatin can be bought with a prescription.

The Division of Cancer Treatment, and Diagnosis, NCI, will provided you with PS-341 free of charge for this study. Every effort will be made to ensure adequate supplies of PS-341, free of charge, for all participants. If the drug becomes commercially available for this indication there is a remote possibility

that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should this situation arise. You and/or your health plan will need to pay for all costs associated with this treatment.

You and/or your health plan will need to pay for all tests and procedures that are part of this study because they are needed for your regular medical care. You and your health plan might also have to pay for other drugs or treatment that are given to help you control side effects. Radiation therapy will need to be paid by you or your health plan. Before you take part in this study, you should call your health insurer to find out if the cost of these tests and/or procedures will be paid for by the plan. Some health insurers will not pay for these costs. You will have to pay for any costs not covered by your health insurer.

**What happens if I am injured because I took part in this research study?**

If you have side effects from the study treatment, you need to report them to the researcher and your regular physician, and you will be treated as needed. You and your insurer will be billed for these services at the usual charge. You will not be offered free medical care or payment for any bad side effects from taking part in this study. Medical services will be given at the usual charge.

**What are my rights if I take part in this research study?**

Taking part in this research study does not take away any other rights or benefits you might have if you did not take part in the study. Taking part in this study does not give you any special privileges. You will not be penalized in any way if you decide not to take part or if you stop after you start the study. Specifically, you do not have to be in this study to receive or continue to receive medical care. If you stop the study you would still receive medical care for your condition although you might not be able to get the study drugs.

You will be told of important new findings or any changes in the study or procedures that may affect you or your willingness to continue in the study.

**Who can answer my questions?**

You may talk to Dr. ( \_\_\_\_\_ ), at any time about any questions or concerns you have on this study.

You can get further information about policies, the conduct of this study, or the rights of research subjects from \_\_\_\_\_

**Where can I get more information about clinical trials?**

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI Web site: <http://www.cancer.gov/>

**What about confidentiality?**

Information from this study may be published or presented at scientific meetings. However, your name and other identifying information will not be sent outside of NCCTG without written permission unless the law allows it. Your medical record will be used by the researchers in this study. Representatives of NCCTG and Millennium Pharmaceuticals will be able to look at your medical records to check the accuracy of the forms completed for the study. Information from your medical records may also be made available to the Food and Drug Administration (FDA), National Cancer Institute (NCI), other U.S. government agencies including the Office for Human Research Protections or other offices within the Department of Health and Human Services, and/or the Office of the Inspector General.

**I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to take part in this research study.**

\_\_\_\_\_  
(Date)                      \_\_\_\_\_  
(Printed Name of Participant)

\_\_\_\_\_  
(Signed Name of Participant)

\_\_\_\_\_  
(Date)                      \_\_\_\_\_  
(Printed Name of Individual Obtaining Consent)

\_\_\_\_\_  
(Signature of Individual Obtaining Consent)

**Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be tried to be used in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.**

**Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This should be specific for each institution.**

## Appendix IB

**TITLE:** N0321, Phase I/II Study of PS-341 in Combination with Paclitaxel, Carboplatin, and Concurrent Thoracic Radiation Therapy for Non-small Cell Lung Cancer (NSCLC) (Phase II Component)

### **PARTICIPANTS:**

**This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.**

#### **Why is this research study being done?**

This study is being done to find out what effects (good and bad) the combination of PS-341, paclitaxel, carboplatin and radiation therapy has on you and your cancer.

#### **How many people will take part in the research study?**

The plan is to have about 66 people take part in this study.

#### **What will happen in this research study?**

You will have a full medical history and physical exam taken along with blood tests, chest x-ray, CT scan, and other tests that the researcher might feel are needed to fully learn about your disease and see if you can be on this study.

Add 1  
Add 1,3  
You will be given PS-341 into a vein in your arm over a very short period of time on days 1, 4, 8, 11, 22, 25, 29, 32; paclitaxel will be given into a vein in your arm over 3 hours on days 2 and 23; and following the paclitaxel infusion, carboplatin will be given into a vein in your arm over 30 minutes on days 2 and 23. Radiation therapy will begin on day 1 and continue Monday-Friday for 6 weeks. Four weeks after the radiation therapy is done, you will have routine blood tests and scans to see how your disease has responded to the treatment. If your disease has not gotten worse at the 4-week post radiation therapy evaluation, you will also have routine blood tests done 3 months after radiation therapy is done, then every 3 months for 1 year after radiation therapy, and then every 6 months for up to 5 years from the time you went on study.

Add 1

<b>Before Study Entry</b>			
Add 1	<table border="1" style="width: 100%;"> <tr> <td style="width: 30%;">Before Study entry</td> <td> <ul style="list-style-type: none"> <li>• Tissue blocks from surgery submitted for research</li> <li>• Routine blood tests</li> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Pregnancy test for women of child bearing potential</li> <li>• Discuss radiation therapy with your doctor</li> </ul> </td> </tr> </table>	Before Study entry	<ul style="list-style-type: none"> <li>• Tissue blocks from surgery submitted for research</li> <li>• Routine blood tests</li> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Pregnancy test for women of child bearing potential</li> <li>• Discuss radiation therapy with your doctor</li> </ul>
Before Study entry	<ul style="list-style-type: none"> <li>• Tissue blocks from surgery submitted for research</li> <li>• Routine blood tests</li> <li>• History and exam</li> <li>• CT chest scan</li> <li>• Pregnancy test for women of child bearing potential</li> <li>• Discuss radiation therapy with your doctor</li> </ul>		
<b>During Treatment</b>			
Add 1	Days M-F x 6 weeks		
Add 1	Days 1, 4, 8, 11, 22, 25, 29, 32		
Add 1	Day 2		
Add 1,13	Day 23		
Add 1	Weekly		
<b>4 Weeks Post Radiation Therapy</b>			
Add 1			
Add 1			
<b>After Treatment is Done and Disease is the Same or Better</b>			
Add 1,3	3 months after radiation therapy, then every 3 months for 1 year after radiation therapy, and then every 6 months for up to 5 years from time of study registration		

Add 1 The researchers in this study will also use part of your left over tissue from the biopsy that was done to diagnose your cancer. The researchers will be looking to see if a certain mutation in the tumor tissue relates to how you might respond to treatment. The results of these tests will not be sent to you or your doctor and will not be used in planning your care.

Add 1 You can take part in the treatment part of this study without taking part in submission of tissue for research purposes.

***Please read the following statements and mark your choice:***

1. I agree to tissue samples being given to laboratories associated with NCCTG for research testing.

Yes     No    Please initial here: \_\_\_\_\_    Date: \_\_\_\_\_

**How long will I be in the research study?**

You will get treatment for six weeks. You will be followed for up to five years from the time you started treatment on this study so that the researchers can watch your health status.

**Are there reasons I might leave the research study early?**

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the researcher if you decide to stop and you will be informed if any additional tests may need to be done for your safety.

In addition, the researchers may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped.

**Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG)?**

Add 1 Another part of this research study is taking a small sample of your left over tissue to be stored for future research studies of cancer. The sample may be stored indefinitely. You have a say in how your stored sample is used in future research. You can still take part in the treatment study without giving your sample.

Your sample will be stored safely at NCCTG and will be given a code (rather than your name) when it is used in research. This code will allow your sample to be used without anyone knowing that it is your sample just by looking at the label.

Your samples will be used only for research and will not be sold. You will not be paid for allowing your sample to be used in research even though the research done on this sample may help to develop new products in the future.

Sometimes tissue is used for genetic research (research about diseases that are passed on in families). Even if your sample is used for genetic research, the findings will not be linked with your medical records and they will not be given to people outside of the research process.

***Please read the following statements and mark your choice:***

1. I permit my sample to be stored and used for future research of cancer:

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

2. I permit my sample to be stored and used in future research to learn, prevent, or treat other health problems:

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

If you want your sample destroyed at any time, write to the Secretary of the \_\_\_\_\_ Institutional Review Board \_\_\_\_\_. NCCTG has the right to end storage of the sample without telling you.

The sample will be the property of NCCTG. Outside researchers may one day ask for a part of your sample for studies now or future studies.

**How do outside researchers get the sample?**

Researchers from universities, hospitals, and other health organizations do research using tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the tissue samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample for future research, they will decide if you will be contacted and, if so, they would have to contact you through the researchers at NCCTG.

I permit NCCTG to give my sample to outside researchers:

***Please mark one box:***

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

## What are the risks of the study?

While you are taking part in this study, you are at risk for these side effects. You should talk to the researcher and/or your medical doctor about these side effects. There also may be other side effects that are not known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the PS-341, carboplatin, and paclitaxel are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death.

### **Paclitaxel** (Taxol®)

#### Add 1, 8 **Likely risks of Paclitaxel (Taxol®)** *(events occurring greater than 20% of the time)*

- Add 1 • Loss of appetite
- Add 1 • Nausea (feeling sick to your stomach)
- Add 1 • Vomiting (throwing up)
- Diarrhea
- Loss of body fluids
- Redness, soreness, and/or irritation of the linings of the mouth, throat, and digestive system
- Fall in white blood cell counts leading to an increased risk of infection
- Hair loss
- Nerve damage with numbness and tingling, usually of the hands and feet. This usually goes away when the drug is stopped.

#### Add 8 **Less likely risks of Paclitaxel (Taxol®)** *(events occurring less than or equal to 20% of the time)*

- Muscle and/or joint aching
- Low blood pressure
- Lightheadedness
- Blurred vision
- Sensation of seeing flashing lights
- Skin rash
- Increase in tests of liver function
- Fall in platelet count leading to an increased risk of bleeding
- Fall in red blood cell count causing anemia

#### Add 8 **Rare but serious risks of Paclitaxel (Taxol®)** *(events occurring less than 2-3% of the time)*

- Damage to liver function, which may lead to skin yellowing
- Inflammation of the lungs that may cause shortness of breath
- Escape of the drug from the vein injection site may cause local mild swelling, tenderness, and/or chronic skin sores
- Severe skin reaction which may require hospitalization
- Loss of bearings and confusion
- Swelling and soreness of the pancreas
- Seizures
- Abnormal heart rhythms that may be serious. You will be carefully watched for any heart problems.
- Allergic reactions with hives, itching, wheezing, or a severe drop in blood pressure with difficult breathing (rare). This allergic reaction is thought to be caused by Cremophor®, a necessary part of the paclitaxel drug mixture, rather than by the paclitaxel itself. This goes away with medication. Before treatment begins, you will be given a drug so that this reaction will be less likely and you will be closely watched for such a reaction.
- Add 1 • Development of a hole in the wall of the bowel that may be life-threatening

Carboplatin:

- Add 1,10 Likely side effects:
- Change in appetite or weight
  - Nausea (feeling sick to your stomach)
  - Vomiting (throwing up)
  - Low white blood cell counts leading to an increased risk of infections with or without fever
  - Low red blood cell count causing anemia
  - Low platelet count leading to an increased risk of bleeding
  - Abnormal mineral levels in the blood

- Add 10 Less likely side effects:
- Difficult bowel movements (constipation)
  - Mouth sores
  - Change in taste
  - Hearing problems
  - Fever
  - Numbness and/or tingling of the hands and feet, usually this goes away after the drug I stopped, however, for some patients this may not ever go away
  - Hair loss or thinning
  - Loose stools (diarrhea)
  - Abnormal kidney tests
  - Abnormal liver tests
  - Low or high blood pressure
  - Vision problems
  - Allergic reactions (rash, hives, redness, itching, swelling, and difficulty in breathing with wheezing)
  - Other skin rashes

- Add 10 Rare but serious side effects:
- Secondary leukemia and/or myelodysplastic syndrome (damage to the bone marrow that affects the making of normal blood cells)

Add 1 As with any medication, allergic reactions are a possibility.

PS-341:

- Add 1,3,4,5,6,7,9,11,13 Likely related side effects of PS-341 (events occurring greater than 20% of the time):
- Fatigue or tiredness
  - Loss of appetite
  - Nausea (feeling sick to your stomach)
  - Vomiting (throwing up)
  - Swelling and fluid buildup in the arms or legs
  - Diarrhea (loose stools)
  - Constipation (difficulty passing stool)
  - Fever
  - Decreased number of blood cells that help to clot the blood
  - Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning

- Lack of enough red blood cells (anemia)
- Infection
- Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)

Add  
4,5,6,7,9,  
11,13

Less likely related side effects of PS-341 (events occurring greater than 3% but less than 20% of the time):

- Chills, shivering
- Heartburn
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel
- Irritation or sores in the lining of the throat
- Fever with dangerously low white blood cell count
- Double or blurred vision
- Back pain
- Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs
- Infection which occurs due to a decreased number of a type of white blood cell (lymphocyte)
- Dehydration (loss of body fluids)
- Nerve damage causing numbness, tingling, burning (sensory neuropathy)
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Anxiety, feelings of dread or danger
- Cough
- Shortness of breath
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Low blood pressure
- Pneumonia
- Difficulty sleeping or falling asleep
- Decreased total number of white blood cells (lymphocyte)
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decrease in the total number of white blood cells (leukocytes)
- Bleeding of the digestive tract
- Nosebleed
- Blood infection
- Muscle weakness of the whole body
- Fainting
- Belly pain
- Bone pain
- Leg and/or arm pain
- Headache or head pain
- Joint pain
- Muscle pain
- Nerve pain

Add  
1,3,4,6,7,  
11,13

Rare but serious side effects of PS-341 (events occurring less than 3% of the time):

- A hole in the digestive tract
- Syndrome associated with high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings
- Sudden or traumatic injury to the kidney
- Progressive necrosis (tissue death) of a part (the white matter) of the brain without inflammation (swelling and redness)
- imaging findings
- Kidney failure

### Chest radiation

#### More common side effects

- Tiredness
- Hard time swallowing due to injury to the esophagus
- Damage to the skin
- Scarring of the lung, which can be life threatening
- Any organ in the chest (heart, esophagus, skin, muscle, bone, spinal cord or lung) can be injured.

#### Rare side effects

- Life-threatening injury due to severe injury to the chest organs

It is possible that these side effects may be more severe when PS-341, taxol, and carboplatin are combined with radiation therapy.

The study drugs carboplatin and paclitaxel may be harmful to an unborn or breast-fed child. No studies have been performed to determine if there are any harmful effects of PS-341 on an unborn or breast-fed child. There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child in a woman who takes part in this study. One of the following birth control measures must be used by all women who can become pregnant and are sexually active or by their sexual partners while in this study: condoms, diaphragm, birth control pills, injections, intrauterine device (IUD), surgical sterilization, subcutaneous implants, or abstinence. Breast-feeding mothers must stop breast-feeding. Women who can still become pregnant must have a pregnancy test before taking part in this study. Blood will be taken from a vein in your arm with a needle 7 days before you enter the study. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study. During this study if you are female and miss a period or think you may be pregnant, you must notify the Investigator immediately. If you are male and your partner misses her period or thinks she may be pregnant, you must notify the Investigator immediately.

Whether you are male or female, you are strongly urged to use an effective birth control method for 6 months during and after the last treatment you received on this study.

### **Are there benefits to taking part in this research study?**

This study may not make your health better. However, the combination of radiation and these chemotherapy agents may make your tumors shrink.

### **What other choices do I have if I don't take part in this research study?**

You do not have to be in this study to receive treatment for your condition. Your other choices may include radiation in combination with standard chemotherapy drugs, not including PS-341, which is experimental. You could also get radiation treatments alone without chemotherapy, or you could be treated on some other investigational program. You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

### **Will I need to pay for the tests and procedures?**

The drugs paclitaxel and carboplatin can be bought with a prescription.

The Division of Cancer Treatment, and Diagnosis, NCI, will provide you with PS-341 free of charge for this study. Every effort will be made to ensure adequate supplies of PS-341, free of charge, for all participants. If the drug becomes commercially available for this indication there is a remote possibility that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should

this situation arise. You and/or your health plan will need to pay for all costs associated with this treatment.

You and/or your health plan will need to pay for all tests and procedures that are part of this study because they are needed for your regular medical care. You and your health plan might also have to pay for other drugs or treatment that are given to help you control side effects. Radiation therapy will need to be paid by you or your health plan. Before you take part in this study, you should call your health insurer to find out if the cost of these tests and/or procedures will be paid for by the plan. Some health insurers will not pay for these costs. You will have to pay for any costs not covered by your health insurer.

**What happens if I am injured because I took part in this research study?**

If you have side effects from the study treatment, you need to report them to the researcher and your regular physician, and you will be treated as needed. You and your insurer will be billed for these services at the usual charge. You will not be offered free medical care or payment for any bad side effects from taking part in this study. Medical services will be given at the usual charge.

**What are my rights if I take part in this research study?**

Taking part in this research study does not take away any other rights or benefits you might have if you did not take part in the study. Taking part in this study does not give you any special privileges. You will not be penalized in any way if you decide not to take part or if you stop after you start the study. Specifically, you do not have to be in this study to receive or continue to receive medical care. If you stop the study you would still receive medical care for your condition although you might not be able to get the study drugs.

You will be told of important new findings or any changes in the study or procedures that may affect you or your willingness to continue in the study.

**Who can answer my questions?**

You may talk to Dr. ( \_\_\_\_\_ ), at any time about any questions or concerns you have on this study.

You can get further information about policies, the conduct of this study, or the rights of research subjects from \_\_\_\_\_  
\_\_\_\_\_.

**Where can I get more information about clinical trials?**

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI Web site: <http://www.cancer.gov/>



## Appendix II

### New York Heart Association Classifications

#### Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

<u>Class</u>	<u>Cardiac Symptoms</u>	<u>Limitations</u>	<u>Need for Additional Rest*</u>	<u>Physical Ability to work**</u>
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

---

\* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

\*\* At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

### **Appendix III Radiation Therapy Quality Control Guidelines**

#### 1. Dose

Dose will be specified at isocenter for isocentric treatments and at central axis midplane for parallel opposed treatments. The total dose as well as the daily dose must be within 5% of that specified in the protocol. Deviations of  $\geq 5-10\%$  will constitute a minor deviation and deviations of greater than 10% will result in a major deviation.

Dose to critical normal structures will not exceed that specified in protocol by more than 5%. Treatment of normal structures to doses exceeding that in the protocol by  $>5-10\%$  will result in a minor deviation. Treatment of normal structures to doses which exceed those specified in the protocol by more than 10% will result in a major deviation.

#### 2. Treatment Volumes

Radiation therapy fields must be designed to encompass the target volume, as specified in the protocol completely. A minor deviation will result when the target volume extends to the edge of the radiation therapy field. A major deviation will result when the target volume extends outside the radiation therapy field.

Normal structures are only to be included within the radiation field in as much as this is necessary to treat the primary tumor volume. A minor deviation will result when normal structures are unnecessarily included, but this is not felt to result in unacceptable toxicity which would interfere with the scientific aims of the protocol. A major deviation will result when the normal structures are unnecessarily included in the radiation therapy field and such inclusion is felt likely to result in a major increase in toxicity which would potentially compromise the scientific goals of the study. A major deviation will result if the  $V_{20}$  is  $\geq 40\%$ .

#### 3. Treatment Interruptions

Unless explicitly noted in the protocol, treatment is to be given five times per week. Interruptions for reasons other than toxicity, intervening medical conditions or holidays which prolong treatment by  $<10\%$  will not result in a protocol deviation. Interruptions which prolong treatment by 10-20% will result in a minor deviation and interruptions which prolong treatment by  $>20\%$  will result in a major deviation. Treatment breaks which occur under conditions allowed for by the protocol will be included in the calculation of overall "normal" treatment time.

#### 4. Treatment Planning

The minimum and maximum doses received by the tumor volume should be within 5% of that specified in the protocol. Deviations of  $\geq 5-10\%$  will result in a minor deviation and deviations greater than 10% will result in a major deviation. Small areas, less than  $2\text{ cm}^2$ , which receive doses higher or lower than specified in the protocol will not result in a deviation.

#### 5. Any individual minor deviation will result in an overall score of minor deviation; any major deviation will result in an overall score of a major deviation. Multiple minor deviations will not add up to a major deviation.

## Appendix IV

### NCI/Millennium Pharmaceuticals Cooperative Research and Development Agreement for Development of PS-341

The agent(s) (hereinafter referred to as “Agent(s)”), PS-341, used in this protocol is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Millennium Pharmaceuticals (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment, Diagnosis and Centers. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and should be maintained as such by the investigators.
2. For a clinical protocol where there is an investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as “Multi-Party Data”):
  - a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI’s participation in the proposed combination protocol.
  - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational Agent.
  - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (see #5). Clinical trial data developed under a CRADA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator’s wish to contact them.
5. Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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

Regulatory Affairs Branch, CTEP, DCTDC, NCI  
Executive Plaza North, Room 7111  
Bethesda, Maryland 20892  
Fax 301/402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

**Appendix V**

**Deleted as of Addendum 14**