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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Dawne Wenzel, M.A., Protocol Coordinator (E-mail: dwenzel@swog.org)

RE: **S1206**, "A Dose Finding Study Followed by Phase II Randomized, Placebo-Controlled Study of Veliparib (ABT-888) Added to Chemoradiotherapy with Carboplatin and Paclitaxel for Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC), (NCI Study Number 8811)." Study Chairs: Drs. A. Argiris, M. Cristea, A.M. Chen and J.M. Sands

REVISION #7

Study Chair: Athanassios Argiris, M.D.
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IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Editorial / Administrative changes

REVISION #7

Please note that this study is referenced as "**8811**" in the OPEN, RSS and SpecTrac systems. Please use the protocol number "**8811**" when accessing these databases.

1. The Version Date of the protocol and Model Consent Form have been updated.

2. **Page 29, Section 7.3b**: In the chart the route of administration for carboplatin has been changed from "IV 30 minutes after completion of paclitaxel" to "30 minute IV infusion immediately following paclitaxel."

3. **Page 37, Section 7.8**: The following has been removed from this paragraph "Sites utilizing the CIRB must use the intake calendar provided." In the next sentence, "not utilizing the CIRB" has been removed as this is not a study which utilizes the CIRB.

4. **Page 45, Section 8.4d**: In the chart for Hepatic Toxicity (Paclitaxel dose modification only), the symbol ≤ in the Bilirubin column for Grade 3 has been changed to >.

5. **Page 51, Section 9.2**: Footnote 5 has been added to indicate that the EKG must be performed within 28 days prior to registration. All other numbered footnotes have been renumbered accordingly.

6. **Page 62, Section 13.2**: This section has been deleted as slot reservation is no longer necessary in the current Phase II portion of the study. Subsequent sections have been renumbered accordingly.

7. **Page 63, Section 13.2c.1**: The entire second paragraph about using the CIRB has been removed from this section as this is not a study which utilizes the CIRB.

8. **Page 64, Section 13.2c.3**: "For sites not participating via the NCI CIRB" has been removed from this section as this is not a study which utilizes the CIRB.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date: October 1, 2012

SWOG

A DOSE FINDING STUDY FOLLOWED BY PHASE II RANDOMIZED, PLACEBO-CONTROLLED STUDY OF VELIPARIB (ABT-888) ADDED TO CHEMORADIOTHERAPY WITH CARBOPLATIN AND PACLITAXEL FOR UNRESECTABLE STAGE III NON-SMALL CELL LUNG CANCER (NSCLC), (NCI STUDY NUMBER 8811)

NCT #01386385

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AGENTS:

NCI Supplied Investigational Agent:
ABT-888 (veliparib, NSC 737664)

IND Exempt Agents (Commercially Supplied):
Carboplatin (CBDCA) (NSC-241240)
Paclitaxel, Taxol® (NSC-673089)

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ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via: **ONLINE**: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) **EMAIL**: CTSURegulatory@ctsu.coccg.org (regulatory documentation only) **FAX**: 215-569-0206 **MAIL**: CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 For regulatory questions call the CTSU Regulatory Help Desk at 1-866-651-CTSU	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through SWOG CRA Workbench at https://crawb.crab.org/TXWB/ctsulogon.aspx. Please see the data submission section of the protocol for further instructions. **SWOG** Operations Office, SWOG 4201 Medical Dr., Ste. 250 San Antonio, TX 78229-5631 **Phone:** 210-614-8808 Do <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> copy the CTSU on data submissions. <u>Other Tools and Reports</u>: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS. Note: Non-lead group institutions will order the following supplies from the CTSU Operations Office:		
<u>For patient eligibility or data submission</u> questions contact the SWOG Data Operations Center by phone or email: 206/652-2267 lungquestion@crab.org **<u>For clinical</u> questions (i.e. patient eligibility or treatment-related)** contact the Study Chairs by email: Athanassios Argiris, M.D. at: athanassios.argiris@gmail.com, Mihaela Cristea, M.D. at mcristea@coh.org, or Jacob Sands, M.D. at Jacob.M.Sands@lahey.org		
<u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA

Phase I portion (open to limited institutions as listed on the Title Page):

First Registration

↓

Chemoradiation Phase
6 weeks of external beam radiation + paclitaxel + carboplatin + ABT-888
at assigned dose level (see Section 7.3a)

↓

Re-evaluation and Second Registration

↓

Consolidation Phase (ABT-888 + carboplatin + paclitaxel)
(Two 21-day cycles)

Phase II portion (open to all SWOG institutions):

First Registration/Randomization

↓

Chemoradiation Phase
6 weeks of external beam radiation + paclitaxel + carboplatin + ABT-888/placebo
at assigned dose level (see Section 7.3b)

↓

Re-evaluation and Second Registration

↙ or ↘

ABT-888
Carboplatin
Paclitaxel
(2 cycles)

Placebo
Carboplatin
Paclitaxel
(2 cycles)

A patient may be enrolled to either the Phase I portion or the Phase II portion, not both.

1.0 OBJECTIVES

This study will be conducted in two different parts:

1.1 Phase I Portion Objectives

To establish the MTD and the recommended Phase II dose of ABT-888 when given concurrently with standard carboplatin/paclitaxel and radiotherapy in patients with unresectable Stage III non-small cell lung cancer (NSCLC).

1.2 Phase II Portion Objectives

a. To assess whether carboplatin/paclitaxel plus ABT-888 compared with carboplatin/paclitaxel plus placebo improves progression-free survival (PFS) in patients with unresectable Stage III NSCLC.

b. To compare overall survival (OS) in patients treated with carboplatin/paclitaxel and radiotherapy plus ABT-888 to those treated with carboplatin, paclitaxel and radiotherapy plus placebo.

c. To assess the response rate (confirmed and unconfirmed, complete and partial responses) and disease control rate in the subset of patients with measurable disease by RECIST criteria

d. To assess the safety and toxicity profile of the regimen

1.3 Tertiary Objectives

a. To collect tumor tissue from pretreatment biopsies (archival samples) for biomarker studies, including PARP activity by measuring the levels of poly-ADP-ribose, γ-H2AX, and mRNA expression levels of DNA repair enzymes such as ERCC1/XRCC1.

b. To collect blood samples for evaluation of γ-H2AX (circulating tumor cells) and other relevant future studies.

2.0 BACKGROUND

Locally Advanced Non-Small Cell Cancer

Combined modality therapy with chemotherapy and radiation has become the standard of care for the treatment of patients with locally advanced NSCLC. A number of Phase III randomized trials have established chemotherapy with concurrent radiation to be superior to sequential administration of chemotherapy and radiation. (*1*-*2*) The RTOG conducted a 3-arm, randomized Phase III trial in patients with Stage III NSCLC (**RTOG 9410**). Sequential therapy (Arm 1) consisted of 2 cycles of cisplatin and vinblastine, followed by 6,000 cGy external beam radiation, administered in once-daily fractions, beginning on Day 501. In Arm 2, the same chemotherapy regimen was used but radiation was administered concurrently starting on Day 1 of chemotherapy cycle. In Arm 3, hyperfractionated radiation therapy with 6,920 cGy was administered with twice-daily fractions. Patients in Arm 3 received concurrent chemotherapy that consisted of cisplatin and oral etoposide. The median survival was superior (17.0 months vs 14.6 months, p=0.038) for patients with concurrent chemoradiation (Arm 2) compared to the sequential arm, whereas hyperfractionated radiation did not result in improved survival compared to the sequential arm (15.6 months vs 14.6 months). Esophagitis and pneumonitis were the principal toxicities associated with concurrent chemoradiation.

The LAMP (Locally Advanced Multimodality Protocol) Trial was a randomized 3- arm Phase II study in patients with Stage III NSCLC. (3) In Arm 1, patients received 2 cycles of induction chemotherapy with carboplatin (AUC =6 mg/ml.min) and paclitaxel (200 mg/m2) followed by 6,300 cGy external beam radiotherapy (sequential); Arm 2 consisted of 2-cycles of induction chemotherapy with carboplatin and paclitaxel which was followed by concurrent chemoradiation with weekly carboplatin (AUC 2) and paclitaxel (45 mg/m2) for 7 weeks (induction-concurrent); Arm 3 consisted of initial concurrent chemoradiation with weekly carboplatin and paclitaxel, followed by consolidation chemotherapy with 2 cycles of carboplatin and paclitaxel (concurrent-consolidation). The study enrolled 276 patients. Among patients randomized to Arm 2, less than 60% received the planned combined therapy after induction. An interim analysis projected an inferior median survival for patients on Arm 2 and this arm was closed to accrual. There was no statistically significant difference in survival between the study arms.

The Cancer and Leukemia Group B (CALGB) conducted a randomized Phase II study of two cycles of induction chemotherapy followed by two additional cycles of the same drugs with concomitant radiotherapy for patients with locally advanced NSCLC. (4) Cisplatin was administered in combination with gemcitabine, paclitaxel or vinorelbine as induction therapy followed by chemoradiotherapy. Median survival for all patients was 17 months. Subsequently, CALGB conducted a Phase III trial that compared induction chemotherapy with carboplatin and paclitaxel followed by concurrent chemoradiation versus chemoradiation alone. The results of this trial demonstrated similar survival rates between the 2 arms. (5)

SWOG evaluated the role of consolidation chemotherapy following concurrent chemoradiation in a Phase II trial (**SWOG-9504**). (6) Initial therapy consisted of cisplatin and etoposide with concurrent radiation (6,100 cGy) followed by three cycles of consolidation chemotherapy with docetaxel. This study enrolled 83 eligible patients and demonstrated a median survival of 26 months. The 2-year and 3-year survival rates were 53% and 40% respectively. The treatment was well tolerated with an incidence of Grade 3 esophageal toxicity during concurrent chemoradiation of 11%. Based on the results noted in this study, the SWOG investigators adopted the treatment regimen from **SWOG-9504** as the control arm for their future trials for patients with locally advanced NSCLC. However, the benefit of consolidation chemotherapy has been questioned. A more recent Phase III study by HOG showed that the addition of consolidation docetaxel to concurrent radiation, cisplatin, and etoposide does not improve survival. (7) In an ongoing Phase III trial (**RTOG 0617**), RTOG is using weekly carboplatin and paclitaxel with concurrent chest radiotherapy followed by 2 cycles of consolidation chemotherapy with carboplatin and paclitaxel as the reference regimen. This ongoing Phase III trial is a 4-arm randomized trial that is evaluating standard versus high dose (6,000 vs 7,400 cGy) chest radiotherapy as well as treatment with or without the addition of cetuximab in patients with Stage III NSCLC.

Despite these improvements in treatment of unresectable, locally advanced NSCLC, long- term survival is achieved in less than 25% of patients. Therefore there is a major need to investigate novel approaches in this clinical setting.

Clinical Investigations

A single-dose pharmacokinetic and pharmacodynamic endpoint study in cancer patients was initiated under an exploratory IND by the National Cancer Institute as the initial study in their Phase 0 program. (9) In this study, participants had baseline assessments of PAR in peripheral blood mononuclear cells (PBMCs) and at higher dose levels, in tumor from needle biopsies, assessed by a validated immunoassay. Participants received a single dose of ABT-888 at 10, 25, or 50 mg. PBMCs were collected over a 24 hour period at all dose levels, and tumor biopsies were obtained at the 25 mg dose level, approximately 3 to 6 hours after administration of ABT-888. A total of 6 patients have been studied so far, 3 each for the 10 mg and 25 mg cohorts. No treatment related adverse events have been observed. The target plasma C_{max} of 210 nM was

exceeded in 2 of 3 patients at the 10 mg dose level, and in all three patients for at least 4 hours at the 25 mg dose level. Levels of PAR were reduced 80-99% from baseline levels after administration of ABT-888 in both the PBMCs and tumor samples at the 25 mg dose level. Thus, there is reason to believe that target inhibition is seen at least at the 25 mg dose level, and may be occurring at doses lower than 25 mg.

Currently, several combination Phase I trials are underway. Also, single agent trials have been initiated in patients with BRCA mutations.

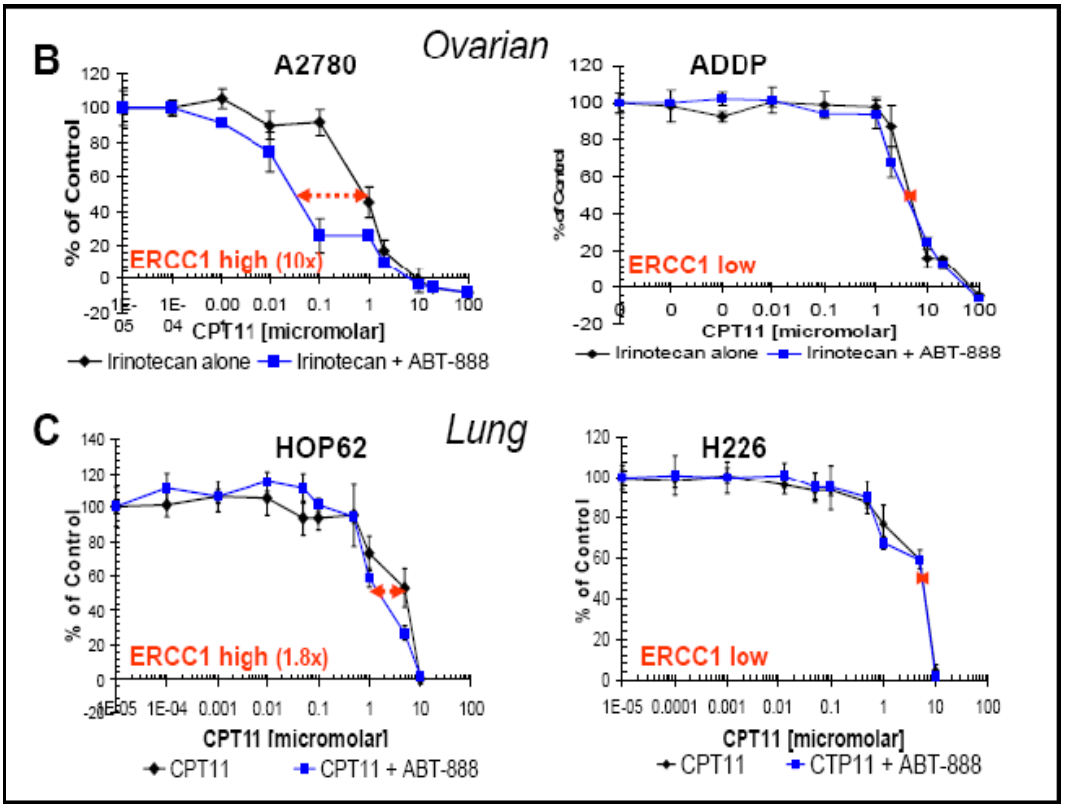
Experience with ABT-888 plus carboplatin and paclitaxel

At the University of Pittsburgh and CCCP two Phase I clinical trials of carboplatin, paclitaxel plus ABT-888 in patients with advanced solid tumors are near completion. In the first Phase I trial, an every-3-week schedule of carboplatin and paclitaxel is being used. In this study the first cycle is administered without ABT-888. ABT-888 is initiated on Day 1 of Cycle 2 and carboplatin and paclitaxel are given on Day 3 of Cycle 2 and all subsequent cycles (cycle duration is 21 days). DLT is determined during Cycle 2 only. Currently, patients are being treated at a dose of ABT-888 of 100 mg BID for 7 days, Days 1-7 of the cycle with standard doses of carboplatin and paclitaxel (AUC of 6 and 200 mg/m^2, respectively). A dose of 80 mg was safe and will be used in the consolidation chemotherapy part. However, dose-limiting myelotoxiticy occurred at a dose of 120 mg. Additional patients are being treated at 100 mg.

Another ongoing Phase I study at the University of Pittsburgh is evaluating weekly carboplatin and paclitaxel in combination with ABT-888. The dose of carboplatin is ACUS of 2 and paclitaxel 80 mg/m^2. Patients receive carboplatin and paclitaxel on Days 3, 10, and 17 and ABT-888 BID on Days 1-5, 8-12, and 15-19. The 50 mg and 100 mg dose levels were safe (3 patients treated at each without DLT). The current dose level is 150 mg of ABT-888 twice daily. One patient developed Grade 4 thrombocytopenia which was DLT and this cohort is expanded (S. Puhalla, personal communication).

Rationale

Investigation of new CTEP-sponsored agents plus radiotherapy usually lags far behind that of new drug-chemotherapy combinations. From a clinical standpoint, study designs adding a new agent to a standard radiation (or chemoradiation) backbone are most desirable. Although combined modality therapy with concurrent chemoradiation is considered standard of care in unresectable Stage III NSCLC, long-term survival is low and recent advances have been limited, creating an area of major need for new therapeutic strategies. We propose to use a backbone of standard chemoradiotherapy with carboplatin and paclitaxel to investigate the addition of oral ABT-888. ABT-888 potentiates the anti-cancer effects of various cytotoxic agents including carboplatin in preclinical studies. Albert et al have shown that ABT-888 has a synergistic effect when combined with radiation in lung cancer models. *(8)* The primary mechanism of action of carboplatin involves formation of platin-DNA adducts and subsequent DNA damage. While repair of platin-induced DNA damage is likely multifactoral, nucleotide excision repair (NER) is prominent. Pre-clinical studies suggest overlap between PARP-induced repair and other mechanisms such as NER or BER. As shown here, preclinical studies by our collaborators at Karmanos Cancer Center (unpublished) of ABT-888 show variable effects in regard to potentiation of cytotoxicity of the DNA-damaging agent irinotecan. In particular, in ovarian cancer cell lines, potentiaton by ABT-888 occurs exclusively in a high ERCC1-expressing cell line (NER-mediated), whereas ABT-888 shows no potentiation in HOP62 or H226 lung cancer lines, regardless of ERCC1 expression.



We believe that these observations should be studied further in preclinical models, and in an exploratory way, in this trial. We hypothesize that co-administration with ABT-888 with carboplatin and radiation is likely to result in enhanced DNA damage and therefore, greater anti-tumor activity, and that this potentiation can be determined by assessing baseline DNA repair genes in either the tumor or the host (polymorphisms in DNA repair genes). We further hypothesize that selectivity of ABT-888 to tumor cells will also be advantageous. This study will evaluate the toxicities and establish the optimal doses of ABT-888 given with standard chemoradiotherapy with weekly carboplatin and paclitaxel.

Correlative Studies Background

With the limitations of patient numbers in this Phase I trial, the correlative data are not likely to provide a statistically significant finding, however these studies are expected to be hypothesis supporting or generating for studies of larger patient cohorts, as a result of identifying trends in the data.

Immunoassay for poly-ADP-ribosylated (PAR) substrates

Because the product of the PARP enzyme is poly-ADP-ribosylated (PAR) molecules, an immunoassay to quantify the amount of cellular PAR was developed as a clinical biomarker of PARP inhibition. Abbott Laboratories and the NCI-Frederick laboratories developed and cross-validated a quantitative immunoassay for PAR. (*9*-*10*) The validated assay is a sandwich enzyme chemiluminescence immunoassay employing commercially obtained antibodies to PAR, and pure PAR as a standard. Assay dynamic range is 31 to 2000 pg/ml PAR, with a lower limit of quantization of approximately 15 pg/ml PAR. The standard curve is linear throughout the range (with an adjusted R2 typically better than 0.98). The assay uses high, midrange, and low controls produced from the human melanoma line Colo829. Specimen handling was optimized for both

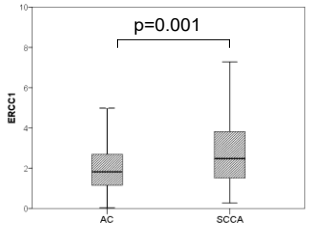
PBMCs and tumor needle biopsies (18 ga), and harmonized for use with the same standards and controls. Specimens could be subjected to at least 3 freeze-thaw cycles without a detectable loss of antigen binding. Assay precision was determined at both Abbott Laboratories and the NCI-Frederick, to be better than 80% (estimated total imprecision at Abbott Laboratories, 7% or less). Accuracy, as assessed by spike recovery of pure PAR into PBMC lysates, was 100% +/- 20%. Assay dilution linearity was established for the Colo829 controls and tumor lysates, although deviations from linearity are observed in some tumor homogenates, and assay conditions are controlled to compensate for that lack of linearity. The validated assay was used to measure PAR levels in PBMCs of healthy donors, in animal models after administration of a single and multiple dosing of ABT-888, and has been used successfully in real time to measure PAR in PBMCs and tumor biopsies in a Phase 0 clinical trial at the NCI.

The level of PARP activity is determined by measuring the levels of poly-ADPribose. The enzymatic assay for PARP activity provides enzyme substrates in excess to achieve zero-order kinetics such that enzyme product formation is directly proportional to amount of active enzyme. The enzyme product will be poly-ADP-ribose that will be quantified using the capture antibody configuration for the immunoassay of poly-adenylated PARP.

mRNA expression levels of DNA repair genes

RNA from laser-captured microdissected FFPE tumor samples will be analyzed by the UC Davis group together with their long-term collaborator, Response Genetics, Inc. (RGI) using a patented quantitative RT-PCR assay as previously described in a CLIA-certified laboratory. Recently, Gandara et al (ASCO, 2010) have reported ERCC1 mRNA expression levels in 2,540 patients and correlated results with NSCLC histologic subtype**.** As shown, ERCC1 mRNA expression levels are strongly correlated with NSCLC histologic subtype, with higher levels in SCC compared with ADCA (median 2.5 versus 1.8, *p*=0.001). These data, representing 2,540 NSCLC patients (the largest patient-based ERCC1 study yet reported), translate into differences in estimated platinum responsiveness between these histologies, with 46% of ADCA below the ERCC reference sensitivity level of < 1.7, compared with only 31% of SCC. These studies, conducted by our group in collaboration with RGI, set the stage for the current trial incorporating the PARP inhibitor into combined modality therapy in Stage III NSCLC.

ERCC1 mRNA Expression Levels in NSCLC (N=2,540):
Adenoca (AC) versus Squamous (SCCA)



ERCC1 (Reference <1.7)	% Below Reference Level
NSCLC-Total	43.4%
NSCLC-Adenoca	46%
NSCLC-SCCA	30.7%

Assessment of host genomic DNA from PBMC/plasma for DNA repair SNPs, including ERCC1 and ERCC2

Assessment of host DNA repair capacity for relevant polymorphisms will be done as previously described (See also Correlative Science section in Appendix 18.2). For example, previous studies by our group (Gandara et al: JCO, 2009) have shown an association of ERCC2 K751Q for response to carboplatin-paclitaxel chemotherapy in advanced NSCLC (HR, 0.33; 95% CI, 0.13 to 0.83; p= .02). These associations will be evaluated in an exploratory manner in this trial.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	81	77	158
Total Ethnic	83	79	162
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	2	2	4
Black or African American	8	9	17
Native Hawaiian or other Pacific Islander	0	0	0
White	73	68	141
Racial Category: Total of all Subjects	83	79	162

The total number of subjects above assume 30 patients enrolled on the Phase I portion and 132 patients enrolled on the Phase II portion.

3.0 DRUG INFORMATION

For information regarding Investigator's Brochure, please refer to SWOG Policy 15.

For this study, carboplatin and paclitaxel are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, ABT-888 is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator Brochure may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 240/276-6575.

3.1 Carboplatin (CBDCA) (NSC-241240)

a. DESCRIPTION

Carboplatin (CBDCA) is a hydrophilic platinum coordination compound and is an analog of cisplatin, producing intrastrand DNA cross-links.

b. TOXICOLOGY

Human Toxicology: Side effects of carboplatin (CBDCA) include myelosuppression, nausea, vomiting, abdominal pain, diarrhea and constipation. Other toxicities include allergic reaction (including hypersensitivity, i.e., rash, urticaria, erythema, pruritus, bronchospasm and hypotension), peripheral neuropathy, paresthesia, loss of hair, hearing loss, visual disturbances and change in taste. Serum creatinine elevations and blood urea elevations have occurred as well as abnormal liver function tests and decreased serum electrolyte values. Although rare, pain, asthenia, cardiovascular, respiratory, genitourinary and mucosal side effects have occurred in some patients. Cancer-associated hemolytic uremic syndrome has been reported rarely. The renal effects of nephrotoxic compounds may be potentiated by carboplatin. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds or mannitol. This drug should not be used in patients with severe bone marrow depression or significant bleeding. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Pregnancy and Lactation: Carboplatin may cause fetal harm, therefore women of childbearing potential should be advised to avoid becoming pregnant.

c. PHARMACOLOGY

Kinetics: The differences in potencies of carboplatin and cisplatin are due to differences in aquation rates. The initial half-life is 1.1 - 2.0 hours and the post-distributional half-life is 2.6 - 5.9 hours. Sixty-five percent of the dose is excreted in the urine within twelve hours. Carboplatin is not bound to plasma proteins.

Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous injection. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water, or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/mL. Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride Injection, USP (NS).

Carboplatin is also supplied as a solution for injection in vials containing 50 mg, 150 mg, 450 mg and 600 mg with a concentration of 10 mg/mL.

Storage and Stability: Unopened vials of carboplatin for injection are stable for the life indicated on the package when stored at controlled room temperature 15° - 30°C, and protected from light. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for 8 hours at room temperature (25°C). Like cisplatin, this drug should not be given through aluminum needles.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded eight hours after dilution.

Administration: Intravenous.

Supplier: Carboplatin is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.2 Paclitaxel, Taxol® (NSC-673089)

a. DESCRIPTION

Chemistry: Paclitaxel is a diterpene plant product found in the needles and bark of the western yew, Taxus brevifolia. The marketed formulation is prepared in a semi-synthetic process.

Molecular Weight: 853.9

Empirical Formula: $C_{47}H_{51}NO_{14}$

Description: Clear viscous fluid

b. TOXICOLOGY

Human Toxicity:

Dose-limiting toxicity is myelosuppression with reversible granulocytopenia, anemia, and thrombocytopenia. Allergic reactions occur in up to 8% of patients receiving paclitaxel as an intravenous infusion over 6 to 24 hours. These can be acute anaphylactoid reactions to include flushing, hypotension, and bronchospasm; dermatitis and pruritus are also observed. Hypertension has also been seen, and may be related to concomitant medication with dexamethasone. Premedication with diphenhydramine, cimetidine, and dexamethasone appears to diminish the incidence of these reactions. Neurotoxicity can include distal painful paresthesias. Rarely, this toxicity has required discontinuation of drug due to pain, impairment of fine motor skills, or difficulty ambulating. Experience to date suggests that this neuropathy is reversible. Rarely, associated forms of neurotoxicity have included taste perversion, seizures, and mood changes. Some patients have reported vision abnormalities such as blurred vision, "flashing lights" and scintillating scotomata. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has also been seen. Patients reporting abdominal discomfort should be monitored closely. These events generally occurred while the patients were severely neutropenic. They may be most consistent with neutropenic enterocolitis (typhlitis). Although increased SGOT, SGPT, bilirubin and alkaline phosphatase, as well as hepatic failure and hepatic necrosis have been seen, one patient receiving this drug has also experienced hepatic encephalopathy, and two incidences of pancreatitis have been noted. Neuroencephalopathy has also been reported. Pulmonary toxicities that have occurred are pneumonitis and radiation pneumonitis (following concomitant paclitaxel and radiation).

Other non-hematologic reactions include: diarrhea, alopecia, myalgias and arthralgias, nausea or vomiting, mucositis (stomatitis and pharyngitis), light-headedness, myopathy and fatigue. Less commonly, cardiotoxicity has been associated with paclitaxel administration, to include arrhythmias (sinus bradycardia, ventricular tachycardia, atrial arrhythmia, and heart block), and myocardial infarction. Skin reactions including erythema, induration, tenderness, ulceration, radiation recall, rash and nail changes have occurred including discoloration of fingernails and separation from nail bed.

Pregnancy and Lactation: Paclitaxel may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, paclitaxel was shown, to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorption and embryo-fetal deaths. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

c. PHARMACOLOGY

Formulation: Sterile solution containing 6 mg/ml in a 5 ml vial (30 mg per vial) in polyoxyethylated castor oil (Cremaphor EL) 50% and dehydrated alcohol, USP, 50%. There are also vial sizes of 100 mg and 300 mg.

Solution Preparation: Paclitaxel is reconstituted by diluting the total dose in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (D5W) to maintain a paclitaxel concentration between 0.3 and 1.2 mg/ml. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremaphor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration.

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

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

Storage and stability: The intact vials of paclitaxel should be stored between 2 - 25°C. Based on stability data for Taxol® made from either natural or semi-synthetic paclitaxel, stored for up to 12 months at 40°C, potency losses were within the range of 2.0 to 2.4 percent per year. Samples stored for up to 3

months at 60°C lost potency at rates corresponding to 20 to 40% per year. Accordingly, vials left out in a warm place for a few days should still be satisfactory for use. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3 - 1.2 mg/ml) are physically and chemically stable for 27 hours. Vials will be labeled with a firm expiration date.

Supplier: Paclitaxel is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.3 Veliparib (ABT-888) (NSC 737664)

a. DESCRIPTION

Chemical Name: 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide

Other Names: A-861695.0, Veliparib

Classification: Poly (ADP-ribosome) polymerase (PARP) Inhibitor

Molecular Formula: $C_{13}H_{16}N_4O$

Molecular Weight: 244.29

Description: Light orange opaque capsule with black bands

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks List (CAEPR) for ABT-888 (NSC 737664)

The Comprehensive Adverse Events 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 Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2310 patients.* Below is the CAEPR for ABT-888 (Veliparib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, March 4, 2016[1]

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 4.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event[2]	

[1] 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. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.

Adverse events reported on ABT-888 (Veliparib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ABT-888 (Veliparib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (bone marrow failure); Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Cardiac disorders - Other (Takotsubo cardiomyopathy); Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dental caries; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Lower gastrointestinal hemorrhage; Mucositis oral; Obstruction gastric; Rectal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)
INFECTIONS AND INFESTATIONS - Appendicitis; Catheter related infection; Infections and infestations - Other (peritonsillar abscess); Infections and infestations - Other (shingles); Lung infection; Lymph gland infection; Mucosal infection; Sepsis; Skin infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Injury, poisoning and procedural complications - Other (radiation proctitis)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome; Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS – Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Extrapyramidal disorder; Intracranial hemorrhage; Lethargy; Memory impairment; Movements involuntary; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (emotional instability); Psychosis; Restlessness

RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Renal and urinary disorders - Other (dysuria)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail bed changes)
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Vascular disorders - Other (brainstem infarction)

Note: ABT-888 (Veliparib) 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.

c. **PHARMACOLOGY**

Storage: Store intact bottles between 15° and 25°C (59°–77°F).

Stability: Shelf-life stability studies for ABT-888 capsules are ongoing.

Route(s) of Administration: Oral. ABT-888 and matching placebo capsules may be administered without regard to meals.

d. **SUPPLIER**

ABT-888 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

ABT-888 and matching placebo are provided to the NCI under a Collaborative Agreement between Abbott Laboratories and the DCTD, NCI (see Section 16.0).

Clinical Supplies: ABT-888(NSC 737664) and matching Placebo will be provided free of charge by Abbott Laboratories and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

ABT-888 20 mg and 0 mg matching placebo for ABT-888 will be supplied as immediate release capsules. The ABT-888 capsule contains ABT-888, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5. The matching placebo capsule contains microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5.

ABT-888 and matching Placebo will be supplied in bottles containing 64 – 20 mg capsules (ABT-888) or 64 – 0 mg capsules (Placebo for ABT-888) with a child-resistant cap and a tamper-evident seal.

Note: In order to dispense a single cycle at a time, ABT-888(veliparib)/placebo capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. The bottles should be labeled according to State regulations and also include the information from

the original patient specific bottle sent from the PMB. Expiration will be 30 days from the repackaging date (or the original retest date, whichever is earlier) when stored at 15°C to 25°C (59°F to 77°F).

Each blinded, patient-specific bottle will be labeled with …

- the protocol number (i.e., "8811")
- the bottle number (i.e., "Bottle 1 of 2" and "Bottle 2 of 2")
- the number of capsules (i.e., "64 capsules")
- the patient ID number (e.g.,"XXXXXX", where "XXXXXX" represents the protocol number and sequence number which is the unique patient identifier assigned at registration)
- the patient initials (i.e., first initial, last initial [e.g., "LFM"])
- the agent identification (i.e., "ABT-888 20 mg" or "ABT-888 20 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take __ capsules two times daily as directed.")
- storage instructions (i.e., "Store at room temperature (15ºC to 25ºC; 59ºF to 77ºF)."
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2009 = 09, 2010 = 10) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2009 would have a Julian date of '09001' and a bottle labeled and shipped on December 31, 2009 would have a Julian date of '09365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both ABT-888 and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact the PMB via e-mail at PMBAfterHours@mail.nih.gov.

Agent Orders: No starter supplies will be available for the open-label (Phase I) or blinded (Phase II) portion of this study. Patient-specific supplies will be sent to the registering investigator at the time of registration/randomization and should arrive within 3 to 5 days. Patients will be registered/randomized by the SWOG Statistical Center in Seattle, WA. The assigned patient ID number must be recorded by the registering institution at the time of randomization for proper clinical supply dispersion. Once a patient has been randomized, the SWOG Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the SWOG Statistical Center the day the patient is randomized and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx (generally one to two business day delivery). Thus, if a patient is registered on Monday, the SWOG Statistical Center would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. Sites could expect to receive their order approximately Thursday or Friday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the SWOG Statistical Center at the time the patient is randomized.

Phase I: The initial request will be for a sufficient supply to complete ABT-888 treatment for the initial **6** weeks of radiation treatment. **If a patient is found to be eligible to continue on to consolidation treatment (4-6 weeks after radiation ends), sites may reorder an additional 2 – 64 capsule bottles (a 2-cycle / 6-week supply at a dose of 80 mg BID on days 1-7 of a 21 day cycle). This supply (2 x 64 capsule bottles) will be sufficient to complete the prescribed two cycles of consolidation therapy. Orders must be submitted** through the PMB Online Agent Order Processing (OAOP) application (https://eappsctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. The assigned patient ID number (e.g., "XXXXXX") and the patient initials (e.g., "LFM") should be entered in the "Patient or Special Code" field. All drug orders should be shipped directly to the physician responsible for treating the patient.

Phase II: The initial request will be for a sufficient supply to complete ABT-888/placebo treatment at the recommended Phase II dose (120 mg BID for 43 days – 9 x 64 capsule bottles) for the initial **6** weeks of radiation treatment. **If a patient is found to be eligible to continue on to consolidation treatment (4-6 weeks after radiation ends), sites may reorder an additional 2 – 64 capsule bottles (a 2-cycle / 6-week supply at a dose of 80 mg BID on days 1-7 of a 21 day cycle). This supply (2 x 64 capsule bottles) will be sufficient to complete the prescribed two cycles of consolidation therapy. Orders must be submitted** through the PMB Online Agent Order Processing (OAOP) application (https://eappsctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. The assigned patient ID number (e.g., "XXXXXX") and the patient initials (e.g., "LFM") should be entered in the "Patient or Special Code" field. The agent name for the ABT-888 must be written on the order form as "ABT-888 or Placebo". All drug orders should be shipped directly to the physician responsible for treating the patient.

Agent Transfers: Bottles **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240/276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "XXXXXX"') and the patient initials (e.g., "LFM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "8811").

Agent Returns: Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240/276-6575. The

patient ID number (e.g., "XXXXXX") and the patient initials (e.g., "LFM") should be entered in the "Lot Number" field. Opened bottles with remaining capsules should be documented in the patient-specific NCI Oral Drug Accountability Record Form (i.e., logged in as "returned by patient" and logged out as "destroyed on site") and destroyed on-site in accordance with institutional policy.

Agent Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Oral Drug Accountability Record Form available on the CTEP home page (http://ctep.cancer.gov). A separate NCI Oral Drug Accountability Record Form must be maintained for each patient ID number (e.g., "XXXXXX") on this protocol.

Emergency Unblinding:
In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the **Washington Poison Center (WPC) at 206-526-2121** (see Appendix 18.4). This service is available 24 hours a day, 365 days a year. The WPC will require the protocol number (i.e., "8811 or S1206"), the patient ID number (e.g., "XXXXXX"), and the patient initials (e.g., "LFM") to unblind the patient. Please note that, if a patient is emergently unblinded, he/she is considered to be off-therapy and must discontinue protocol treatment.

4.0 STAGING CRITERIA

Definition of TNM (AJCC Cancer Staging Manual, 7th edition)

Primary Tumor (T)

T1 A tumor that is 3.0 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.

T2 Tumor more than 3 cm but 7 cm or less or tumor with any of the following features: involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina1 but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe.

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe.

Regional Lymph Nodes (N)

N0 No demonstrable metastasis to regional lymph nodes.

N1 Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension.

N2 Metastasis to ipsilateral mediastinal lymph nodes or subcarinal lymph nodes.

N3 Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes

Distant Metastasis (M)

M0 No known distant metastasis*

Stage Grouping of the TNM Subsets

Stage IIIA	T4 N0-1 M0 T3 N1 M0 T1-3 N2 M0
Stage IIIB	T4 N2 M0 T1-4 N3 M0

* In AJCC 7th edition, pleural and pericardial are now considered Stage M1a disease.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S1206** Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-226, lungquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 REGISTRATION #1

_____ a. Patients must have histologically or cytologically-proven new diagnosis of unresectable Stage IIIA/IIIB*, non-small cell lung cancer (adenocarcinoma, bronchioloalveolar cell carcinoma, large cell carcinoma, squamous cell carcinoma, or mixed).

* Per the AJCC 7th edition, pleural and pericardial are now considered Stage M1a disease. When pleural fluid is visible on the CT scan or on a chest x-ray, a thoracentesis is required to confirm that the pleural fluid is cytologically negative. Patients with exudative pleural effusions are excluded, regardless of cytology. Patients with effusions that are minimal (i.e. not visible on chest x-ray) that are too small to safely tap are eligible. A small effusion that has positive FDG uptake on PET has to be proven to be malignant per standard of care diagnostic procedures for the patient to be excluded.

_____ b. Patients must have measurable or non-measurable disease (see Section 10.1) documented by CT, MRI or PET/CT. The CT from a combined PET/CT may be used to document only non-measurable disease unless the scan is of diagnostic quality as defined in Section 10.1a. Measurable disease must be assessed by CT within 28 days prior to registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

_____ c. Patients with brain metastases are ineligible. All patients must have a pretreatment CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to registration.

_____ d. Patients must not have received any prior systemic therapy (chemotherapy or other biologic therapy) for lung cancer.

_____ e. Patients must not have received prior chest radiation therapy for NSCLC.

_____ f. Patients must not have had a previous surgical resection. However, patients may have undergone exploratory thoracotomy, mediastinoscopy, excisional biopsy or similar surgery for the purpose of determining the diagnosis, stage or potential resectability of newly diagnosed lung tumor. At least 28 days must have elapsed since thoracic surgery (excluding mediastinoscopy or other minor surgeries) and patients should have recovered from all associated toxicities at the time of registration. Patients must not be planning to undergo a minor surgical procedure while on this study.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ g. Patients must be ≥ 18 years old.

_____ h. Patients must have Zubrod performance status 0-1 (See Section 10.4).

_____ i. Patients must have tumor tissue available for submission to assess gene expression of ERCC1 and XRCC1. (See Section 15.2) Patients must also be offered participation in banking for future use of specimens as described in Section 15.3.

_____ j. Patients must have adequate bone marrow function as evidenced by all of the following: absolute neutrophil count ≥ 1,500/ mcl; platelets ≥ 100,000/mcl; hemoglobin ≥ 9.0 g/dl. These results must have been obtained within 28 days prior to registration.

_____ k. Patients must have adequate hepatic function as defined by total bilirubin within Institutional Upper Limit of Normal (IULN) and SGOT (AST) or SGPT (ALT) ≤ 2.5 x IULN. These results must be obtained within 28 days prior to registration.

_____ l. Patients must not be pregnant or nursing because of increased risk of harm to a nursing infant or fetus including fetal death from the chemotherapeutic and biologic agents. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ m. Patients must have a serum creatinine ≤ the IULN AND measured or calculated creatinine clearance ≥ 60 cc/min using the following Cockroft-Gault Formula:

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

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to registration.

_____ n. Patients must have pulmonary function tests (PFTs) including FEV1 within 84 days prior to registration; for FEV1, the best value obtained pre- or post bronchodilator must be ≥ 1.2 liters/second and/or ≥ 50% predicted.

_____ o. Patients may not be planning to receive any other investigational agents.

_____ p. Patients must not have more than 10% weight loss in the past 6 months.

_____ q. Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to ABT-888, carboplatin, paclitaxel or other agents used in study.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ r. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

_____ s. Patient must not have any uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ t. Patients must not currently have a > Grade 1 symptomatic neuropathy-sensory (NCI Common Terminology Criteria Version 4.0).

_____ u. Patients must not have a history of seizures.

_____ v. Patients must not have any known immune deficiencies. Patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy. Therefore, known HIV positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with carboplatin, paclitaxel and ABT-888 or other agents administered during the study.

_____ w. Patients must be able to swallow whole capsules.

_____ x. Prestudy history and physical must be obtained within 28 days prior to registration.

_____ y. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ z. As a part of the OPEN registration process (see Section 13.2 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 REGISTRATION #2 – PRIOR TO CONSOLIDATION CHEMOTHERAPY

Following completion of chemoradiotherapy, patients without local progression of disease or distant metastases will receive consolidation chemotherapy. Patients must be reregistered to consolidation chemotherapy within 6 weeks after completing chemoradiotherapy.

_____ a. Patients must have completed chemoradiotherapy per protocol and at least four weeks but no more than six weeks must have elapsed from the last day of induction therapy (the last day of radiation).

_____ b. Patients must have undergone restaging tests according to the study calendar and determined to have no evidence of disease progression (as defined in Section 10.2d).

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.2 REGISTRATION #2 – PRIOR TO CONSOLIDATION CHEMOTHERAPY (Contd.)

_____ c. Patients must have a serum creatinine ≤ (IULN) AND measured of calculated creatinine clearance ≥ 60 cc/min using the following Cockroft-Gault Formula:

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

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 14 days prior to re-registration.

_____ d. Patients must have adequate bone marrow function as evidenced by all of the following: absolute neutrophil count ≥ 1,500 mcl; platelets ≥ 100,000/mcl; hemoglobin ≥ 9.0 g/dl. These results must have been obtained within 14 days prior to re-registration.

_____ e. Patients must have adequate hepatic function as defined by total bilirubin ≤ IULN and SGOT (AST) or SGPT (ALT) ≤ 2.5 x IULN. These results must be obtained within 14 days prior to re-registration.

_____ f. Patients must have Zubrod performance status 0-1 (See Section 10.4).

6.0 STRATIFICATION FACTORS

For the Phase II portion of the trial, patients will be randomized using a dynamic balancing algorithm with stratification based on (12):

1. Stage IIIA vs. IIIB

2. Histologic subtype: Squamous cell vs. Non-squamous

7.0 TREATMENT PLAN

For chemotherapy-related treatment or dose modification questions, please contact Dr. Argiris at athanassios.argiris@gmail.com, Dr. Cristea at 626/256-4673 or mcristea@coh.org or Dr. Sands at 781/744-8400 or Jacob.M.Sands@lahey.org. For radiation therapy-related treatment or dose modification questions, please contact Dr. Chen at achen5@kumc.edu. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Treatment Overview

The study will be conducted in two sequential parts. A patient may be enrolled to either the Phase I portion or the Phase II portion, but not both.

Phase I – Details are in Section 7.3a.

Phase II – Details are in Section 7.3b.

7.2 Pre-Medication

a. Premedications: Paclitaxel

All patients should be premedicated with:

AGENT	DOSE	ROUTE	DURATION
Dexamethasone	20 mg*	PO/IV	12 and 6 hours prior to paclitaxel**
Diphenhydramine	50 mg	IV	30 minutes prior to paclitaxel
	plus one of the following		
Ranitidine	50 mg	IV	30 minutes prior to paclitaxel
or			
Cimetidine	300 mg	IV	
Famotidine	20 mg	PO/IV	30 minutes prior To paclitaxel

* 20 mg is the dose for each administration.
** Alternatively, a single intravenous dose of 20 mg may be given 30 minutes prior to paclitaxel injection.

Following the initial cycle of paclitaxel, if the patient has not experienced a hypersensitivity reaction to paclitaxel, then the investigator, at his/her discretion, may decrease dexamethasone and/or diphenhydramine as follows:

- Dexamethasone 8 mg or 10 mg i.v.
- Diphenhydramine 25 mg i.v.
- H2 blocker i.v. (e.g. ranitidine 50 mg or cimetidine 300 mg)

b. Premedications: Carboplatin

Patients should receive antiemetics of the treating physician's choice prior to carboplatin administration. Dose modifications in the antiemetic regimen may be made at the discretion of the treating physician as clinically indicated.

c. Other Ancillary Therapy

Patients should receive full supportive care including transfusions of blood products, antibiotics, antiemetics, antidiarrheals, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be noted in the "Comments" portion of the **S1206** Concurrent Chemotherapy Treatment Form or **S1206** Consolidation Chemotherapy Treatment Form.

7.3 Concurrent Chemoradiation

Chemotherapy and radiotherapy to begin within 24 hours of each other. Day 1 of radiotherapy must be on a Monday or a Tuesday.

Protocol will allow a +/- 24 hour window for chemotherapy and correlatives for Week 1.

a. Phase I Drug Administration Schedule During Concurrent Radiation Therapy

Each proceeding dose level will not open until all patients enrolled on the prior dose level have completed radiation and have been followed for 2 weeks (total of 9 weeks).

AGENT	DOSE	DAYS	ROUTE	SCHEDULE
Paclitaxel[a]	45 mg/m^2 during RT over 1 hour	1	IV over 1 hour during RT	Weekly during RT
Carboplatin	AUC = 2 during RT over 30 minutes[b]	1	IV 30 minutes after completion of paclitaxel	Weekly during RT
ABT-888[c]	20 mg (Level -1*) 40 mg (Level 0) (Starting Dose) 80 mg (Level 1) 120 mg (Level 2)	1-43	PO twice Daily	Daily continuously throughout RT and one day after RT completion
Radiotherapy	6,000 cGy x 30 fractions (see Section 7.4)			6 weeks

* Per dose
[a] See paclitaxel premedication guidelines in Section 7.2a.

[b] AUC=2 by modified Calvert formula. Carboplatin is given after paclitaxel infusion is completed. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing. This change is an addition to the requirement not to exceed a maximum dose of carboplatin of 300 mg (see Appendix 18.3 for the Carboplatin Dosing Worksheet). See also premedication guidelines in Section 7.2b.
[c] ABT-888 capsules are supplied as 20 mg capsules. Capsules may be taken without regard to meals.

b. Phase II Drug Administration Schedule During Concurrent Radiation Therapy

After defining the MTD for ABT-888, patients will be randomized 1:1 between the control arm (concurrent chemoradiotherapy + placebo followed by consolidation chemotherapy + placebo) versus the investigational arm (concurrent chemoradiotherapy + ABT-888 followed by consolidation chemotherapy + ABT-888).

AGENT	DOSE	DAYS	ROUTE	SCHEDULE
Paclitaxel[a]	45 mg/m^2 during RT over 1 hour	1	IV over 1 hour during RT	Weekly during RT up to 6 doses
Carboplatin	AUC = 2 during RT over 30 minutes[b]	1	30 minute IV infusion immediately following paclitaxel	Weekly during RT up to 6 doses
ABT-888 or Placebo	120 mg[c]	1-43	PO twice daily	Daily continuously throughout RT and one day after RT Completion
Radiotherapy	6,000 cGy x 30 fractions (see Section 7.4)			6 weeks

[a] See paclitaxel premedication guidelines in Section 7.2a.
[b] AUC=2 by modified Calvert formula. Carboplatin is given after paclitaxel infusion is completed. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing. This change is an addition to the requirement not to exceed a maximum dose of carboplatin of 300 mg (see Appendix 18.3 for the Carboplatin Dosing Worksheet and premedication guidelines in Section 7.2b).
[c] ABT-888/placebo capsules are supplied as 20 mg capsules. Capsules may be taken without regard to meals.

c. ABT-888 will be administered orally without regards to meals.

On the Phase I, ABT-888 will be given twice a day starting the first day of RT and continuously during RT until one day after RT completion.

During the consolidation chemotherapy part (that will start 4-6 weeks after RT completion) ABT-888 will be given on days 1-7 of each of the 2 cycles (every 21 days) of carboplatin and paclitaxel.

On the Phase II portion of the study patients will be randomized 1:1 to ABT-888 versus placebo during concurrent chemoradiotherapy and during consolidation chemotherapy.

Missed doses should not be made up.

On the days when the patient is scheduled to undergo sampling of blood for correlative studies, the dose of ABT-888 will be administered under supervision (to record the time and coordinate collection of subsequent samples). Please see Appendix 18.1.

Because there is a potential for interaction of ABT-888 with other concomitantly administered drugs, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies should be noted in the patients chart.

ABT-888 is not known to be a potent inhibitor of the major human CYPs *in vitro*, indicating a low risk for drug-drug interactions at the proposed dosing concentrations.

d. Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the Version 4.0 of the NCI Common Terminology Criteria for Adverse Events. This can be reviewed at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Toxicities must be attributable to the study regimen (i.e. possibly, probably or definitely related to one of the 3 study drugs or to radiation therapy) to constitute a Dose-Limiting Toxicity (DLT). Only adverse events which occur during RT or during the 2 weeks following completion of RT will be counted as DLTs:

Dose-limiting toxicities will be defined as follows

1. Radiation esophagitis or dermatitis radiation Grade 3 that lasts > 7 consecutive days or Grade 4.

2. Grade 4 neutropenia for more than 7 days or neutropenic fever (defined as ANC < 500 and a temperature of 38.5^0 C or above).

3. Grade 4 thrombocytopenia.

4. Grade 4 nausea/vomiting despite appropriate antiemetic therapy.

5. Delays in radiotherapy or chemotherapy or ABT-888 due to toxicity of more than 3 weeks.

6. All other non-hematologic toxicities of Grade 3 or higher, with the following exceptions:

    a. anorexia

    b. fatigue

    c. infection without neutropenia

d. Grade 3 AST/ALT elevations ≤ 7 days

e. Infusion reactions. Patients with Grade 3 or worse infusion reactions will be removed from study and replaced and will not be considered evaluable for DLT.

f. Grade 3 or 4 lymphopenia

g. Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours.

h. Grade 3 dehydration lasting less than 7 days in duration.

Any laboratory abnormalities should be considered clinically relevant and related to the study drugs to be considered DLT.

Patients will be considered evaluable for DLT if they receive at least 66% of the planned doses of ABT-888 at the assigned dose level, and at least one dose each of carboplatin and paclitaxel, and began radiation therapy during the concurrent chemoradiotherapy step, or if they experience a DLT. Patients who are not evaluable for DLT will be replaced. Patients with Grade 3 or worse infusion reactions will be removed from study and replaced and will not be considered evaluable for DLT.

Management and dose modifications associated with the above adverse events are outlined in Section 8.0.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

No intra-patient dose escalation is allowed.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 1 out of 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended Phase II dose. At least 5 patients evaluable for DLT must be entered at the recommended Phase II dose. If no DLTs are observed among the first 5 patients evaluable for DLT enrolled at the maximum dose, then accrual to the Phase I portion may be terminated at 5 evaluable patients. However, if one (1) DLT is observed among the first 5, the total accrual must be 6 evaluable patients.

Each proceeding dose level will not open until patient of the prior level have completed radiation and have been followed for 2 weeks (total of 9 weeks).

7.4 Radiotherapy

a. Introduction

Patients will receive a total dose of 6,000 cGy in 30 fractions over 6 weeks utilizing standard fractionation (one fraction per day). Either 3D conformal treatment planning or IMRT will be utilized. Each institution must complete applicable benchmarks prior to entering patients on trial, and all treatment plans must be submitted to QARC within 3 days of the start of radiation therapy for review. See Section 12.0 for benchmark and data submission requirements.

IMRT is allowed on this study as long as the method of motion management is documented.
Proton therapy is not allowed on this study.
NOTE: Digital submission of treatment plans is required on this study.

b. Localization, Simulation, Immobilization

CT simulation is required. Portal verification shall be done at the initiation of treatment and thereafter for all treatment fields every 5 fractions.

1. Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices with slice thickness less than or equal to 3 mm are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. The GTV, CTV, and PTV and normal organs will be outlined on all appropriate CT slices.

2. A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged to assist with target delineation. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

3. Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, i.v. contrast should be given during the planning CT. If contrast is used, the densities can be over-ridden or the contrast scan must be registered to a non-contrast scan for planning purposes. Optimal immobilization is critical for this protocol. Immobilization to assure reproducibility of the set up is necessary.

4. The use of four-dimensional radiation treatment planning is highly encouraged. Acceptable methods of accounting for tumor motion include: design of the PTV to cover the excursion of the lung primary cancer and nodes during breathing such as an ITV approach, a maximum intensity projection (MIP) approach, automatic breath-hold (i.e., Elekta ABC device) or a gating approach (e.g., Varian RPM system).

c. Target Volumes

The nomenclature and definitions of ICRU Reports 50 and 62 shall be followed in this study.

1. Definition of the GTV: The primary tumor and clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged. The ITV includes the envelope that encompasses the tumor motion for a complete respiratory cycle.

2. Definition of the CTV: The CTV is defined to be the GTV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension. If an ITV approach is used then the ITV plus 0.5 cm to 1 cm is added to the ITV to form the CTV. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

   Ipsilateral supraclavicular irradiation is allowed when needed for primary tumor coverage. Contralateral hilar or supraclavicular coverage (of uninvolved nodes) is not allowed (elective nodal irradiation will not be performed). Any mediastinal node detected by CT scan >1.0 cm (short axis) or with SUV > 3 on pre-treatment PET scan should be included as GTV, with the appropriate margin to create the CTV.

3. Definition of the PTV: The planning target volume (PTV) is the CTV plus a margin to ensure that the prescribed dose is actually delivered to the GTV. This margin is a geometric concept, which accounts for variations in treatment delivery, including variations in set-up between treatments, patient motion during treatment, movement of the tissues that contain the GTV, and size variations in the tissue containing the GTV. The PTV should be within a range of 0.5 to 1.5 cm, depending on the above factors. This margin should include consideration for, most notably, organ motion.

4. PTV guidelines when 4D planning is used:

   Free-breathing non-ITV approach (i.e. standard CT simulation without 4DCT or fusion of inhalation and exhalation scans):

   There are two components to the PTV expansion. the internal motion (IM margin) which should be at least 1 cm in the inferior-superior direction, and 0.5 cm in the axial plane and an additional set-up margin (SU margin) of 0.5 cm. Thus, the total PTV includes the CTV plus a total margin of at least 1.5 cm to the superior-inferior dimensions and at least 1.0 cm in the axial plane.

   Breath-hold or gating non-ITV approach:
   For breath-hold or gating approaches, the PTV margin should be at least 1 cm in the inferior-superior direction and 0.5 cm in the axial plane. It is expected that daily imaging will be used for both breath-hold and gating techniques.

   ITV approach:
   If the ITV approach is used, then the PTV margin should account for setup uncertainties and may be individualized but should not be less than 1.0 cm. If daily imaging is used to align the vertebral bodies, then the margins for setup margins may be reduced to 0.5 cm. For institutions not using 4DCT, the use of fluoroscopy to determine the margin for motion in the inferior superior direction is encouraged. For institutions with gating technology, the use of respiratory gating is encouraged.

d. Target Doses

Prescribed Dose: The prescribed dose to the PTV is 6,000 cGy delivered in 200 cGy/day over 30 fractions.

Dose Uniformity: The prescribed isodose volume will cover at least 95% of the PTV. The minimum PTV dose must not fall below 95% of the prescription dose. The maximum PTV dose must not exceed a value that is 130% of the prescribed dose. The minimum and maximum doses will be defined as the dose to a 1 cc volume of the PTV.

Acceptable and Unacceptable Variations: See Section 12.4 for Definitions of Deviations in Protocol Performance.

Tissue Heterogeneity: All dose calculations will account for the density differences within the irradiated volume.

Approved Dose Algorithms: Planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. Contact QARC (physics@qarc.org) for information regarding approved dose algorithms.

e. Technical Factors

Beam energy: Megavoltage equipment is required with minimum peak photon energy of 6 MV.

Treatment distance: Minimal treatment distance should be 100 cm for SAD techniques. SSD techniques should not be used.

Blocking: Blocking will be required for the shaping of ports to exclude volume of tissues that are not to be irradiated. Multi-leaf collimation (MLC) or individually-shaped custom blocks should be used to protect normal tissues outside of the target volume.

Filter or Wedges: In the case of large sloping contours (as is often encountered when treating thoracic tumors in patients with larger body habitus), compensating filters are recommended. Therefore, wedges may be used as a 2 dimensional tissue compensator. If necessary, appropriate reduction in field size must be performed to avoid excessive irradiation of critical structures.

f. Radiation Therapy Interruptions

Total dose, number of fractions, and elapsed days should be carefully reported. Every effort should be made to minimize the length of treatment interruptions.

g. Treatment Planning

3D Conformal Therapy: The PTV is to be treated with any combination of coplanar or noncoplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal

conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures. Each field is to be treated daily.

Intensity-Modulated Radiotherapy (IMRT): IMRT is allowed as long as a method of motion management is utilized. Acceptable approaches include abdominal compression, breath hold using ABC device or other computed controlled spirometry, gating, image-guidance or other techniques.

h. Organs at Risk

Normal anatomy to be identified: The normal anatomy to be outlined on each CT image will include the lungs (right and left done separately), heart, skin, esophagus and spinal cord. The heart should be contoured from its base to apex, beginning at the CT slice where the ascending aorta originates. The esophagus should be contoured from the bottom of the cricoid to the gastroesophageal junction. The skin and spinal cord should be contoured on each CT slice.

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, and 4=heart

1. Spinal Cord: The spinal cord dose limitation is the highest priority dose constraint and thus must be met irrespective of other constraints. Total "direct" plus "scatter" dose to the spinal cord must not exceed 5,050 cGy.

2. Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The volume of *both* lungs that receive more than 2,000 cGy (the V20) should not exceed 37% of the total lung volume. Alternatively, the mean lung dose should optimally be ≤ 2,000 cGy. (By total lung volume we mean the total lung minus the CTV).

3. If either of these constraints is exceeded, several solutions can be entertained. First, one might increase the weighting of AP / PA treatments by one and reduce the obliques. This can be done as long as the cord dose (above), which takes precedence, is not exceeded. Second, one can reduce the CTV to the minimum range suggested above. Third, one can try to reduce the PTV by using respiratory gating techniques. If after all attempts to decrease the V20 to below 37%, the V20 value still exceeds this limit, the patient should be treated as outlined in these guidelines. However, this will be classified as a minor protocol deviation if V20 is greater than 37% but less than 40%. If the V20 lies between 40% and 50%, this will be classified as a major protocol deviation. NOTE: Patients with V20 of greater than 50% will be removed from protocol treatment.

4. Esophagus: The mean dose to the esophagus is optimally kept below 3,400 cGy. This is not an absolute requirement, but is strongly recommended unless other, more critical constraints force the situation. The V60 (% volume of esophagus exceeding 6,000 cGy) should be calculated for each patient.

5. Heart: The following limits are recommended 6,000 cGy to < 1/3, 4,500 cGy to < 2/3, and 4,000 cGy to < 100% of the heart.

i. Documentation Requirements

See Section 12.3 for documentation requirements.

j. Variation of Dose Prescription

See Section 12.4 for definitions of deviation in protocol performance.

7.5 Consolidation Chemotherapy

All patients without disease progression after completion of chemoradiation will continue with 2 cycles (every 21 days) of consolidation therapy with paclitaxel 200 mg/m^2, carboplatin 6 AUC and ABT-888 80 mg or placebo BID (dose of ABT-888 established at the ongoing Phase I trial of carboplatin, paclitaxel, and ABT-888).

Consolidation chemotherapy should start within 4-6 weeks of completion of RT, assuming criteria for initiating treatment are met, see Section 8.3.

Qualifying laboratory tests can be obtained up to 72 hours before planned initiation of therapy.

AGENT	DOSE	ROUTE	SCHEDULE
Paclitaxel[a]	200 mg/m^2 over 3 hours	IV over 3 hours	Day 1 and Day 22 (Cycle 2)
Carboplatin	AUC=6 over 30 minutes during consolidation[b]	IV 30 minutes after completion of paclitaxel	Day 1 and Day 22 (Cycle 2)
Phase I: ABT-888	80mg[c]	PO twice Daily	Days 1-7 (Cycle 1), Days 22-28 (Cycle 2)
Phase II: ABT-888 or Placebo	80mg[c]	PO twice Daily	Days 1-7 (Cycle 1), Days 22-28 (Cycle 2)

NOTE: ABT-888 doses are "flat" and **not** calculated based on weight or BSA.

[a] See paclitaxel premedication guidelines in Section 7.2a.

[b] AUC=6 by modified Calvert formula. Carboplatin is given after paclitaxel infusion is completed. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing. This change is an addition to the requirement not to exceed a maximum dose of carboplatin of 900 mg (see Appendix 18.3 for the Carboplatin Dosing Worksheet and premedication guidelines in Section 7.2b).

[c] ABT-888/placebo capsules are supplied as 20 mg capsules. Capsules may be taken without regard to meals.

Patients are expected to start on a Monday. Protocol will allow a +/- 24 hour window for chemotherapy and correlatives for Week 1.

7.6 Supportive Care Measures

See Section 8.4 regarding the use of prophylactic granulocyte colony stimulating factor during RT and during consolidation therapy. The use of growth factors for the treatment of anemia is not allowed.

7.7 General Concomitant Medical and Supportive Care Guidelines

Because there is a potential for interaction of carboplatin and paclitaxel with other concomitantly administered drugs through the cytochrome P450 system, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be noted in the patients chart. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. (See Appendix 18.5)

7.8 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.1). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.9 Full CDUS Reporting Requirements

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4d and 14.4g, the **S1206** Concurrent Chemotherapy Treatment Form, the **S1206** Consolidation Chemotherapy Treatment Form, and the **S1206** Adverse Event Form. A cycle is defined as ***21*** days. During the Phase I portion of the trial, the **S1206** Concurrent Chemotherapy Treatment Form and the **S1206** Adverse Event Form must be submitted every 7 days (see Section 14.4i).

7.10 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration as defined in Section 10.2d.

b. Grade 3 or worse infusion reactions

c. Ineligible for Second Registration (see Sections 5.2a-f)

d. Completion of protocol treatment.

e. Unacceptable toxicity.

f. Treatment delay for any reason > ***3*** weeks.

g. Normal lung V20 greater than 50% (see Section 7.4).

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

7.11 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.12 Follow Up Period

All patients will be followed until death or ***5*** years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Dose Modification Guidelines

If multiple toxicities are experienced, use the worst grade.

8.3 Dose Modifications During Concurrent Therapy (common for the Phase I and Phase II)

No dose reductions of chemotherapeutic agents are required during concurrent chemoradiotherapy. Doses that are missed during the weekly schedule concurrent with radiation therapy will not be made up. Any treatment delays will be documented.

a. **ABT- 888 Dose Levels**

Dose level 2	**120 mg***
Dose level 1	**80 mg***
Dose level 0 (Starting Dose)	**40 mg***
Dose level -1	**20 mg***
Dose level -2	**Permanently remove patient from protocol treatment.**

* Dose given twice a day.

NOTE: **Carboplatin and paclitaxel doses missed will not be made up. All dose reductions are permanent.**

b. Paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity During Concurrent Therapy (same for both Phase I and Phase II parts of the study)

Toxicity NCI CTCAE Grade (CTCAE v4.0) on the day of due treatment*	Paclitaxel Dose At Start of Subsequent Cycles Of Therapy[a]	Carboplatin Dose at Start of Subsequent Cycles Of Therapy[a]	ABT-888 Versus Placebo
Neutropenia 1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	No change
2 (1000-1499/ mm^3	Maintain dose level	Maintain dose level	No change
3 (500-999/ mm^3	Hold therapy[b]	Hold therapy[b]	Hold therapy[b]
4 < 500/mm^3	Hold therapy[b]	Hold therapy[b]	Hold therapy[b]

Toxicity NCI CTCAE Grade (CTCAE v4.0) on the day of due treatment*	Paclitaxel Dose At Start of Subsequent Cycles Of Therapy[a]	Carboplatin Dose at Start of Subsequent Cycles Of Therapy[a]	ABT-888 Versus Placebo
Neutropenic fever	Hold therapy[b]	Hold therapy[b]	Hold therapy[b]
Thrombocytopenia 1 (< LLN-75,000/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (50,000-74,999/mm^3)	Hold therapy[b]	Hold therapy[b]	Hold therapy[b]
3 (25,000-49,999/mm^3)	Hold therapy[b]	Hold therapy[b]	Hold therapy[b]
4 (< 24,999/mm^3)	Hold therapy[b]	Hold therapy[b]	Hold therapy[b]

* RT should be held for all Grade 4 hematologic toxicity except for Grade 4 lymphopenia, (at the discretion of the treating physician). RT should be resumed when hematologic toxicity is ≤ Grade 3.

[a] Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

[b] Repeat lab work weekly and resume chemotherapy and ABT-888 based on this table.

If paclitaxel and/or carboplatin doses must be withheld for greater than 3 consecutive weeks, the drug(s) will be held permanently for the duration of concurrent therapy.

c. Paclitaxel/Carboplatin Dose Modifications for Non-Hematologic Toxicity During Concurrent Therapy (same for both Phase I and Phase II parts of the study)

Dose reductions in ABT-888/placebo will be permanent during concurrent therapy

Worst Toxicity NCI CTCAE Grade (CTCAE v4.0)[a]	Paclitaxel Dose At Start of Subsequent Cycles Of Therapy[b]	Carboplatin Dose at Start of Subsequent Cycles Of Therapy[b]	ABT-888 Versus placebo
Neuropathy ≤ Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	**Hold therapy until Grade ≤ 1; restart at full dose**	Maintain dose level	Maintain dose level
Grade 3 or 4	Discontinue therapy	Hold therapy, until ≤ Grade 2	Hold therapy , until ≤ Grade 2

Worst Toxicity NCI CTCAE Grade (CTCAE v4.0)[a]	Paclitaxel Dose At Start of Subsequent Cycles Of Therapy[b]	Carboplatin Dose at Start of Subsequent Cycles Of Therapy[b]	ABT-888 Versus placebo
Other non-hematologic toxicities[c] Grade 3 or 4	Hold therapy until ≤ Grade 2	Hold therapy until ≤ Grade 2	Hold therapy until ≤ Grade 2 and decrease ABT-888/placebo by 1 dose level, unless not possibly attributable to ABT-888/placebo
For in-field toxicities please see Section 8.3d.			

[a] For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, follow the guidelines listed above.

[b] Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

[c] Radiation therapy should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field, with the exceptions noted in Table 8.2d. RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2.

NOTE: If there is a decline in performance status to ≥ 2 for greater than 2 weeks while under treatment, radiotherapy should be held with no further chemotherapy administered. Re-evaluate patient after one week for resumption of radiotherapy.

d. Paclitaxel/Carboplatin/RT Dose Modifications for in RT In-Field, Non-Hematologic Toxicity During Concurrent Therapy (same for both Phase I and Phase II parts of the study).

Treatment Modification for In-field Non-Hematologic Toxicity				
In-field	CTCAE Toxicity Grade	XRT	Paclitaxel	Carboplatin
Esophagus/pharynx* (*on day of XRT)*	4	Hold treatment Until ≤ Grade 2	Hold treatment Until ≤ Grade 2	Hold treatment Until ≤ Grade 2
Esophagus/pharynx* (*on day of chemo)*	3	No change or hold ≤ 5 days	Hold treatment Until ≤ Grade 2	Hold treatment Until ≤ Grade 2
Esophagus/pharynx* (*on day of chemo)*	2	No change	No change	No change

Treatment Modification for In-field Non-Hematologic Toxicity				
Pulmonary	4	Discontinue	Discontinue	Discontinue
Pulmonary	3	Hold treatment Until ≤ Grade 2	Hold treatment Until ≤ Grade 2	Hold treatment Until ≤ Grade 2
Skin	4	Hold treatment Until ≤ Grade 2	Hold treatment Until ≤ Grade 2	Hold treatment Until ≤ Grade 2
Skin	3	No change	No change	No change

* Radiation esophagitis or dermatitis radiation will use CTCAE v4.0.

The grading for esophagitis as per CTCAE v4.0 is:

Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Symptomatic; altered eating/swallowing; oral supplements indicated.

Grade 3: Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated.

Grade 4: Life-threatening consequences; urgent operative intervention indicated.

On day of chemotherapy administration during any treatment week, omit paclitaxel and carboplatin until toxicity resolves to Grade ≤ 2 as detailed in the table above that refers to Concurrent therapy.

Radiotherapy should be interrupted for any Grade 4 toxicity or Grade 3 pulmonary toxicity and resumed according to the table above. If treatment is interrupted for > 3 weeks, the patient should be removed from study treatment.

RT should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field (with the exceptions noted in Section 8.3d for in-field non-hematologic toxicities). RT should be held for Grade 4 non-hematologic toxicities in or outside the treatment field and resumed only when non-hematologic toxicity is ≤ Grade 2. RT should be held for Grade 4 hematologic toxicity, except for Grade 4 lymphopenia (at the discretion of the treating physician). RT should be resumed when hematologic toxicity is ≤ Grade 3.

Radiation therapy will be continued without interruption even if chemotherapy and/or ABT-888/placebo are held for toxicity or any other reason. However, if radiation therapy is held for toxicity, chemotherapy and/or ABT-888 will be held as well.

8.4 Dose Modifications During Consolidation Therapy

- Patients should meet the laboratory parameters and the performance status outlined in eligibility before initiation of each cycle of consolidation therapy.

- All toxicities (except alopecia and lymphopenia, hyperglycemia, hypoalbuminemia, elevated serum alkaline phosphatase) should have resolved to Grade 1 or lesser severity before initiation of the first or second cycle of consolidation therapy. Treatment should be delayed until recovery of blood counts to the following levels: absolute neutrophil count ≥ 1,500/ mcl; platelets ≥ 100,000/mcl; hemoglobin ≥ 9.0 g/dl.
- **Only patients without disease progression based on repeat tumor measurements using RECIST will receive consolidation therapy.**
- **If the patient is found to be eligible to continue on to consolidation therapy (4 weeks, +/- 3 days), additional ABT-888 or ABT-888/placebo supplies should be ordered.**

Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. Treatment delay of > 3 weeks due to toxicity will lead to removal of the patient from the study.

Since fatigue can be a symptom of cancer progression, dose reduction will only be done if it is deemed to be drug-related in the opinion of the investigator.

The prophylactic use of granulocyte-colony growth stimulating factors on Cycle 1 of consolidation is allowed at the discretion of the treating physician.

Dose levels of ABT-888 during Consolidation Treatment:

ABT-888 80 mg BID (starting dose level) for Days 1-7 and Days 22-28

ABT-888 40 mg BID (-1 dose level) for Days 1-7 and Days 22-28

Carboplatin AUC 6, Paclitaxel 200 mg/m^2 (starting dose level)

Carboplatin AUC 5, Paclitaxel 175 mg/m^2 (-1 dose level)

a. Paclitaxel/Carboplatin Dose Modifications During Consolidation Therapy for Hematologic Toxicity (same for both Phase I and Phase II parts of the study)

Toxicity NCI CTCAE Grade (CTCAE v4.0) On day of treatment	**Paclitaxel Dose At Start of Second Cycle Of Therapy[a,c]**	**Carboplatin Dose at Start of Second Cycle Of Therapy[a,c]**	**ABT-888 versus Placebo**
Neutropenia 1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	No change
2 (1000-1499/mm^3	Hold therapy[b] Maintain dose level, if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1500 mm^3	Hold therapy[b] Maintain dose level, if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1500 mm^3	Hold therapy; resume when chemotherapy is resumed
3 (500-999/mm^3)	Hold therapy[b] Maintain dose level, if fully recovered in 1 week and add growth factor. If not, decrease by 1 dose level when ≥ 1500 mm^3 and add growth factor	Hold therapy[b] Maintain dose level, if fully recovered in 1 week and add growth factor. If not, decrease by 1 dose level when ≥ 1500 mm^3 and add growth factor	Hold therapy; resume when chemotherapy is resumed and decrease ABT-888/placebo by 1 dose level

Toxicity NCI CTCAE Grade (CTCAE v4.0) On day of treatment	Paclitaxel Dose At Start of Second Cycle Of Therapy[a,c]	Carboplatin Dose at Start of Second Cycle Of Therapy[a,c]	ABT-888 versus Placebo
Neutropenia (contd.) 4 <500/mm^3	Hold therapy[b] Decrease by 1 dose level when ≥ 1500 mm^3 and add growth factor	Hold therapy[b] Decrease by 1 dose level when ≥ 1500 mm^3 and add growth factor	Hold therapy; resume when chemotherapy is resumed and decrease ABT-888/placebo by 1 dose level
Neutropenic fever	Hold therapy[b] and decrease by 1 dose level when ≥ 1500 mm^3 Add growth factor	Hold therapy[b] and decrease by 1 dose level when ≥ 1500 mm^3 Add growth factor	Hold therapy; resume when chemotherapy is resumed and decrease ABT-888/placebo by 1 dose level
Thrombocytopenia 1 (≥75,000/mm^3)	Hold therapy until platelets ≥ 100,000/mcl and maintain dose level	Hold therapy until platelets ≥ 100,000/mcl and maintain dose level	Hold therapy; resume when chemotherapy is resumed and maintain dose level
2 (50,000-74,999/mm^3)	Hold therapy[b] Maintain dose level, if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 100,000 mm^3	Hold therapy[b] Maintain dose level, if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 100,000 mm^3	Hold therapy; resume when chemotherapy is resumed
3 (25,000-49,999/mm^3)	Hold therapy[b] Maintain dose level, if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 100,000 mm^3	Hold therapy[b] Decrease by 1 dose level when ≥ 100,000 mm^3	Hold therapy; resume when chemotherapy is resumed and decrease ABT-888/placebo by 1 dose level
4 (<25,000/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 100,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 100,000 mm^3	Hold therapy; resume when chemotherapy is resumed and decrease ABT-888/placebo by 1 dose level

If During the Cycle (worst toxicity)	Paclitaxel	Carboplatin	ABT-888/placebo
ANC < 0.5 x 10^9	Add growth factor	Add growth factor	Decrease ABT-888/placebo by 1 dose level
Fever (≥ 38ºC) with ANC < 0.5 x 10^9	Reduce dose by 1 dose level for all subsequent cycles	Reduce dose by 1 dose level for all subsequent cycles	Decrease ABT-888/placebo by 1 dose level
Platelets < 5 0 x 10^9	No Change	Reduce dose by 1 dose level for all subsequent cycles	Decrease ABT-888/placebo by 1 dose level

[a] Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the –1 dose level will not be allowed.
[b] Repeat lab work weekly and resume chemotherapy based on this table.
[c] Dose delays greater than 3 weeks will warrant discontinuation of chemotherapy or the consolidation cycles.

b. Paclitaxel/Carboplatin Dose Modifications During Consolidation for Non-Hematologic Toxicity During Consolidation Therapy (same for both Phase I and Phase II parts of the study)

Toxicity NCI CTCAE Grade (CTCAE v4.0)[a]	Paclitaxel Dose At Start of Second Cycle Of Therapy[b]	Carboplatin Dose at Start of Second Cycle Of Therapy[b]	ABT-888/placebo
Neuropathy			
≤ Grade 1	Maintain dose level	Maintain dose level	No change
Grade 2	Hold therapy until Grade ≤ 1 restart at full dose; if persistent reduce by 1 dose level	Hold therapy until Grade ≤ 1 restart at full dose	Hold therapy until Grade ≤1 restart at full dose
Grade 3	Discontinue paclitaxel	Hold therapy until Grade ≤ 2 and restart at full dose	Hold therapy until Grade ≤ 2 and restart at full dose
Other Non-Hematologic Toxicities[c] Grade 2, 3 or 4	Hold treatment until ≤ Grade 1; reduce by 1 dose level	Hold treatment until ≤ Grade 1; reduce by 1 dose level	Hold therapy. Resume when chemotherapy is resumed and decrease ABT-888/placebo by 1 dose level, unless not possibly attributable to ABT-888/placebo

[a] For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study drugs. For neuropathy, follow the guides above.
[b] Dose levels are relative to the worst toxicities in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
[c] With the exception of alopecia or Grade 2 nausea. For arthralgias/myalgias, hepatotoxicity, gastrointestinal, and allergic/hypersensitivity reactions please see below.

When a chemotherapy dose reduction is required during the consolidation course of therapy re-escalation of the chemotherapy dose will not be allowed.

If chemotherapy or ABT-888/placebo doses must be withheld for greater than 3 consecutive weeks, the drug will be held permanently for the duration of consolidation therapy.

c. Arthralgia/Myalgia

The following dose adjustments are based on the worst grade experienced of arthralgia/myalgia of any preceding treatment course.

Arthralgia/Myalgia	Paclitaxel	Carboplatin	ABT-888/placebo
Grade 0-1 (Normal-mild)	No change	No change	No change
Grade 2 (decreased ability to move)	Decrease by 1 dose level	No change	No change
Grade 3 (disabled)	Hold treatment until resolution to ≤ Grade 1. *	Hold therapy until Grade ≤1 restart at full dose	Hold therapy until Grade ≤ 1 restart at full dose

* If post-medication dexamethasone (4 mg orally BID for 3-5 days) was incorporated in regimen. If no dexamethasone was used, must add regimen to subsequent courses prior to dose level reductions. Hold treatment until resolution to ≤ Grade 1.

d. Hepatic Toxicity (Paclitaxel dose modification only)

The following dose adjustments for paclitaxel are based on ALT and bilirubin serum levels and should be obtained within seven days of treatment.

ALT		Bilirubin	Paclitaxel	ABT-888/placebo
≤ Grade 1	and/or	≤ Grade 2	No change	No change
≥ Grade 2	and/or	≥ Grade 3	HOLD*	HOLD*

* Hold until ALT resolution to ≤ Grade 1 and Bilirubin is ≤ Grade 2. If recovery of toxicity exceeds two weeks, discontinue further therapy and remove patient from study.

<u>If recovery of toxicity occurs within two weeks, reduce dose by 1 level above for both agents. No dose reduction will be done for carboplatin</u>

e. Gastrointestinal Toxicity

<u>Nausea and/or vomiting</u> should be controlled with adequate antiemetic therapy. Prophylactic anti-emetic therapy can be used at the discretion of the treating physician. Patients are encouraged to take plenty of oral fluids. If symptoms persist despite maximal anti-emetic therapy, ABT-888/placebo should be withheld until recovery to ≤ Grade 1.

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Diarrhea should be managed with appropriate anti-diarrheal therapy. Patients should be encouraged to take plenty of oral fluids. If symptoms do not decrease to Grade 1 or less with adequate anti-diarrheal therapy, ABT-888/placebo should be held until recovery from symptoms to ≤ Grade 1. ABT-888/placebo can be re-started at the same dose following recovery to ≤ Grade 1 if worst grade of toxicity is ≤ Grade 2). For worst Grade ≥ 3, re-start with dose reduction by one dose level.

If symptoms recur, the dose of ABT-888/placebo should be re-started with a reduction by one dose level

f. Hypersensitivity Reactions to Paclitaxel

Caution: Patients who had a **mild** to moderate hypersensitivity reaction have been successfully rechallenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

1. Mild symptoms (e.g., mild flushing, rash, pruritus) -Complete infusion. Supervise at bedside. No treatment required.

2. Moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort) -Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate, 20 mg/hr. For 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop infusion. *The patient should receive no additional paclitaxel for that cycle, but may be retreated after discussion with the principal investigator.* Record toxicity on flow sheets..

   Severe life threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria)-stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodialtors if indicated. If wheezing is present, that is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. Patient should be removed from further protocol therapy. Report as serious adverse event.

g. Hypersensitivity Reactions to Carboplatin:

If the allergy develops during the consolidation part of the treatment, patients will have carboplatin deleted and will be evaluable, as they had completed the 9 week DLT evaluation.

If the allergy develops during the concurrent part of the treatment, patients will come off study and be replaced (if in the Phase I).

h. Other Toxicities

For any Grade 2, 3 or 4 toxicity not mentioned above, excluding hemoglobin, lymphocytes, alopecia or Grade 2 nausea, the treatment should be withheld until the patient recovers to ≤ Grade 1. If an abnormal laboratory value is reported, the toxicity should be possibly related to paclitaxel and carboplatin treatment to result in dose reduction. The paclitaxel and carboplatin treatment should then be resumed at dose level (-1) (permanent dose reduction). Dose reduction will be done for the drug that is most likely to have caused the toxicity. For Grade 1 toxicities, no dose reduction should be made.

In case participants develop nausea/vomiting/diarrhea or myelosuppression, supportive medications will be prescribed as per Clinical Center and ASCO guidelines.

8.5 Assessment and Management of Esophageal Toxicity

Esophagitis remains the major acute toxicity experienced during thoracic radiation. With concurrent chemoradiation, there is an approximately 25% incidence of Grade 3/4 esophagitis. Esophagitis presents mainly as dysphagia and odynophagia.

Management of esophagitis is initially with a soft diet and the use of topical anesthetics, such as lidocaine and diphenhydramine and agents that coat the irritated surfaces, such as sucralfate. If symptoms progress, systemic narcotics may be used as needed. Severe, acute esophagitis should prompt aggressive supportive therapy including hydration and enteral or parenteral feeding so that lengthy treatment breaks can be avoided.

8.6 Colony Stimulating Factors

G-CSF (Amgen) has been licensed by the Food and Drug Administration for the prevention of chemotherapy induced neutropenia. In this study, G-CSF will not be administered to all patients to prevent neutropenia. However, it may be used for patients who develop Grade 3 - 4 neutropenia. For patients who experience Grade 3 or 4 neutropenia or develop neutropenic fever between cycles of chemotherapy, G-CSF may be added to all subsequent cycles of chemotherapy. G-CSF is commercially available and should be purchased through third party mechanisms. The NCI will not provide G-CSF for this study.

If G-CSF is used, it is recommended that it be used in the following manner:

If a patient develops neutropenia following chemotherapy, all dose modifications outlined in the protocol will be followed according to the original protocol. However, G-CSF will be added to all subsequent cycles of chemotherapy, unless there is clinical suspicion that the neutropenia was due to an unrelated medical condition and not due to the chemotherapy. The use of prophylactic G-CSF with the first cycle of consolidation is at the discretion of the treating physician.

8.7 Dose Modification Contacts

For chemotherapy-related treatment or dose modification questions, please contact Dr. Argiris at athanassios.argiris@gmail.com, Dr. Cristea at 626/256-4673 or mcristea@coh.org or Dr. Sands at 781/744-8400 or Jacob.M.Sands@lahey.org. For radiation therapy-related treatment or dose modification questions, please contact Dr. Chen at achen5@kumc.edu. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

8.8 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Phase I Study Calendar

		First Registration												Second Registration						
		Chemoradiation						Pre-Consolidation Phase√						Consolidation PhaseΦ≠						F/U After Off Treatment Prior to Progression[7]
														Cycle 1			Cycle 2			
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	
	STUDY	1	2	3	4	5	6	1	2	3	4≠	5≠	6≠	1	2	3	1	2	3	
PHYSICAL																				
History and Physical Exam*	X*			X			X				X^{Ω}			X			X			X
Informed Consent	X																			
Weight and Performance Status	X	X	X	X	X	X	X		X					X			X			
Adverse event evaluation		X	X	X	X	X	X		X		X^{Ψ}	X^{Ψ}	X^{Ψ}	X			X			
Capsule Count/patient diary		X^{9}	X^{9}	X^{9}	X^{9}	X^{9}	X^{9}							X			X			
Baseline Abnormailities	X																			
LABORATORY																				
CBC/Differential/Platelets[1]	X	X	X	X	X	X	X		X		XΨ	XΨ	XΨ	X^{Σ}			X			X
Creatinine, Electrolytes (K^{+}, Na^{+}, Cl^{-}, CO_2), Mg^{++}, Ca^{++}	X	X	X	X	X	X	X		X		XΨ	XΨ	XΨ	X^{Σ}			X			X
Liver enzymes[2]	X	X	X	X	X	X	X		X		XΨ	XΨ	XΨ	X^{Σ}			X			X
Pulmonary function tests¥	X																			X^{8}
Pregnancy test[3]	X																			
Creatinine Clearance	X	X	X	X	X	X	X							X^{Σ}			X			
Albumin	X																			
LDH	X																			
X-RAYS AND SCANS																				
Brain CT or MRI	X																			
CT of the chest, abdomen [4]	X										X^{4}								X^{4}	X^{4}
Bone scan, if clinically indicated	X																			
EKG	X																			

Calendar continued on next page. Click here for Footnotes.

		First Registration												Second Registration						
		Chemoradiation						Pre-Consolidation Phase√						Consolidation PhaseΦ≠						F/U After Off Treatment Prior to Progression[7]
														Cycle 1			Cycle 2			
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	
	STUDY	1	2	3	4	5	6	1	2	3	4≠	5≠	6≠	1	2	3	1	2	3	
SPECIMEN SUBMISSION																				
Paraffin-embedded tissue[5]	X																			
CTC Submission[6]		X			X						X^{Ψ}	X^{Ψ}	X^{Ψ}							
Peripheral blood mononuclear cells and serum/plasma/DNA/ RNA[6]		X			X						X^{Ψ}	X^{Ψ}	X^{Ψ}							
TREATMENT																				
Radiation		X	X	X	X	X	X													
ABT-888[$]		X	X	X	X	X	X∞							X			X			
Carboplatin		X	X	X	X	X	X							X			X			
Paclitaxel		X	X	X	X	X	X							X			X			

Click here for Footnotes.

Footnotes:
* Baseline evaluation by Radiation Oncology and Medical Oncology.

During chemoradiotherapy patients need a focused evaluation of toxicities on a weekly basis. However, a complete history and physical examination is only needed every 3 weeks during chemoradiotherapy, at 4 weeks (+/- 3 days) after chemoradiotherapy and prior to each cycle of consolidation chemotherapy.

NOTE: If the patient is found to be eligible to continue on to consolidation therapy (4 Weeks, +/- 3 days), additional ABT-888 supplies should be ordered.

1 Complete blood counts with differential and platelet count should be performed <24 hours prior to chemotherapy administration (with the exception of baseline CBC which must be obtained within 28 days prior to registration and Cycle 1 which must be obtained < 72 hours prior to chemotherapy administration). In the event of grade 3 or 4 hematologic toxicity, follow-up CBC with differential and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery.

2 Liver function tests should include: Bilirubin, AST (SGOT), ALT (SGPT)

3 All females of childbearing potential must have a negative pregnancy test done within 3 days of initiation of treatment to rule out pregnancy.

4 Tumor measurements will be made using CT scan. CT scan MUST be of diagnostic quality. Tumor assessments will be performed at 4 Weeks (+/- 3 days) after completion of chemoradiotherapy and after completion of consolidation therapy. Subsequently, repeat imaging with CT scans of chest and abdomen will be performed every 4 months for up to 2 years after initial registration, then every 6 months for up to 3 years after initial registration.

5 The following materials will be submitted: paraffin-embedded tumor specimens for immunohistochemistry and molecular studies.

6 Blood samples (Peripheral Blood Mononuclear Cells, serum/plasma/DNA/RNA and Circulating Tumor Cells). See Sections 15.3b and 15.4b for the time points for the blood correlatives. Blood sampling will be performed on all patients on the Phase I and Phase II.

7 Patients will be followed every 4 months for the first 2 years then every 6 months until 5 years from the date of randomization.

8 Pulmonary function tests (PFTs) will be performed at baseline and 6 months after completion of consolidation therapy.

9 For assessment of compliance every time a new box of ABT-888 capsules is given to the patient (the patient diary is in Appendix 18.1).

√ 4-6 weeks is the pre-consolidation phase; patients will not receive any drug during that phase.

∞ ABT-888 to be given 1 day after completion of RT.

$ Twice daily

¥ Within 12 weeks prior to registration

Ψ To be performed only once during Weeks 4-6

Ω Within +/- 3 days

Φ Only patients without disease progression will receive consolidation therapy.

≠ Consolidation should start within 4-6 weeks of completion of RT. See Section 7.5

∑ To be performed within 14 days prior to second registration.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf.

9.2 Phase II Study Calendar

		First Registration												Second Registration						
		Chemoradiation						Pre-Consolidation Phase√						Consolidation PhaseΦ≠ Cycle 1			Cycle 2			F/U After Off Treatment Prior to Progression [8]
REQUIRED STUDIES	PRE STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 1	Wk 2	Wk 3	Wk 4≠	Wk 5≠	Wk 6≠	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
PHYSICAL																				
History and Physical Exam*	X*			X			X				X^{Ω}			X			X			X
Informed Consent	X																			
Weight and Performance Status	X	X	X	X	X	X	X		X					X			X			
Adverse event evaluation		X	X	X	X	X	X		X		X^{Ψ}	X^{Ψ}	X^{Ψ}	X			X			
Capsule Count/patient diary		X^{10}	X^{10}	X^{10}	X^{10}	X^{10}	X^{10}							X			X			
Baseline Abnormalities	**X**																			
LABORATORY																				
CBC/Differential/Platelets [1]	X	X	X	X	X	X	X		X		XΨ	XΨ	XΨ	X^{Σ}			X			X
Creatinine, Electrolytes (K^+, Na^+, Cl^-, CO_2), Mg^{++}, Ca^{++}	X	X	X	X	X	X	X		X		XΨ	XΨ	XΨ	X^{Σ}			X			X
Liver enzymes [2]	X	X	X	X	X	X	X		X		XΨ	XΨ	XΨ	X^{Σ}			X			X
Pulmonary function tests¥	X																			X^{9}
Pregnancy test [3]	X																			
Creatinine Clearance	X	X	X	X	X	X	X							X^{Σ}			X			
Albumin	X																			
LDH	X																			
X-RAYS AND SCANS																				
Brain CT or MRI	X																			
CT of the chest, abdomen [4]	X										X^{4}								X^{4}	X^{4}
Bone scan, if clinically indicated	X																			
EKG [5]	X																			

Calendar continued on next page. Click here for Footnotes

		First Registration												Second Registration						
		Chemoradiation						Pre-Consolidation Phase√						Consolidation PhaseΦ≠ Cycle 1			Cycle 2			F/U After Off Treatment Prior to Progression[8]
REQUIRED STUDIES	PRE STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
SPECIMEN SUBMISSION																				
Paraffin-embedded tissue[6]	X																			
CTC Submission[7]		X			X						X^{Ψ}	X^{Ψ}	X^{Ψ}							
Peripheral blood mononuclear cells and serum/plasma/DNA/ RNA[7]		X			X						X^{Ψ}	X^{Ψ}	X^{Ψ}							
TREATMENT																				
Radiation		X	X	X	X	X	X													
ABT-888/Placebo[$]		X	X	X	X	X	X∞							X			X			
Carboplatin		X	X	X	X	X	X							X			X			
Paclitaxel		X	X	X	X	X	X							X			X			

Click here for Footnotes.

Footnotes for Calendar 9.2

* Baseline evaluation by Radiation Oncology and Medical Oncology.

During chemoradiotherapy patients need a focused evaluation of toxicities on a weekly basis. However, a complete history and physical examination is only needed every 3 weeks during chemoradiotherapy, at 4 weeks (+/- 3 days) after chemoradiotherapy and prior to each cycle of consolidation chemotherapy.

NOTE: If the patient is found to be eligible to continue on to consolidation therapy (4 Weeks, +/- 3 days), additional ABT-888 supplies should be ordered.

1 Complete blood counts with differential and platelet count should be performed <24 hours prior to chemotherapy administration (with the exception of baseline CBC which must be obtained within 28 days prior to registration and Cycle 1 which must be obtained < 72 hours prior to chemotherapy administration). In the event of grade 3 or 4 hematologic toxicity, follow-up CBC with differential and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery.

2 Liver function tests should include: Bilirubin, AST (SGOT), ALT (SGPT)

3 All females of childbearing potential must have a negative pregnancy test done within 3 days of initiation of treatment to rule out pregnancy.

4 Tumor measurements will be made using CT scan. CT scan MUST be of diagnostic quality. Tumor assessments will be performed at 4 Weeks (+/- 3 days) after completion of chemoradiotherapy and after completion of consolidation therapy. Subsequently, repeat imaging with CT scans of chest and abdomen will be performed every 4 months for up to 2 years after initial registration, then every 6 months for up to 3 years after initial registration.

5 EKG must be performed within 28 days prior to registration.

6 The following materials will be submitted: paraffin-embedded tumor specimens for immunohistochemistry and molecular studies.

7 Blood samples (Peripheral Blood Mononuclear Cells, serum/plasma/DNA/RNA and Circulating Tumor Cells). See Sections 15.3b and 15.4b for the time points for the blood correlatives. Blood sampling will be performed on all patients on the Phase I and Phase II.

8 Patients will be followed every 4 months for the first 2 years then every 6 months until 5 years from the date of randomization.

9 Pulmonary function tests (PFTs) will be performed at baseline and 6 months after completion of consolidation therapy.

10 For assessment of compliance every time a new box of ABT-888 capsules is given to the patient (the patient diary is in Appendix 18.1).

√ 4-6 weeks is the pre-consolidation phase; patients will not receive any drug during that phase.

∞ ABT-888 to be given 1 day after completion of RT.

$ Twice daily

¥ Within 12 weeks prior to registration

Ψ To be performed only once during Weeks 4-6

Ω Within +/- 3 days

Φ Only patients without disease progression will receive consolidation therapy.

≠ Consolidation should start within 4-6 weeks of completion of RT. See Section 7.5

∑ To be performed within 14 days prior to second registration.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of Lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

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

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

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

   Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

   1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

   2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

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

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Treatment Failure

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), early discontinuation of treatment, or death due to any cause. Patients last known not to have failed treatment are censored at the date of last contact.

10.6 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.7 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual

This study will initially be open in limited institutions, with an expected accrual of 10-30 patients in the Phase I portion of the trial. The estimated accrual rate for this part of the study is 2-3 patients/ month. The Phase II portion of the trial will be open Group-wide. Based on data from previous studies in similar patient populations the estimated accrual rate is 8-9 patients/month for the phase II portion of the study.

11.2 Phase I Study:

Section 7.3a-b provides the details of the study design for the Phase I portion of the study. The Phase I study will be a limited dose-escalation study with the following dose levels:

Dose Level	Dose		
	ABT-888	**Carboplatin 2 AUC**	**Paclitaxel 45 mg/ m^2**
Level -1	20 mg BID	Weekly during RT	Weekly during RT
Level 0	40 mg BID	Weekly during RT	Weekly during RT
Level 1	80 mg BID	Weekly during RT	Weekly during RT
Level 2	120 mg BID	Weekly during RT	Weekly during RT

The primary objective of this study is to determine the maximum tolerated dose (MTD) of ABT-888 used in combination with carboplatin and paclitaxel (CP) in chemonaive patients with Stage III unresectable NSCLC. The regimen will be considered safe and the MTD determined if the dose-limiting toxicity rate of ABT-888 + CP is ≤ 33%.

11.3 Phase II Study

The primary objective of the Phase II portion of this study is to evaluate the efficacy of ABT-888 in combination with carboplatin and paclitaxel in comparison with carboplatin, paclitaxel and placebo in chemonaive patients with unresectable Stage III NSCLC.

11.4 Sample Size and Power Justification

It is assumed that the addition of ABT-888 would not be promising if the true median PFS were ≤ 11 months, but would be of considerable interest if the true median PFS where ≥ 19.2 months (corresponding to a 1.75 hazard ratio). A design with 85% power and a 10% type I error rate would require 68 progression events to evaluate a 75% improvement in median PFS using a 1-sided log-rank test. The resulting target sample size is 120 eligible patients accrued over 15 months and followed for a minimum of 12 months. Assuming a 10% ineligibility rate, the projected accrual is 132 patients.

11.5 Analyses and Timepoints

Primary analyses will be performed on an intent-to-treat basis. A stratified log-rank test at the 10% level will be used to test the primary hypothesis. The final analysis will take place upon the observation of 68 progression events.

An interim analysis is planned upon the observation of 50% of the expected progression events (34 events at 15 months after study activation, the time of expected completion of accrual). This analysis will evaluate futility alone. Specifically, the planned analysis is a test of the alternative hypothesis of a hazard ratio equal to 1.75 with consideration for early stopping if the alternative hypothesis is rejected at the 0.05 level.

Secondary analyses include the comparison of overall survival, response, and toxicity between study arms. A stratified log-rank test will be used to compare overall survival; a stratified chi-square test will be used to compare response and toxicity between the two arms. This design has 81% power to detect a 100% improvement in median survival time from 22 to 44 months using a 0.10 level test. Additionally, this design has at least 85% power to detect > 20% difference in toxicity, for any given toxicity (also using a 1-sided 0.10 level test). Within each arm, any toxicity occurring with at least a 5% probability is likely to be seen at least once (94% chance).

Sixty patients/arm will be sufficient to estimate the 6-month overall survival probability and individual toxicity proportions to within at least 13% (95% confidence interval).

Assuming 80% of participants will have measurable disease (as defined by RECIST); then approximately 48 patients/arm will be evaluable for response and disease control rates. This design, with 96 patients with measurable disease has at least 84% power to detect at least a 25% increase in rates with ABT-888 using a 1-sided 0.10 level test. 48 patients/arm will be sufficient to estimate the response rate (confirmed and unconfirmed complete and partial responses) and DCR to within at least 14% (95% confidence interval).

11.6 Adverse Event Monitoring

The Phase I portion of the trial will employ careful adverse event monitoring as previously established for regimens where there are limited or no pre-existing data for the specific combination under study, but where combination data for the targeted agent plus other chemotherapy regimens suggest that full doses of the study combination can be safely administered. Adverse event monitoring will performed by the Study Chair, Study Statistician and the Disease Committee Chair and include weekly toxicity reports and biweekly conference calls. A temporary closure will occur prior to opening this study for the Phase II portion in order to assess dose and to evaluate the safety profile more fully prior to implementation of the Phase II trial.

11.7 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of the randomized Phase II portion of the study. The Committee consists of four members from outside of SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (nonvoting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's biannual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

12.1 Radiation Therapy Review

All patients registered to this study will undergo radiation therapy review by the Quality Assurance Review Center (QARC). Materials must be submitted within 3 days after initiation of radiotherapy. The purpose of this rapid review is to verify that the

radiotherapy will be given according to the protocol and to allow for enough time to make modifications if necessary. In addition, the Radiation Therapy Study Chair will assess the adherence to the protocol by reviewing the complete documentation of the administration after completion of all radiotherapy. Any changes in patient status (i.e., discontinuation of protocol treatment, delay, or break in treatment) should be communicated in writing to QARC by fax (401/753-7601) or email at swog@qarc.org.

12.2 Required Benchmarks

Centers participating in this protocol using 3D-CRT are required to complete the 3D benchmark; those using IMRT must complete the IMRT questionnaire and benchmark or irradiate the RPC head and neck phantom. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center (www.qarc.org) and must be submitted before patients on this protocol can be evaluated. For information regarding the IMRT phantoms, please contact the RPC (http://rpc.mdanderson.org/rpc).

If techniques are used to compensate for or limit respiratory motion, the QARC Motion Management Questionnaire must also be submitted. If patients are treated with IMRT and gating or tracking methods are used to compensate for respiratory motion, the RPC's Thorax-Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion.

12.3 Quality Assurance Documentation

Required Benchmarks: See Section 12.2 for required benchmarks.

Digital Submission: Submission of treatment plans in digital format (either DICOM RT or RTOG format) is required. Digital data must include CT scans, structures, plan and dose files. Submission may be either by SFTP or CD. Instructions for data submission are on the QARC Web site at www.qarc.org. Any items on the list below that are not part of the digital submission may be submitted as screen captures along with the digital data.

Within 3 days from start of radiotherapy, the following data should be submitted for pre-treatment review:

Treatment Planning System Output

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) of the GTV, spinal cord, right and left lungs, heart, esophagus, and liver. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field if 3D conformal planning is used. DRRs should show field outlines but not target volumes or organs at risk. Please include two sets, one with and one without overlays of the target volumes and organs at risk.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- Copies and reports of CT scans, PET scans, and other diagnostic materials used for planning target volumes.
- Prescription Sheet for Entire Treatment
- Documentation of an independent check of the calculated dose when IMRT is used.

- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by QARC and the radiation oncology reviewers.

Forms

- RT-1 Dosimetry Summary Form
- Motion Management Reporting Form

Within one week of the completion of radiotherapy the following data shall be submitted.

- The RT-2 Radiotherapy Total Dose Record form.
- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas, critical organ and reference points
- Documentation listed above showing any modifications from original submission.

Supportive Data and Forms may be included with the transmission of the digital RT data via sFTP or submitted separately via e-mail (swog@QARC.org) or mailed to:

Quality Assurance Review Center
640 George Washington Highway
Building A, Suite 201
Lincoln, RI 02865
Tel: (401) 753-7600
Fax: (401) 753-7601

Questions regarding the dose calculations or documentation should be directed to: SWOG Protocol Dosimetrist

Quality Assurance Review Center
640 George Washington Highway
Building A, Suite 201
Lincoln, RI 02865
Tel: (401) 753-7600
Fax: (401) 753-7601

Questions regarding the radiotherapy section of this protocol, including treatment interruptions, should be directed to:

Allen M. Chen, M.D. (Radiation Oncology)
Department of Radiation Oncology
University Rainbow Boulevard, MS 4033
Kansas City, KS 66106
Phone: 913/588-3612
FAX: 913/588-3663
E-mail: achen5@kumc.edu

12.4 Definitions of Deviations in Protocol Performance

Prescription Dose

- **Minor Deviation:** The dose to the prescription isodose surface differs from that in the protocol by between 6% and 10%.
- **Major Deviation:** The dose to the prescription isodose surface differs from that in the protocol by more than 10%.

Dose Uniformity

- **Minor Deviation:** The prescribed dose covers between 90% and 95% of the PTV or the minimum dose to 1 cc of the PTV is between 90% and 95% of the prescribed dose or the maximum dose to 1 cc of the PTV exceeds 130% of the prescribed dose
- **Major Deviation:** The prescribed dose covers less than 90% of the PTV or the minimum dose to 1 cc of the PTV is less than 90% of the prescribed dose or the maximum dose to 1 cc of tissue outside the PTV exceeds 120% of the prescribed dose.

Volume

- **Minor Deviation:** Margins less than specified, or field(s) excessively large as deemed by the study chair.
- **Major Deviation:** GTV incorrectly defined resulting in fields that transect tumor.

Critical Organ

- **Minor Deviation:** The lung V20 exceeds 37% but is less than 40%.
- **Major Deviation:** The maximum dose to the spinal cord exceeds 5,000 cGy or the lung V20 exceeds 40% but is less than 50%.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than ten working days prior to planned start of treatment). **NOTE: No open label OR blinded starter supplies will be available for this study.** Initial patient-specific clinical supplies of ABT-888 (Phase I) or ABT-888/placebo (Phase II) will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient registration and should arrive within 7 to 10 days (see Section 3.3d**)**.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. **IRB Approval:**

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

2. **Downloading Site Registration Documents:**

Site registration forms may be downloaded from the ***#8811*** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol #*[NCI Protocol #8811]*

- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. Requirements For S1206 (NCI Protocol #8811) Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

4. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE:
www.ctsu.org (members' section) → Regulatory Submission Portal

EMAIL: CTSURegulatory@ctsu.coccg.org
(for regulatory document submission only)

FAX: 215/569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

5. **Checking Your Site's Registration Status:**

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American

- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

NOTE: S1206 is listed as NCI #8811 in the OPEN, RSS, and Specimen Tracking Systems).

a. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

b. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

c. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms are included on the **S1206** abstract page on the SWOG web page and (with the exception of the sample consent form and the Registration Worksheet) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

Institutions participating through the CTSU have access to data submission tools available on the SWOG workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/CTSU/logon.aspx.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF INITIAL REGISTRATION SUBMIT:

S1206 Prestudy Form

S1206 Baseline Abnormalities Form

Baseline Tumor Assessment Form (RECIST 1.1)

Submit radiology reports from all scans performed to assess disease at baseline.*

Pathology report*

Tissue submission (see Section 15.2)

* NOTE: These must be faxed (see Section 14.3b)

b. IF PATIENT CONSENTS, SUBMIT BLOOD SPECIMENS FOR RESEARCH SUBMIT:

Blood specimens as specified in Section 15.3

c. THREE DAYS WITHIN THE START OF RADIOTHERAPY SUBMIT:

Materials for radiation therapy review as described in Section 12.3

d. DURING CONCURRENT CHEMORADIATION TREATMENT SUBMIT:

1. **During Phase I portion ONLY**

AFTER EVERY 7 DAYS, SUBMIT:

a. **S1206** Adverse Event Form

b. **S1206** Concurrent Chemotherapy Treatment Form

2. **During Phase II portion ONLY**

AFTER COMPLETION OF EVERY CYCLE (1 CYCLE = 21 DAYS), SUBMIT:

a. **S1206** Adverse Event Form

b. **S1206** Concurrent Chemotherapy Treatment Form

e. AFTER COMPLETION OF CHEMORADIATION TREATMENT:

1. **During Phase I portion ONLY**

AFTER EVERY 7 DAYS FOR 3 WEEKS, THEN ONCE MORE AT 6 WEEKS POST CHEMORADIATION, SUBMIT:

S1206 Adverse Event Form

2. **During Phase II portion ONLY**

AT 3 WEEKS AND AGAIN AT 6 WEEKS POST CHEMORADIATION, SUBMIT:

S1206 Adverse Event Form

f. WITHIN 7 DAYS AFTER COMPLETION OF RADIATION THERAPY, SUBMIT:

Lung Carcinoma Radiation Therapy Form

Materials as specified in Section 12.3 directly to QARC at the address in Section 12.3

S1206 Checklist for Submission of Radiation Oncology Quality Assurance Materials. This is available on the QARC website at www.qarc.org

g. WITHIN 7 DAYS OF SECOND REGISTRATION (CONSOLIDATION CHEMOTHERAPY) SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting Step 1 restaging.

Radiology reports from restaging

Off Treatment Notice for Registration Step 1

S1206 Consolidation Therapy Eligibility Form

h. AFTER EVERY CYCLE OF CONSOLIDATION CHEMOTHERAPY (1 CYCLE=21 DAYS) SUBMIT:

S1206 Consolidation Chemotherapy Treatment Form

S1206 Adverse Event Form

i. AFTER EVERY DISEASE ASSESSMENT (SEE Sections 9.1-9.2), UNTIL PROGRESSION SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology report(s)

j. WITHIN 7 DAYS OF DISCONTINUATION OF ALL TREATMENT SUBMIT:

Off Treatment Notice documenting reasons for off treatment

S1206 Concurrent Chemotherapy Treatment Form or the **S1206** Consolidation Chemotherapy Form

S1206 Adverse Event Form

k. ONCE OFF PROTOCOL TREATMENT SUBMIT EVERY 4 MONTHS FOR THE FIRST 2 YEARS, THEN EVERY 6 MONTHS UNTIL 5 YEARS FROM THE DATE OF RANDOMIZATION:

Lung Carcinoma Follow Up Form

l. WITHIN 14 DAYS OF PROGRESSION/RELAPSE SUBMIT:

Lung Carcinoma First Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology report(s)

If the patient was still on protocol treatment submit material specified in Section 14.4h if patient was off protocol treatment, submit the Lung Carcinoma Follow Up Form.

m. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information. In addition, if the patient was still on protocol treatment, submit materials specified in Section 14.4h or if patient was no longer on treatment, submit a final Lung Carcinoma Follow Up Form.

15.0 SPECIAL INSTRUCTIONS

15.1 Rapid Reporting

RAPID REPORTING OF TREATMENT-RELATED DOSE-LIMITING TOXICITIES FOR PHASE I PORTION OF TRIAL

Participation in the Phase I portion of the trial requires weekly reporting of Adverse Events and Treatment information on patients who have initiated treatment.

Institutional participation in the Phase I portion of the trial requires the identification of a contact CRA and back-up CRA. **Prior to registration of the first patient, each institution must provide the contact and back-up CRA names, e-mail addresses, and phone numbers to the SWOG Data Operations Center.** Institutions will be responsible for keeping this information up-to-date and must notify the study Data Coordinator (Larry Kaye, LarryK@crab.org, 206/652-2267) of any changes.

The contact CRA and back-up CRA will receive weekly e-mails including a list of the Adverse Event and Treatment forms that are overdue, currently due, or due in the next week. These e-mails will include a reply-to address and phone number to contact the Data Operations Center when questions arise.

Upon activation of the Phase I portion of the study, participating institutions will receive an e-mail with information on current dose level, as well as specifications for e-mail and conference call communication among investigators participating in the Phase I portion.

Participation in bi- weekly conference calls is mandatory.

15.2 Paraffin Embedded Tissue Specimens (Required Submission) for correlative studies and banking

a. 1-2 paraffin embedded tissue blocks containing pathologically confirmed tumor from time of diagnosis (or subsequent, but prior to therapy) must be submitted. If blocks are unavailable, 16 unstained slides are an acceptable alternative. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

b. Specimens must be submitted within 7 days after initial registration.

c. Tissue specimens are to be submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201

d. Collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S1206** protocol abstract page on the SWOG website (www.swog.org).

15.3 Peripheral Blood (Optional Submission) for Circulating Tumor Cells for γH2Ax determination.

a. Collect at least 7.5 mL of peripheral blood using a CellSave Preservation Tube (Veridex #7900005). Gently invert tube 8 times to prevent clotting. Label tube with the SWOG study number **S1206 (8811)**, patient study ID, date of collection, and time of collection. Sample should be kept at ambient temperature and shipped on the day of collection following the directions provided in the CTC collection kits.

b. With patient's consent, peripheral blood must be obtained and submitted at the following timepoints:

1. Cycle 1, Day 1 prior to the morning's dose of ABT-888 dose
2. Cycle 1, Day 2 (24 hours after the first ABT-888 dose and before receiving the second morning dose of ABT-888)
3. Week 1, Friday after XRT (4 to 6 hours after ABT-888 morning's dose)
4. Week 4 Monday before RT
5. 4-6 weeks after RT completion and before starting consolidation chemotherapy

c. **Prior to enrolling patients to this protocol**, see the following website for sample collection and shipping information: http://dctd.cancer.gov/ResearchResources/biomarkers/docs/ctc/LHTP003.08.03_CellSave_Collection_Subm.pdf.

d. Kits must be ordered at least **2 weeks in advance of enrolling your first patient**. To order CTC collection kits, contact: NCI_PD_Support_CellSearch@mail.nih.gov.

e. Peripheral Blood for Circulating Tumor Cells Specimens are to be submitted to Lab #217: NCI-F/FNLCR. Contact: Dan Danner Phone: 301/846-5748.

15.4 Peripheral blood samples (serum/plasma/buffy coat) (Optional Submission) will be used to analyze host genomic DNA for DNA repair SNPs including ERCC1 and ERCC2.

a. Collect at least one 1x 8 mL EDTA (purple-top) and one 1x 8 mL tube with no additives (red-top) at the times noted. Allow red-top tube to clot at room temperature for 30-60 minutes. Place purple-top tube on ice until processing.

Within 1 hour of collection, centrifuge purple-top tube at 800 x g for 15 minutes. Immediately after centrifuging, transfer plasma in 1 mL aliquots to labeled 2 mL cryovials. Pipette slowly to avoid disturbing the buffy coat (the off-white layer between the red blood cells and the plasma) and leave a small amount of plasma (about 0.5 cm) to avoid contamination. Next, pipetting in a circular motion, collect the buffy coat and transfer to a labeled 2 mL cryovials. Cryovials should be labeled with SWOG study number (**S1206 [8811]**), Patient study ID, date and time of collection, and specimen type (serum/plasma/buffy). Snap freeze cryovials in liquid nitrogen (if available) and store at -70° until shipment.

Centrifuge the red-top tube at 2500 x g for 15 minutes. Immediately after centrifuging, transfer the serum in 1 mL aliquots to labeled 2 mL cryovials. Store cryovials at -70° until shipment.

b. With patient's consent, peripheral blood must be obtained and submitted at the following timepoints: (see Section(s) 9.1-9.2):

1. Cycle 1, Day 1 prior to the morning's dose of ABT-888 dose

2. Cycle 1, Day 1, 3 hours after the morning's dose of ABT-888 dose

3. Week 4 before RT

4. 4-6 weeks after RT completion and before starting consolidation Chemotherapy

c. Sites will use institutional supplies for the collection of serum/plasma/buffy coat.

d. Serum/plasma/buffy coat specimens are to be submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201

e. Collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/members/clinicaltrials/specimens/stspecimens.asp), or via the specimen submission link on the Biospecimen Resources (Collaborative Use of Specimens for Translational Medicine Research) page on the SWOG website (www.swog.org).

15.5. Shipping of Specimens

a. SWOG Specimen Tracking System (STS)

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. First time non- SWOG users must refer to start-up instructions located at https://spectrack.crab.org.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used. To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

b. Federal guidelines for the shipment of blood products:

1. The tube must be wrapped in an absorbent material.

2. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and tube in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. Mark the box "Biohazard".

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent 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 shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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 Collaborative Agreements, 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 will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, 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 solely 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 Agent.

2. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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 the Collaborator(s) for Phase III studies 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 must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies 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. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

<u>Monitoring</u>

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines describe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301/897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1, as applicable.

Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is ABT-888/placebo. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210-614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] ABT-888 in the Phase I portion and ABT-888/placebo in the Phase II portion.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a Non-CTEP IND:**

1) **Group-specific instructions.**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via AdEERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210/614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 Intake Form

18.2 Correlative/Special Studies

18.3 Carboplatin Dosing Worksheet

18.4 Emergency Unblinding Guidelines

18.5 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

18.1 Intake Form

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**

Institution/Affiliate _____ Physician _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

18.2 Correlative/Special Studies

a. Samples for correlative studies

Patients are expected to start on a Monday. The protocol will allow a +/- 24 hour window for chemotherapy and correlatives, except for week 1.

1. Tumor tissue samples

Tumor tissue samples will include:

a. Archived tumor biopsy obtained prior to treatment, which will be used for gene expression of ERCC1 and XRCC1. (Required)

2. Peripheral blood samples (Circulating Tumor Cells)

Circulating Tumor Cells (CTC) will be collected at the following time points:

a. Cycle 1, day 1 prior to the morning's dose of ABT-888 dose

b. Cycle 1, day 2 (24 hours after the first ABT-888 dose and before receiving the second morning dose of ABT-888)

c. Week 1 Friday after XRT (4 to 6 hours after ABT-888 morning's dose)

d. Week 4 Monday before RT

e. 4-6 weeks after RT completion and before starting consolidation chemotherapy

CTC will be used for γH2Ax determination.

3. Peripheral blood samples (Peripheral blood mononuclear cells and serum/plasma/DNA/RNA)

Peripheral blood mononuclear cells (PBMC) and serum/plasma/DNA/RNA will be collected at the following time points:

a. Cycle 1, day 1 prior to the morning's dose of ABT-888 dose

b. Cycle 1, day 1, 3 hours after the morning's dose of ABT-888 dose

c. Week 4 Monday before RT

d. 4-6 weeks after RT completion and before starting consolidation chemotherapy

PBMC will be used to analyze host genomic DNA for DNA repair SNPs including ERCC1, ERCC2 and to determine PAR concentration.

b. Special Studies

1. Analysis of DNA repair capacity in tumor and host

Our hypothesis is that efficacy will be related to underlying DNA repair capacity.

In archival baseline tumor tissue, we will evaluate gene expression of ERCC1 and XRCC1. Also, we will test host genomic DNA from PBMC/plasma for DNA repair SNPs, including ERCC1 and ERCC2. (11). Selected genotypic variants related to platinum-related DNA repair enzymes *ERCC1* (118C→T, silent) and ERCC2 (XPD, K751Q) previously reported to be of functional consequence were analyzed by polymerase chain reaction (PCR) or pyrosequencing, as previously described. Briefly, PCR will be conducted by using Amplitaq Gold PCR master mix (ABI, Foster City, CA), 5 pmol of each primer, and 5 to 10 ng of DNA. Pharmacogenetic analysis will be conducted by using the Pyrosequencing hsAPSQ96 instrument and software (Biotage, Uppsala, Sweden). The genotype will be considered variant if it differed from the Reference Sequence consensus sequence for the single-nucleotide polymorphism (SNP) position (http://www.ncbi.nlm.nih.gov/RefSeq/). The *ERCC1* polymorphism will be analyzed by PCR restriction fragment length polymorphism, as previously described.

a. Paraffin-embedded tissue blocks or slides from the time of diagnosis (or subsequent, but prior to therapy) should be submitted for assessment as described above. It is strongly requested that 1-2 paraffin-embedded tissue blocks containing pathologically confirmed tumor be submitted. If blocks are unavailable, 16 unstained slides are an acceptable alternative.

2. γ-H2AX Determination in Tumor Biopsies and Peripheral Blood Samples (Circulating Tumor Cells)

γ-H2AX determination will be performed in tumor tissue obtained at baseline and after 2 weeks on treatment and circulating tumor cells (CTCs) at baseline as well as at various timepoints during treatment.

Methodology for preparing tissue biopsies suitable for immunocytochemical analysis of γ-H2AX foci has been developed using normal rodent tissues by Kinders et al. (Development and Validation of a Quantitative Assay for γ-H2AX in Needle Biopsies, using Topoisomerase I Inhibitors; AACR-EORTC Conference, Molecular Targets and Cancer Therapeutics, 2007). The method for collection and stabilization of the biopsy has been successfully employed in the Phase 0 trial of ABT-888 and the Phase I trial of ABT-888 and topotecan. (9)

The biopsies are transported to the Pathology and Histology Laboratory at SAIC-Frederick and upon removal from storage, slides are allowed processed as follows: The biopsies are first fixed for 16-24 hours in 10% NBF, followed by immersion in graded ethanols, then xylene, and finally paraffin embedding. Five consecutive 5-micron sections are cut to prepare slides, and staining for γ-H2Ax is performed on a Vision Biosystems automated processor. The third section is processed for H&E staining. The first and the fifth sections are processed for γ-H2AX, and the remaining two sections are processed according to need: either additional γ-H2AX or CD31. The remainder of the block is catalogued and stored for follow up studies for this clinical protocol.

Phosphorylated (*i.e.*, γ-) H2AX is detected by immunostaining with MAb JBW301 (biotin conjugated, Upstate Biotechnology, then Alexafluor 488 Streptavidin labeling) of formalin-fixed, paraffin embedded biopsies. DAPI counterstaining is performed. The staining protocol is performed on a Vision Biosystems Bondmax instrument, and slides are read on a Nikon microscope with an automated stage and Retiga 2000R CCD camera. Data is collected and analyzed in ImagePro as percent of nuclear area (in the entire field of view) that is positive for γ-H2AX staining. At least 3 fields are imaged per slide, and at least 2 slides per biopsy (from non-overlapping sections of the biopsy) are analyzed. H&E sections are also obtained. Statistical analysis is performed in PADIS, with Excel. Specimen processing, imaging, and quantitation are all controlled by SOPs. Permanent photographic records of the biopsy are maintained, and all specimen identification data are coded.

The γ-H2AX nuclear marker is expressed in response to drug-induced DNA damage, but does not signify a cell's commitment either to cell death or to DNA repair and potentially cell recovery. Recent in vitro discoveries about TRAIL-induced apoptosis (Yves Pommier, internal communication) indicate that commitment to cell death is associated with co-localization of γ-H2AX and additional nuclear phosphoproteins along the inner face of the nuclear membrane. When using quantitative immunofluorescence (qIFA) analysis and different colors for γ-H2AX and the second marker (e.g., red and green), this co-localization pattern results in a "halo" shaped staining pattern of the mixed color signal (e.g., yellow) when the images of each marker are overlaid. PADIS/LHTP and NCTVL are validating a qIFA for nuclear γ-H2AX in tumor needle biopsies and cytospin preparations, which is amenable to this multi-color analysis of co-localized markers and the potential quantitation of pro-apoptotic cells resulting from drug exposure. This protocol will permit quantitation not only of the γ-H2AX marker using the validated readout of the assay (% nuclear area positive for γ-H2AX signal), but also of co-localization markers that can achieve halo staining of pro-apoptotic cells. The co-localized markers will include phospho forms of ataxia telangiectasia mutated (ATM), DNA-dependent protein kinase (DNA-PK), ATR and/or Chk2, as well as other nuclear markers co-localizing with γ-H2AX during apoptosis that may be discovered during the time period of this clinical trial. Both the PADIS and NCTVL will conduct this quantitative immunofluorescence assay, and some specimens may be assayed in both laboratories to check assay performance. In addition, PADIS and NCTVL may use the Pathology/Histotechnology Laboratory (PHL) of the NCI-Frederick to process, stain, and analyze the staining of sections from the clinical trial participants.

c. Peripheral Blood Samples to collect CTCs

We will perform γ-H2AX assay in CTCs per SOP on the DCTD website **http://dctd.cancer.gov/ResearchResources/biomarkers/docs/ctc/LHTP003.08.03_CellSave_Collection_Subm.pdf.**

Briefly, collect at least 7.5 mL of peripheral blood using a CellSave Preservation Tube (Veridex #7900005). Gently invert tube 8 times to preventing clotting. Label tube with **S1206 (8811)** patient study ID, date of collection, and time of collection. Sample should be kept at ambient temperature and shipped on the day of collection. Please see CTC collection SOP provided with the CTC collection kits for instructions regarding the labeling and packaging of specimens.

d. Collection and processing of serum/plasma/DNA/RNA

Blood will be collected in 1x 8 mL EDTA (purple-top) and 1x 8 mL tube with no additives (red-top) at the times noted in Section 15.3a.2.

Allow red-top tube to clot at room temperature for 30-60 minutes. Place purple-top tube on ice until processing. Cryovials should be labeled with SWOG study number (**S1206 [8811]**), Patient study ID, date and time of collection, and specimen type (serum/plasma/buffy).

Within 1 hour of collection, centrifuge purple-top tube at 800 x g for 15 minutes. Immediately after centrifuging, transfer plasma in 1 mL aliquots to labeled 2 mL cryovials. Pipette slowly to avoid disturbing the buffy coat (the off-white layer between the red blood cells and the plasma) and leave a small amount of plasma (about 0.5 cm) to avoid contamination.
Next, pipetting in a circular motion, collect the buffy coat and transfer to a labeled 2 mL cryovials. Snap freeze cryovials in liquid nitrogen (if available) and store at -70° until shipment.

Centrifuge the red-top tube at 2500 x g for 15 minutes. Immediately after centrifuging, transfer the serum in 1 mL aliquots to labeled 2 mL cryovials. Store cryovials at -70° until shipment.

18.3 Carboplatin Dosing Worksheet

PATIENT'S INITIALS _____ **MEDICAL RECORD #** _____

SWOG PATIENT # _____

TO CALCULATE Creatinine Clearance (CrCl) from SERUM CREATININE:

CrCl = (140 - age) X wt. in kg.* X 0.85 (if female)
72 X serum creatinine **

CrCl = (140 -) X ( ) X 0.85 (if female)
72 X _____

TO CALCULATE CARBOPLATIN DOSE WITH CALVERT FORMULA:

USE CALCULATED CREATININE CLEARANCE (AS ABOVE) TO SUBSTITUTE FOR GFR.

(AUC) (GFR + 25) = CARBOPLATIN DOSE PER CYCLE IN mg

(X) (_____ +25) = _____ mg of carboplatin

This is the TOTAL DOSE of carboplatin (not mg/m^2).

Please note that: GFR should NOT exceed 125 ml/min. Hence, the maximum total carboplatin dose should NOT exceed 300 mg when AUC = 2 or 900 mg when AUC = 6 for this study.

*** Use current (actual) weight. This should be actual weight but not exceed 140% of IBW.**
**** Carboplatin dose should be calculated using a serum creatinine value obtained within 3 days prior to each course therapy. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing.**

NOTE: PLEASE RETAIN ORIGINAL WORK SHEET as part of patient's PERMANENT RECORD. COPIES MAY BE MADE FOR PHARMACY and/or NURSING RECORDS.

18.4 Emergency Unblinding Guidelines

a. **General Considerations**

The randomized regimen for this study includes a blinded drug, which is either veliparib or placebo. During the course of this study it may become necessary to identify (or unblind) a patient's treatment assignment. The circumstances that will warrant emergency unblinding and the procedure for emergency unblinding are described in this Appendix.

b. **Criteria for Emergency Unblinding**

In general, treatment assignments will not be emergency unblinded unless there is a compelling medical or ethical reason that the treatment should be identified. In most circumstances it will be appropriate to treat the patient or person who received blinded drug as though he or she received veliparib, irrespective of the drug actually received. Therefore, emergency unblinding should seldom be necessary.

The following events MAY require emergency unblinding of treatment assignments in this study:

1. A compelling medical need as determined by a physician, e.g., existence of a condition for which knowledge of the patient's treatment assignment is necessary for the selection of appropriate care.

2. Administration of blinded drug to a person other than the patient.

c. **Procedure for Emergency Unblinding**

Emergency unblinding of treatment assignments for patients on this study will be performed by the Washington Poison Center (WPC), upon approval from a designated physician (either one of the WPC's resource physicians or Dr. Athanassios Argiris). The procedure for emergency unblinding the treatment assignment for a patient on this study is as follows:

1. All requests for emergency unblinding must be made by the registering physician or his/her designee.

2. Call the WPC collect at 206/526-2121 from outside Washington State or toll free at 800/222-1222 from within Washington State. The WPC is accessible 24 hours per day, 365 days per year.

3. The person calling the WPC must be prepared to provide the following information:

   Study number (**S1206**)

   SWOG Patient Number (e.g., "999999")

   Patient Initials

   Name and telephone number of the caller

   Reason emergency unblinding is thought to be required

4. The WPC will contact one of its resource physicians and provide the information received from the caller. If none of the WPC's resource physicians can be contacted, then the WPC will contact Dr. Athanassios Argiris. The contacted physician will evaluate the need for emergency unblinding and provide the WPC either approval to unblind or a recommendation for treatment, if any, while maintaining blinding. The WPC will then call the person who initiated the unblinding request and tell him/her either the treatment assignment or the resource physician's treatment recommendation.

5. If the WPC is unable to contact any of its resource physicians or Dr. Argiris within three hours after receiving the request for emergency unblinding, then the WPC will notify the person who initiated the unblinding request that treatment assignment will not be unblinded at that time and treatment of the patient or person who received blinded drug should proceed as if the blinded drug is veliparib. In such cases, the WPC will continue to attempt to contact the resource physicians, and when one of them is contacted, will proceed as in #4 above.

6. Any patient whose treatment assignment is emergency unblinded will receive no further blinded drug, but should continue all other protocol treatment if his/her medical condition permits.

7. Unblinding of treatment assignments for any reason must be documented on the Off Treatment Notice.

   Questions regarding the unblinding may be directed to any of the following resource physicians:

   Athanassios Argiris, M.D.
   Medical Oncologist, Hygeia Hospital
   5 Erythrou Stavrou
   6th Floor, Office 6.12
   Marousi 15123 Athens, Greece
   Phone: 011 30 210 6867692
   FAX: 011 30 210 6845089
   E-mail: athanassios.argiris@gmail.com

   Anne Schott, M.D.
   SWOG
   24 Frank Lloyd Wright Drive
   P.O. Box 483
   Ann Arbor, MI 48106
   Phone: 734/998- 7172
   E-mail: aschott@umich.edu

   Washington Poison Center
   Phone: 206/526-2121

18.5 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information.

CYP2D6	
SUBSTRATES	
Amitriptyline (hydroxylation)	Methamphetamine
Amphetamine	Metoclopramide
Betaxolol	Metoprolol
Bisoprolol	Mexitetine
Brofaromine	Mianserin
Buturolol	Mirtazapine (hydroxylation)
Bupropion	Molindone
Captopril	Morphine
Carvedilol	Nortriptyline (hydroxylation)
Cevimeline	Olanzapine (minor, hydroxymethylation)
Chlorpheniramine	Ondansetron
Chlorpromazine	Orphenadrine
Cinnarizine	Oxycodone
Clomipramine (hydroxylation)	Papaverine
Clozapine (minor pathway)	Paroxetine (minor pathway)
Codeine (hydroxylation, o-demelhylation)	Penbutolol
Cyclobenzaprine (hydroxylation)	Pentazocine
Cyclophosphamide	Perhexiline
Debrisoquin	Perphenazine
Delavirdine	Phenformin
Desipramine	Pindolol
Dexfenfluramine	Promethazine
Dextromethorphan (o-demethylation)	Propafenone
Dihydrocodeine	Propranolol
Diphenhydramine	Quetiapine
Dolasetron	Remoxipride
Donepezil	Risperidone
Doxepin	Ritonavir (minor)
Encainide	Ropivacaine
Fenlluramine	Selegiline
Flecainide	Sertindole
Fluosetine (minor pathway)	Sertratine (minor pathway)
Fluphenazine	Sparteine
Haiofantrine	Tamoxifen
Haioperidol (minor pathway)	Thioridazine
Hydrocodone	Tiagabine
Hydrocortisone	Timolol
Hydroxyamphetamine	Tolterodine
Imipramine (hydroxylation)	Tramadol
Labetalol	Trazodone
Loratadine	Trimipramine
Maprotiline	Tropisetron
m-Chlorophenylpiperazine (m-CPP)	Venlafaxine (o-desmethylation)
Meperidine	Yohimbine
Methadone	

INHIBITORS	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxeline
Cimelidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Deiavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diitiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Vaiprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	
Carbamazepine	Diazepam (minor; hydroxylation, N-demethylation)
Cevimeline	
Cerivastatin	Nefazodone
Digitoxin	Nelfinavir
Diltiazem	Nevirapine
Disopyramide	Nicardipine
Docetaxel	Nifedipine

Substrates	
Dolasetron	Niludipine
Donepezil	Nimodipine
Doxorubicin	Nisoldipine
Doxycycline	Nitrendipine
Dronabinol	Omeprazole (sulfonation)
Enalapril	Ondansetron
Erylhromycin	Oral contraceptives
Estradiol	Orphenadrine
Ethinyl estradiol	Paclitaxel
Ethosuximide	Pantoprazole
Etoposide	Pimozide
Exemestene	Pioglitazone
Dofetilide (minor)	Pravastatin
Felodipine	Prednisone
Fentanyl	Progesterone
Fexotenadine	Proguanil
Finaxteride	Propafenone
Fluoxetine	Quercetin
FLUTAMIDE	
Substrates	
Glyburide	Quetiapine
Granisetron	Quinidine
Halofantrine	Quinine
Hydrocortixone	Repaglinide
Hydroxyarginine	Retinoic acid
Ifosfamide	Rifampin
Imipramine	Risperidone
Indinavir	Ritonavir
Isradipine	Salmeterol
Itraconazole	Saquinavir
Ketoconazole	Sertindole
Lansoprazole (minor)	Sertraline
Letrozole	Sibutramine
Levobupivicaine	Sildenafil citrate
Lidocaine	Simvastatin
Loratadine	Sirolimus
Losartan	Sufentanil
Lovastatin	Tacrolimus
Methadone	Tamoxifen
Mibefradil	Temazepam
Miconazole	Teniposide
Midazolam	Terfenadine
Mifepristone	Testosterone
Mirtazapine (N-demethylation)	Tetrahydrocannabinol
Montelukast	Theophylline
Navelbine	Tiagabine
Toremifene	Tolterodine
Trazodone	Vincristine
Tretinoin	Warfarin (R-warfarin)
Triazolam	Yohimbine
Troglitazone	Zaleplon (minor pathway)
Troleandomycin	Zatoestron
Venlafaxine (N-demethylation)	Zileuton
Verapamil	Ziprasidone
Vinblastine	Zolpidem
	Zonisamide

INDUCERS	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
INHIBITORS	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Azithromycin	Mibefradil
Cannabinoids	Miconazole (moderate)
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole	Nevirapine
Cyclosporine	Norfloxacin
Danazol	Norfluoxetine
Delavirdine	Omeprazole (weak)
Dexamethasone	Oxiconazole
Diethyldithiocarbamate	Paroxetine (weak)
Diltiazem	Propoxyphene
Dirithromycin	Quinidine
Disulfiram	Quinine
Entacapone (high dose)	Quinupristin and dalfopristin
Erythromycin	Ranitidine
Ethinyl estradiol	Ritonavir
Fluconazole (weak)	Saquinavir
Fluoxetine	Sertindole
Fluvoxamine	Sertraline
Gestodene	Troglitazone
Grapefruit juice	Troleandomycin
Indinavir	Valproic acid (weak)
Isoniazid	Verapamil
Itraconazole	Zafirlukast
	Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371