ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A091101

CARBOPLATIN-PACLITAXEL INDUCTION CHEMOTHERAPY AND ABT-888 (VELIPARIB) – A PHASE 1/RANDOMIZED PHASE 2 STUDY IN PATIENTS WITH LOCOREGIONALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

NCI-supplied agent(s): ABT-888 (Veliparib) (NSC #737664, IND#77840)

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[X]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[ ]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other :		

Expedited review is allowed. IRB (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL:

CTSU Contact Information Table

The table has been updated with the revised CTSU verbiage.

Section 10.0 (Study Calendar)

-Footnote "***" has been updated. The 3-month time point has been removed from the first sentence.
-An "X" has replaced the "C" in the Imaging row under the last column, Clinical Follow-up. Footnote "C" has been removed because the timing was not correct. Imaging should be done per footnote "***". Subsequent footnotes have been re-lettered.

UPDATES TO THE MODEL CONSENT:

No changes have been made to the model consent form.

A replacement protocol and model consent document have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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CARBOPLATIN-PACLITAXEL INDUCTION CHEMOTHERAPY AND ABT-888 (VELIPARIB) – A PHASE 1/RANDOMIZED PHASE 2 STUDY IN PATIENTS WITH LOCOREGIONALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

NCI-supplied agent: ABT-888 (Veliparib) (NSC #737664, IND#77840)

ClinicalTrials.gov Identifier: NCT01711541

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Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, or (where available) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review:	*regulatory@alliancenctn.org*
Questions regarding CTEP-AERS reporting:	Regulatory Affairs Manager, *regulatory@alliancenctn.org,* (773) 702-9814

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Activation	October 22, 2012	Update #4	12/15/2015
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Update #2	08/01/2014	Update #06	06/15/2017
Update #3	08/01/2015	Update #07	XX/XX/2017

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	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 Medidata Rave. Please see the data submission section of the protocol for further instructions.

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. *Include this statement if applicable:* 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.

For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) 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.

Carboplatin-Paclitaxel Induction chemotherapy and ABT-888 (Veliparib) – a Phase 1/Randomized Phase 2 Study in Patients with Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck

Phase 1

Patient Eligibility

Eligible patients are newly diagnosed and treatment naïve:
- Stage IVa-b SCC other than OPC, OR
- OPC HPV-negative, Stage IVa-b

Patients must have measurable disease (see §3.1.2)
ECOG performance status 0-1
Age ≥18 years
Must be able to swallow the drug
Able to understand and sign a written informed consent document
No other investigational agents
No active seizure or history of seizure
No allergies to similar agents of ABT-888 (see §3.1.10)
No impairment of GI function (see §3.1.11)
No uncontrolled intercurrent illness (see §3.1.12)
No pregnant or nursing women (see §3.1.13)
No HIV-positive patients on combination antiretroviral therapy (see §3.1.14)
No patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent (see §3.1.15)
No patients with other malignancies in the past 2 years (except carcinoma of the cervix or basal or squamous cell carcinoma of the skin or surgically treated early stage solid tumors)

Required Lab Values

leukocytes	≥ 3,000/mm^3
ANC	≥ 1,500/ mm^3
platelets	≥ 100,000/ mm^3
total bilirubin	≤ 1.5 Institutional upper limit of normal (ULN)
SGOT(AST) or SGPT(ALT)	≤ 2.5 x ULN
Creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above ULN*

* As calculated by Cockcroft-Gault.

Phase 1 Schema

REGISTER

Induction

Carboplatin-Paclitaxel + ABT-888 (veliparib)
(Two 3-week cycles)

Carboplatin AUC 6 IV on Day 1
Paclitaxel 100 mg/m^2 IV on Days 1, 8, 15

PLUS **ABT-888 (veliparib)**
p.o. b.i.d. Days 1-7 (dose based on dose cohort)

See Section 5.1.1 for more information on dose cohorts

Concomitant Chemoradiotherapy

Concurrent accelerated RT and cisplatin
(One 6-week cycle)

Cisplatin 100 mg/m^2 IV Days 1 and 22
Radiotherapy 72 Gy over 6 weeks

OR

TFHX
(Five 2-week cycles)

Hydroxyurea 500 mg p.o. b.i.d., Days 1-5
5-FU 600 mg/m^2/day IV on Days 1-5
Paclitaxel 100 mg/m^2 IV on Day 1
Radiotherapy 150 cGy b.i.d. on Days 1-5

Carboplatin-Paclitaxel Induction chemotherapy and ABT-888 (Veliparib) – a Phase 1/Randomized Phase 2 Study in Patients with Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck

Phase 2

Patient Eligibility

Eligible patients are treatment naïve and:
- Stage IVa-b SCC other than OPC, OR
- OPC HPV-negative, Stage IVa-b, OR
- OPC HPV positive with greater than 10pack-year smoking history and N2b-N3 disease

Patients must have measurable disease (see §3.2.2)
ECOG performance status 0-1
Age ≥18 years
Must be able to swallow the drug
Able to understand and sign a written informed consent document
No other investigational agents
No active seizure or history of seizure
No allergies to similar agents of ABT-888 (see §3.2.10)
No impairment of GI function (see §3.2.11)
No uncontrolled intercurrent illness (see §3.2.12)
No pregnant or nursing women (see §3.2.13)
No HIV-positive patients on combination antiretroviral therapy (see §3.2.14)
No patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent (see §3.2.15)
No patients with other malignancies in the past 2 years (except carcinoma of the cervix or basal or squamous cell carcinoma of the skin or surgically treated early stage solid tumors)

Required Lab Values

leukocytes	≥ 3,000/mm^3
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platelets	≥ 100,000/ mm^3
total bilirubin	≤ 1.5 Institutional upper limit of normal (ULN)
SGOT(AST) or SGPT(ALT)	≤ 2.5 x ULN
Creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above ULN*

* As calculated by Cockcroft-Gault.

Phase 2 Schema

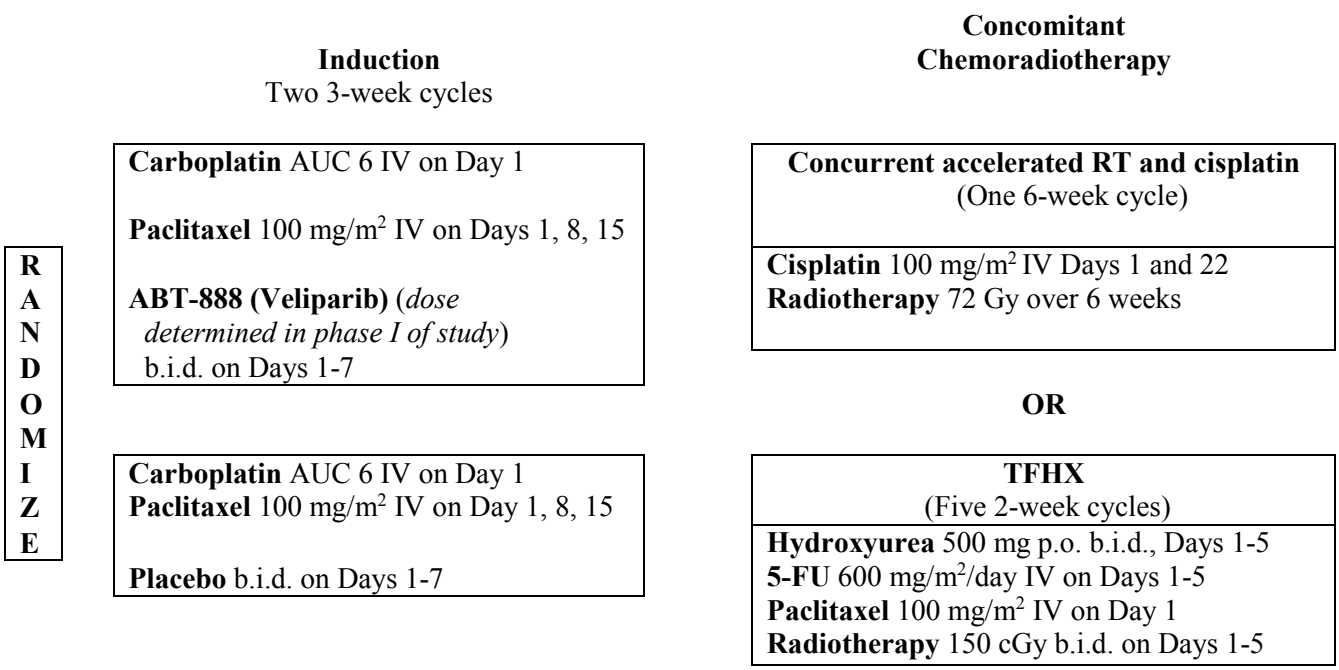


TABLE OF CONTENTS

1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 Phase I

Determine the maximum tolerated dose (MTD), recommended Phase II dose, dose limiting toxicity (DLT), and safety of ABT-888 (veliparib) with carboplatin and paclitaxel induction chemotherapy in locoregionally advanced head and neck (LAHNC) patients.

1.1.2 Randomized Phase II

Compare magnitude of tumor shrinkage (response) following 2 cycles of induction chemotherapy with and without ABT-888 in LAHNC.

1.2 Secondary Objectives (Phase II)

Compare progression-free (PFS), disease-specific (DSS), and overall survival (OS) in subjects treated with or without ABT-888.

2.0 BACKGROUND

2.1 Locally Advanced Head and Neck Cancer (LAHNC)

The paradigm of combined chemoradiotherapy for LAHNC dates to the early 1990s. Several publications on randomized controlled trials of radiation alone versus radiation plus chemotherapy were then reported. The outcome of these trials varied, but several meta-analyses showed consistent increased response rates, increased disease control, and improved survival in the trials incorporating concurrent cisplatin-based chemoradiotherapy.[1-5] When the analysis was restricted to concurrent cisplatin-based chemotherapy with radiation, an 8% absolute survival advantage at 5 years was observed. This benefit corresponded to a 19% reduction in the risk of death. Notably, the meta-analysis data sets represent more than 16,000 patients treated on more than 80 randomized controlled trials with median follow-up in excess of 5 years. Further, a meta-analysis of 32 randomized controlled trials with 10,225 patients in aggregate confirmed the advantage of chemoradiotherapy over radiation when using either hyperfractionated or accelerated radiation.[5] In this meta-analysis, 5-fluorouracil outperformed cisplatin in terms of median survival benefit. Concurrent chemoradiotherapy has thus been the mainstay of treatment for LAHNC.

Improvements in survival have come at the cost of increased acute toxicity and the realization that chemoradiotherapy can impact long-term function which, in turn, is related to radiotherapy volumes. Despite numerous efforts at incorporating protective agents as part of chemoradiotherapy regimens there has been minimal success in improving long-term toxicity in a substantial manner. Radiotherapy planning techniques, especially intensity modulated radiotherapy (IMRT), have the ability to spare normal structures from receiving full doses of radiotherapy compared to conventional methods. This has been best demonstrated by reduction in rates of chronic xerostomia in patients treated with IMRT compared to 3-D conformal planning. Nonetheless, even with IMRT planning, currently accepted standards for radiotherapy volumes based on location of gross disease still incorporate tissues critical to swallowing. Long-term dysphagia is increasingly recognized as having a major impact on quality of life in patients treated with curative intent concurrent chemoradiotherapy. Therefore, strategies that would preserve the survival gains achieved with chemoradiotherapy while improving long-term function are needed.

2.2 Patterns of Failure in LAHNC

A retrospective analysis of 5-FU, hydroxyurea and radiotherapy (FHX) trials utilizing intensive concomitant chemoradiotherapy conducted from 1993 to 1998 including 210 patients has revealed a distinct failure pattern based on TNM staging. That is, patients with T4 tumors tended to fail locally while those with N2 or N3 disease failed distantly, usually in the lungs.[6] Distant failure in these patients is devastating, as there is no opportunity for salvage with either surgery or re-irradiation, supporting the importance of a potentially lower distant failure rate associated with the introduction of induction chemotherapy (neoadjuvant).

2.3 Induction Chemotherapy

Recently, the addition of neoadjuvant (induction) chemotherapy has garnered interest with the completion of phase 3 studies demonstrating the activity and efficacy of a three drug regimen consisting of cisplatin, 5FU, and a taxane (TPF). TPF induction chemotherapy is effective but is associated with significant toxicity especially myelosuppression and mucositis.

Induction chemotherapy has been under investigation for more than two decades in locally advanced squamous cell carcinoma of the head and neck. Most regimens are used for 2 to 3 cycles and consist of drugs with documented single agent activity in patients with recurrent disease (i.e., methotrexate, cis- or carboplatin, 5-fluorouracil, bleomycin, paclitaxel, docetaxel). High overall response rates exceeding 80% and complete response (CR) rates ranging from 20 to 54% have been reported. Some of these will be histologically confirmed at surgery. Achieving a complete response (CR) to chemotherapy, particularly if confirmed histologically, correlates with a good prognosis; and patients not responding to induction chemotherapy generally are unlikely to respond to subsequent standard radiotherapy; the administration of chemotherapy generally does not jeopardize the administration of subsequent standard local therapy.

There is increasing evidence suggesting that systemically active chemotherapy may prevent recurrences at distant sites. Distant recurrence after the eradication of the primary tumor and locoregional disease is presumably due to micrometastatic disease that the lower doses of chemotherapy administered as a component of chemoradiotherapy do not adequately treat. Even though in early trials a survival benefit could not be found, serious methodological deficiencies limit these trials (inadequate design, substandard local therapy, etc.).

Induction chemotherapy continues to be frequently used in centers around the world and represents a good trial approach to investigate novel therapies and/or molecular correlates. In recent years randomized trials have further substantiated the finding that induction chemotherapy including a taxane and cisplatin can increase survival rates. Induction chemotherapy can produce CR rates in 30–65% of patients and overall response rates of 70–85%. Two newer European studies have shown evidence of a survival benefit with induction chemotherapy: the Italian GSTTC study (Gruppo di Studio sui Tumori della Testa) demonstrated increased cure rates in a subset of nonoperable subjects and the French GETTEC trial (Groupe d'Etude des Tumeurs de la Tete et du Cou), which was closed early due to clear benefit. Furthermore a large meta-analysis by Pignon et al demonstrated a 5% increase in survival only for trials using a cisplatin/fluorouracil (5-FU) combination, reaching statistical significance ($P<0.05$).

In addition, two trials comparing the triplet combination of a taxane (docetaxel or paclitaxel), cisplatin, and 5-FU (TPF) with doublet cisplatin/5-FU (PF) showed a survival benefit of the triplet over the doublet combination. However, the high rates of toxicity reported in TAX 323 and TAX 324 led many oncologists to question the feasibility of TPF. In TAX 324, 21% of patients did not proceed to protocol-defined chemoradiotherapy and 7% of patients did not proceed to potentially curative therapy.[7,9] Carboplatin and paclitaxel were used together in a phase II study consisting mainly of stage IV patients where a clinical complete RR of 100%, 3-

year OS of 70% and a 3-year progression-free survival (PFS) of 90% were demonstrated following completion of definitive chemoradiotherapy.[12] Although the regimen was less toxic compared with TPF, RR to induction chemotherapy was preserved; RR to TPF in TAX 323 and TAX 324 was 68 and 72%, respectively. The single institution experience of our center comparing induction chemotherapy with carboplatin and paclitaxel (CT) with TPF showed that the 1 year locoregional control was 80.5% for CT compared to 55.5% for TPF (HR 0.32,P = .0002).[53] The 1 year progression free survival was 73.2% for CT compared to 60.7% for TPF (HR 0.57;P = .02). On multivariable analysis, CT remained significant for LRC (HR 0.28; P = 0.04). TPF induction chemotherapy was associated with worse renal toxicity as measured by peak creatinine increases during induction chemotherapy (P = 0.001). TPF was also associated with a trend toward more chemotherapy dose reductions or changes in systemic agents during concurrent chemoradiotherapy (43.4% for TPF vs. 27.8% for CT; P = 0.06). Further evidence to support not using TFP in this clinical trial comes from an early version of this phase 1 protocol, where three patients with locally advanced disease were treated with ABT-888 40mg bid and TPF. Remarkably, all three patients developed neutropenic fever, what would require dose reductions, even at supposedly low doses of ABT-888 (40mg bid). To justify this statement, the ABT-888 MTD in combination with carboplatin and paclitaxel in the GOG 9923 in metastatic ovarian cancer was 200mg bid. Further, several groups have demonstrated that induction chemotherapy with carboplatin–paclitaxel provided a complete response rate and partial response rate from 8% to 33% and from 50% to 85%, respectively.[54-58] Furthermore, the PFS and OS were consistently between 60-80%. In many of these prospective series, patients tolerated CT and subsequent concurrent chemoradiotherapy with minimal additional toxicity. This protocol thus elected to use carboplatin-paclitaxel as the induction chemotherapy regimen.

Carboplatin is a commonly used platinum compound that acts by binding to DNA and interrupting cell division. It is approved by the FDA for the treatment of patients with ovarian cancer. It is also used for the treatment of non-small cell lung cancer, small cell lung cancer, head and neck cancer, endometrial cancer, metastatic seminoma and more recently in breast cancer. Carboplatin is eliminated by renal excretion. The clearance is related to the glomerular filtration rate. Therefore it is dosed based on the GFR and the target area under the concentration versus time curve (AUC). The main side effect of carboplatin is myelosuppression. Other toxicities include nausea, vomiting, renal and neurotoxicity.

2.4 Concurrent chemoradiotherapy

Results of many recently published phase III trials show that chemotherapy given concurrently with radiation yields better LRC and survival rates than radiation alone in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).[1-5]

2.4.1 Concurrent accelerated radiotherapy and cisplatin

The Radiation Therapy Oncology Group (RTOG) 0522 trial (N = 940) is the most recent Cooperative group trial that showed benefit of concurrent accelerated radiotherapy and cisplatin (AFX-Cis).[5] The primary objective of this study was to evaluate whether the addition of cetuximab to cisplatin would improve disease-free survival. Secondly, the study assessed overall survival, local-regional control, acute and late toxicities and quality of life. It showed no benefit to adding cetuximab to the radiation/cisplatin platform for front-line therapy of advanced head and neck squamous cell carcinoma. At 2 years, progression-free survival was approximately 64% in both arms; overall survival was 79.7% with chemoradiotherapy ($P = .68$) and 82.6% with the addition of cetuximab ($P = .17$). Rates of locoregional relapse and distant metastases were also similar. However, cetuximab increased grade 3/4 mucositis (43% vs 33%;$P < .004$), in-field skin toxicity (25% vs 15%;$P < .001$), and out-of-field skin reactions (19% vs 1%;$P < .001$), but toxicity beyond

90 days was similar between the arms. Given that this was a Cooperative Group Trial with several participating institutions, this protocol will allow concurrent chemoradiotherapy with concurrent accelerated radiotherapy and cisplatin.

2.4.2 TFHX Regimen

Many clinical trials for patients with LAHNC in the Chicago Oral Cancer Center Network have continued to use the hydroxyurea, 5-FU, paclitaxel and radiotherapy (TFHX) regimen as previously defined. Despite the high locoregional control and high survival rates, three problems were identified: distant failure emerged as the predominant site of failure, mucositis was often severe and sometimes resulted in long-term functional impairment, and toxicities related to chemotherapy (specifically neuropathy and myelosuppression) often resulted in dose reduction and patient impairment. To address the first problem, we added induction chemotherapy to precede concomitant chemoradiotherapy. In designing the induction chemotherapy regimen, we selected the combination of carboplatin and paclitaxel, a regimen that is well tolerated and that would not result in mucositis or dermatitis as significant toxicity to avoid overlapping toxicities with the subsequent administration of TFHX.

We also addressed the second goal of reducing toxicity and improving functional performance. The exceedingly high local and regional control rates observed in all TFHX studies suggested that a careful attempt to reduce the radiation therapy field sizes to minimize long-term treatment sequelae would be feasible. The results of this trial 2 involving 69 patients revealed response to induction chemotherapy to be PR 52% and CR 35%. Symptomatically, there was a significant reduction in mouth and throat pain. The most common grade 3 or 4 toxicity was neutropenia (36%) while 33% of patients experienced neuropathy. Best response following completion of TFHX was CR in 83%. Toxicities of TFHX consisted of grade 3 or 4 mucositis (74% and 2%), and dermatitis (47% and 14%). At a median follow up of 28 months, locoregional or systemic disease progression have each been noted in five patients. The overall three year progression-free survival is 80% (95% confidence interval (CI): 71%-90%) and the two and three year overall survival rates are 77% (95% CI: 66%-87%) and 70%, (95% CI: 59%-82%), respectively. At 12 months, 5 patients were completely feeding tube dependent (patients who died without disease progression were censored from the PFS analysis). Similar results were reported in two follow-up studies using the TFHX platform.[9] Thus the TFHX regimen can serve as a solid institutional standard chemoradiotherapy regimen to follow novel investigational induction chemotherapy regimens.

2.4.3 Radiotherapy

Radiotherapy doses currently employed during concurrent chemoradiotherapy are largely empirically derived from tumor control and normal tissue toxicity probabilities of patients treated with radiotherapy alone. The gross tumor volume (GTV) includes all known gross disease detected on physical or radiographic examination both at the primary and neck before. Planning target volume 1 (PTV1) includes the GTV plus a 1.5 cm expansion. PTV2 includes PTV1 plus the first echelon of uninvolved lymph nodes. The PTV1 is a margin of error around visible tumor and this area receives the maximum dose of radiotherapy. In addition, areas at risk for microscopic disease encompassing draining lymph nodes are also treated and usually include bilateral cervical lymph node stations. In a subset analysis of data assessing disease recurrence from multi-institutional studies administering FHX-based chemoradiotherapy, it became apparent that locoregional failures overwhelmingly occurred in PTV1. This was especially true in subjects who attained a complete response to induction chemotherapy where no failures were recorded outside PTV1 in these patients. However,

much of the long-term toxicity of chemoradiotherapy can be directly attributed to inclusion of cervical lymph nodes at risk for microscopic disease.

2.5 Risk Stratification in LAHNC

It is critical that the appropriate patient population be studied if any benefit is to be identified. Under the hypothesis that patients unlikely to develop distant metastases are also unlikely to benefit from the addition of induction chemotherapy, the question of what the best information that might allow us to best select the patients at highest risk for this event is paramount.

Prior published studies at the University of Chicago indicate that advanced nodal stage is a predictor for the development of distant metastatic disease after aggressive concurrent chemoradiotherapy[6]. In addition, there is also evidence that T stage, or local extension of the tumor, is also a predictor of distant failure after concurrent chemoradiotherapy.[11] Thus, nodal and T-stage will be used to stratify patients at randomization into low versus high risk groups for distant metastases. (T1-3 and N0-N2a versus N2b-.N3 and/or T4, respectively).

Given the fact that institutions will be able to select between 2 different chemoradiotherapy regimens prior to treating their patients, patients will be also stratified by treating institution.

2.5.1 Oropharyngeal cancer and Human papillomavirus (HPV)

The presence of HPV DNA is strongly associated with oropharynx cancer and thought to be an etiologic agent. Patients with HPV positive oropharynx cancer not only appear to have a different clinical phenotype than HPV- cancers but multiple large studies have demonstrated a better outcome for these patients even when correcting for other known prognostic factors.[12] Thus, patients with HPV+ oropharynx cancer, compared to their HPV- counterparts, demonstrate higher response rates to induction chemotherapy, better locoregional control when treated with concomitant chemoradiotherapy, and better overall survival. Interestingly, tobacco exposure, especially greater than 10 pack-years, appears to modulate the effect of HPV positivity on outcomes and increases the risk of disease recurrence and mortality. Patients with HPV+ oropharynx cancer with significant tobacco exposure (>10 pack-years) appear to have an intermediate risk of dying from disease between HPV+/non-smokers and HPV- patients. Therefore, the outcome of any therapeutic approach must now be evaluated in the context of subject HPV status while some investigators have advocated for clinical trials de-intensifying treatment to HPV+ patients.

A recently reported large phase III trial of the Radiation Therapy Oncology Group (RTOG 0129) revealed no differences in the overall survival (OS) and progression free survival (PFS) rates between accelerated fractionation and standard fractionation when combined with concurrent high-dose cisplatin.[12] The success rate in collecting a high number of pretreatment tumor specimens enabled the investigators to establish firmly that the tumor HPV status is to date the strongest, independent prognostic factor in patients treated with radiation-cisplatin regimen. In addition, the investigators were able to divide patients into categories of low, intermediate or high risk of death based on HPV status, smoking history, and tumor stage.

Recursive-partitioning analysis showed that the HPV status of the tumor was the major determinant of overall survival, followed by the number of pack-years of tobacco smoking (≤10 vs. >10) and then nodal stage (N0 to N2a vs. N2b to N3), for HPV-positive tumors, or tumor stage (T2 or T3 vs. T4), for HPV-negative tumors. Their analysis classified patients with oropharyngeal squamous-cell carcinoma into three categories with respect to the risk of death: low risk, with a 3-year rate of overall survival of 93.0%; intermediate risk, with a 3-year rate of 70.8% (hazard ratio for the comparison with low risk, 3.54; 95% CI, 1.91 to 6.57); and high risk, with a 3-year rate of 46.2% (hazard ratio for the comparison with low

risk, 7.16; 95% CI, 3.97 to 12.93). Patients with HPV-positive tumors were considered to be at low risk, with the exception of smokers with a high nodal stage (i.e., N2b to N3), who were considered to be at intermediate risk; patients with HPV-negative tumors were considered to be at high risk, with the exception of nonsmokers with tumors of stage T2 or T3, who were considered to be at intermediate risk.

Risk-stratification algorithms based on biomarkers, especially HPV status, in LAHNC have recently been incorporated into clinical trials. The option that CRT and the addition of biologics should focus on HPV-negative patients, and that for HPV-positive patients, researchers should look at less intense options that might spare these patients some of the long-term morbidities of CRT (mainly the radiotherapy component) is very attractive. This approach has been studied by the Eastern Cooperative Oncology Group (ECOG) - trial ECOG 1308 - targeting specifically HPV-positive patients, and the Radiation Therapy Oncology Group (RTOG), with both groups assessing the addition of cetuximab.

In order to differentiate low risk patients from others, we will be applying similar classification criteria for study inclusion, based on Ang et al.[12] Please notice we will be adding non-OPC tumors as high-risk and dividing the patients into 2 groups: low-risk and high-risk. We will be condensing the original Ang et al "intermediate and high-risk groups" into a high risk group, given the similarity of the confidence intervals of overall survival, as below.

The 3-year rates of overall survival were 93.0% (95% CI, 88.3 to 97.7) in the low-risk group, 70.8% (95% CI, 60.7 to 80.8) in the intermediate-risk group, and 46.2% (95% CI, 34.7 to 57.7) in the high-risk group. Adapted from Ang et al.[12]

In summary, the risk classification criteria used for study inclusion will be:

Low risk Locally Advanced Head and Neck Cancer (LAHNC), not eligible for study inclusion:

- Oropharyngeal cancer (OPC), HPV positive, with **less** than 10 pack year smoking history (any nodal status)
- OPC, HPV positive, with **at least** a 10 pack year smoking history, **and N0-N2a** disease

High risk LAHNC:

- Stage IVa-b Squamous Cell Carcinoma (SCC) other than OPC, OR
- OPC, HPV negative, Stage IVa-b SCC
- OPC, HPV positive with at least a 10 pack-year smoking history, **and** N2b-N3 disease are **not eligible for the Phase 1 study component, but eligible for Phase 2**

HPV Determination

Patients with oropharyngeal cancers must have their tumor HPV status (either positive or negative) prior to stratification. There is currently no standard approach for HPV testing of clinical samples and, as such, individual institutions can determine the tumor HPV status by their method of choice. Acceptable methods of determination include:

- P16 by immunohistochemistry (IHC) as a surrogate for the function of the high-risk (HR) HPV E7 protein.
- HPV 16 insitu hybridization (ISH)
- HPV DNA detection by polymerase chain reaction (PCR)

2.6 ABT-888 (Veliparib)

ABT-888 is an orally available, small molecule inhibitor of poly(ADP-ribose) polymerase (PARP). PARP is an essential nuclear enzyme that plays a role in recognition of DNA damage and facilitation of DNA repair. Therefore, inhibition of PARP is expected to enhance the effects of DNA damage. Expression of PARP is higher in tumor cells as compared to normal cells. This overexpression has been linked to drug resistance and the ability of tumor cells to withstand genotoxic stress. Hence, it is anticipated that PARP inhibitors will function as sensitizing agents for chemotherapy and radiation therapy that are designed to cause DNA damage.

2.6.1 Mechanism of Action

Poly (ADP-ribosyl)ation (PAR) occurs after single or double-stranded DNA damage and represents the posttranslational modification of histones and other nuclear proteins by PARP. Based on conserved genetic sequences, encoded for by 18 different genes, 18 nuclear proteins have been classified as members of the PARP superfamily. The superfamily is further subdivided into three branches, the PARP-1 group, the tankyrase group, and other PARP enyzmes. The PARP-1 group of NAD^+-dependent enzymes has been extensively studied, and its members PARP-1 and PARP-2 are generally considered as the primary enzymes involved in DNA repair [13].

PAR has been implicated in many cellular processes including replication, transcription, differentiation, gene regulation, protein degradation, and spindle maintenance. Enhanced PARP-1 expression and/or activity in tumor cells, as compared to normal cells, has been demonstrated in malignant lymphomas [14], hepatocellular carcinoma [15], cervical carcinoma [16], colorectal carcinoma [17], non-Hodgkin's lymphoma [18], leukemic lymphocytes [19], and colon adenomatous polyps [20]. PARP-1 and PARP-2 are nuclear proteins and are the only members of the PARP family with zinc-finger DNA binding domains. These domains localize PARP-1 and PARP-2 to the site of DNA damage. PARP-1 is highly conserved and has three structural domains (N-terminal DNA-binding domain; automodification domain, and the NAD^+-binding domain). The catalytic domain is located at the C-terminus end of the protein. In knockout mouse models, deletion of PARP-1 is sufficient to impair DNA repair [21-23]. The residual PARP-dependent repair activity (~ 10%) is due to PARP-2. This suggests that only PARP-1 and PARP-2 need to be inhibited to impair DNA repair [24-26].

The zinc finger domain of PARP binds to both single- and double-stranded DNA breaks, resulting in increased catalytic activity [24,26,27]. Once activated, PARP cleaves NAD^+ and attaches multiple ADP-ribose units to the target nuclear protein. This results in a highly negative charge on the target protein and affects its function. Overactivation of PARP can be induced by DNA damage, leading to the depletion of NAD^+ and energy stores and, thus, cellular demise by necrosis. An alternate mechanism has been identified where PARP overactivation can induce cell death through apoptosis by releasing the Apoptosis Inducing Factor (AIF) from mitochondria [28]. Consequently, multiple mechanisms to prevent overactivation of PARP exist. First, auto-PAR negatively regulates PARP activity [29]. In addition, the cleavage of PARP by caspases yields a peptide fragment that acts as a trans-dominant negative inhibitor for uncleaved PARP. PAR of proteins is a dynamic process with a short half-life ($t_{1/2}$) of <1 min. The enzymes responsible for degrading these polymers are poly(ADP-ribose) glycohydrolase (PARG), which cleaves ribose-ribose bonds, and ADP-ribosyl protein lyase, which removes the protein proximal to the ADP-ribose monomer.

Increased PARP activity is one of the mechanisms by which tumor cells avoid apoptosis caused by DNA damaging agents. PARP activity is essential for the repair of single-stranded DNA breaks through the base excision repair (BER) pathways [26,30]. Therefore, inhibition of PARP sensitizes tumor cells to cytotoxic agents (*e.g.* alkylators [temozolomide,

cyclophosphamide, BCNU] and topoisomerase I inhibitors [irinotecan, camptothecin, topotecan]) which induce DNA damage that would normally be repaired through the BER system. A significant therapeutic window appears to exist between a PARP inhibitor's ability to potentiate therapeutic benefit *versus* potentiation of undesirable side effects. As expected, PARP inhibitors do not potentiate agents that do not cause DNA damage.

Ionizing radiation induces both double- and single-stranded DNA breaks. While part of the radiosensitization caused by PARP inhibition is through the inhibition of the single-stranded break repair pathways, it appears likely that repair of double-stranded breaks, which are thought to be more cytotoxic, is also affected. Double-stranded breaks are strong activators of PARP-1, resulting in PARP-1 mediated activation of DNA-PK and Ku80, important components of the non-homologous end-joining (NHEJ) double-stranded break repair pathway [31,32]. Also, small molecule inhibitors of PARP can directly inhibit the repair of double-stranded breaks [21,33]. Thus, it is likely that PARP activity is important for repair of both the single- and double-stranded stranded DNA breaks caused by ionizing radiation.

2.6.2 Nonclinical Activity

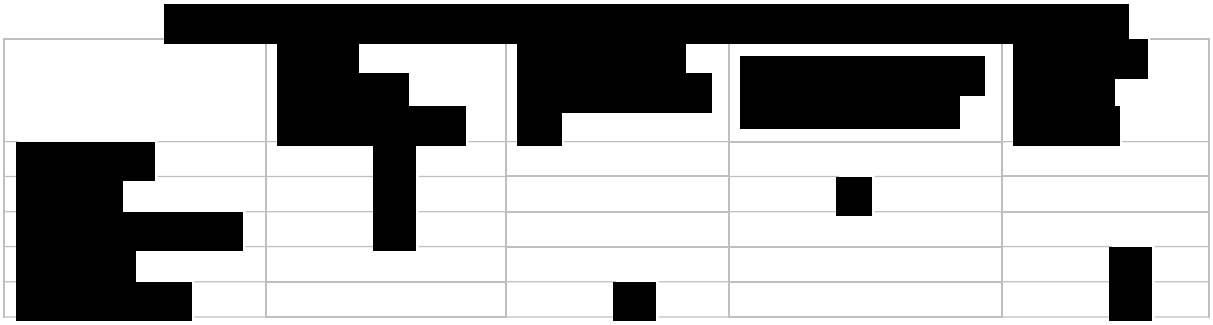
[redacted] The extent of DNA damage in cells was indicated by γ-H2AX levels. To determine the effect of ABT-888 in combination with cytotoxic agents on DNA damage, the cellular content of γ-H2AX in C-41 cells was assayed by flow cytometry using an anti-γ-H2AX antibody. Addition of 1 mM of temozolomide alone resulted in increased numbers of γ-H2AX foci, a result which was further potentiated by ABT-888 in a dose-dependent manner. When cell survival was measured by an AlamarBlue assay, ABT-888 potentiated cytotoxicity in the same concentration range as used in the γ-H2AX assay, demonstrating that ABT-888 potentiates cytotoxicity of temozolomide by delaying DNA repair. ABT-888 achieved a maximal potentiation of approximately 15-fold. ABT-888 also potentiates the DNA damage cause by irinotecan.

[redacted] PARP inhibition was shown to sensitize cells that are mismatch repair (MMR)-deficient to a greater extent than cells that are MMR competent [34]. Alkylating agents such as temozolomide form methyl adducts in DNA and resistance is frequently encountered in the clinic with either the overexpression of O^6-alkylguanine DNA alkyltransferase (AGT) or functional defects in the MMR system. However, when PARP was inhibited, cells were sensitized to methylpurine formation, regardless of their resistance factors [35].

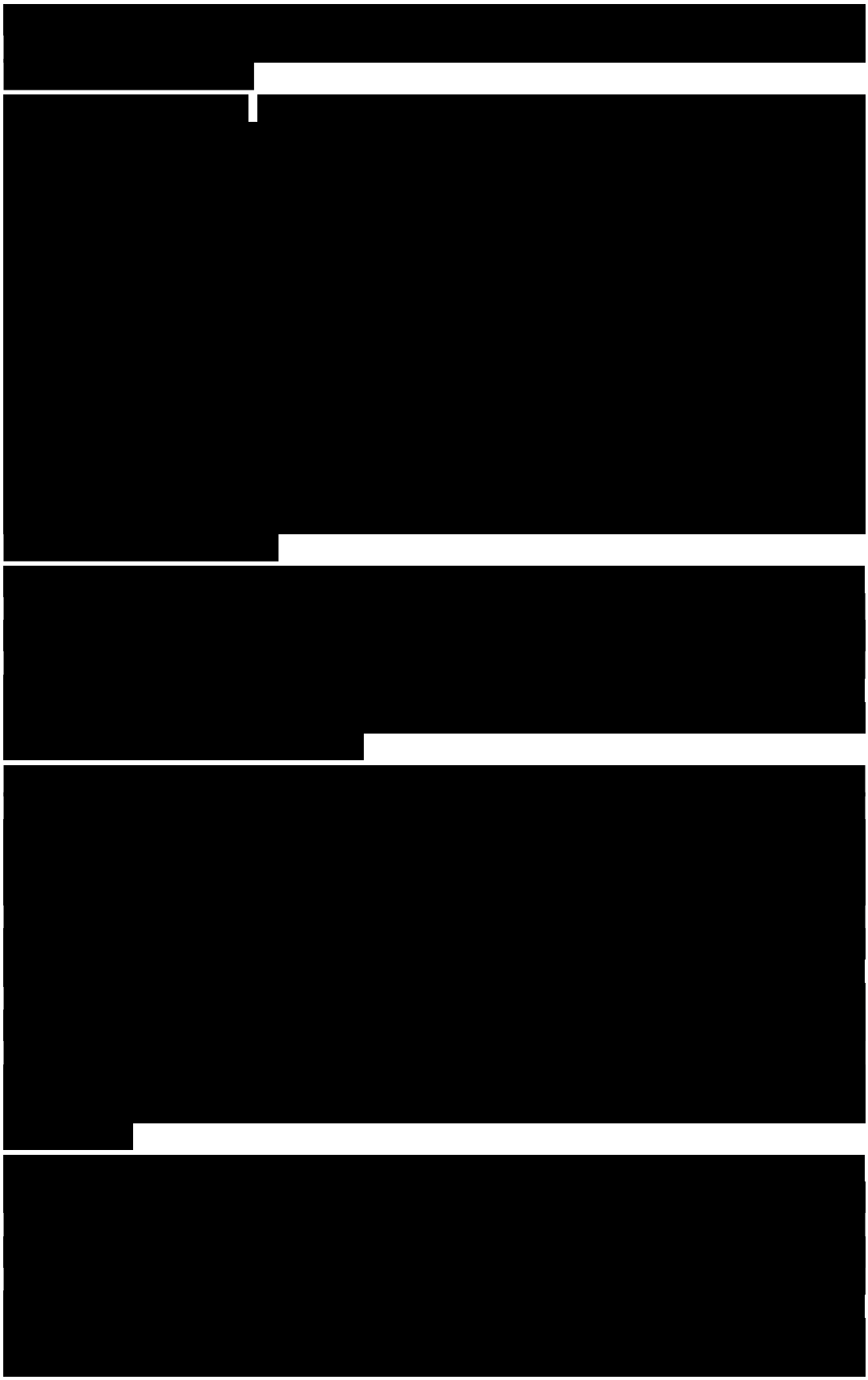
There are data to suggest that PARP inhibitors have activity against some BRCA-deficient cells in the absence of any DNA damaging agent [36,37]. These inhibitors did not demonstrate single agent activity in BRCA-competent cells, and restoring functional BRCA to deficient cells abrogated single agent cytotoxicity. It is possible that, in BRCA-deficient cells, PARP inhibition stops the BER pathway, and thus single-stranded breaks are carried through DNA synthesis, resulting in double-stranded breaks. The increase in double-stranded breaks cannot be repaired by homologous recombination (HR), due to the lack of BRCA1 or 2,

resulting in increased cell death. However, since not all BRCA deficient cells are sensitive to the PARP inhibitors, it is unclear why single agent cytotoxicity is observed in some BRCA-deficient cells.

Consistent with PARP-1 being a radiosensitization target, PARP-1 knockout mice showed enhanced sensitivity to γ-radiation [38,39]. There is evidence to suggest that PARP inhibitors sensitize cancer cells to radiation, both *in vitro* and *in vivo* [40-42]. Furthermore, a PARP inhibitor in the same class as ABT-888 potentiated radiation in the HCT116 colon carcinoma model. ABT-888 was tested, in combination with cytotoxic agents, in several tumor models and demonstrated a similar profile of antitumor activity to that seen in the literature. ABT-888 substantially increased the efficacy of cytotoxic therapies, when measured by either treated/control tumor volumes (%T/C) or by increased time for tumors to grow to a particular size (%ILS).



[redacted]



2.6.4 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 (Kummar *et al.*, 2009). 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 trial had been initiated in the BRCA deficient population. Most recently, a phase I trial of ABT-888 with doxorubicin(A) and cycyphosphamide (C) was reported.[44] ABT-888 (doses ranged from 50 to 150 mg every 12 h on days 1 - 4 with fixed dosing of AC (60/600 mg/m^2) on day 3 every 21 days. Further A was omitted after a cumulative dose of 420 mg/m^2. The MTD of ABT-888 was 100 mg every 12 h with AC every 21 days. Two instances of grade 3 febrile neutropenia were considered dose-limiting at the 150 mg ABT-888 dose level. MTD of ABT-888 was 100 mg every 12 h with AC. Drug-related toxicities included fatigue and myelosuppression.

Another phase I study sought to evaluate ABT-888 with irinotecan in solid tumors.[45] Cycles were administered every 21 days. Irinotecan was given intravenoulsy. 100 mg/m^2 over 90

min on Days 1 and 8. Twice daily (BID) oral dosing of ABT-888 (10-50mg) occurred on days 3-14 (Cycle 1) and Days -1-14 (subsequent cycles) followed by a 6-day rest. The MTD and recommended phase II dose was established as 100 mg/m^2 of irinotecan given days 1 and 8 combined with 40 mg of ABT-888 given BID 15 days on/6 days off in a 21 day cycle. Most frequent drug-related toxicities included: diarrhea (59%), nausea (56%), leukopenia (50%), fatigue (47%), neutropenia (47%), anemia (34%), and vomiting (31%). DLTs included fatigue, diarrhea, febrile neutropenia (grade 3), leukopenia and, neutropenia (grade 4).

Further detailed information regarding ABT-888 clinical development, safety and efficacy is provided in the Investigator's Brochure.

2.7 Rationale for Combination of ABT-888 and Induction Chemotherapy

With respect to chemotherapy and radiotherapy modifiers, a promising new area investigation is the use of PARPi to improve both cytotoxic modalities. PARP is involved in several forms of DNA repair including single and double strand break repair as well as base excision repair. It is likely that PARP also provides accessibility of the chromatin to DNA repair enzymes through relaxation of chromatin structure. Inhibition of PARP decreases the repair of single stranded DNA breaks through an interaction with ERCC1 and newly synthesized replication forks are particularly sensitive to PARP inhibition. It is likely that PARP inhibition directly impedes the repair of double strand DNA breaks although its effects may also be achieved by inhibiting the repair of multiple single strand breaks. PARP is a major pharmacological target for improving chemotherapy and radiotherapy and clinical trials in breast ovary, brain tumors and pancreatic cancer are underway with additional clinical trials in other tumors about to be initiated. The concept of "synthetic lethality" that is blocking a repair pathway in tumors that are defective in another repair pathway has become an important model for the use of PARPi in breast and ovarian cancer patients. Patients defective in BRAC1 and BRAC2 mediated homologous repair are proposed to be sensitive to PARPi which block the non-homologous repair pathway.

However the therapeutic effects of PARPi alone even in patients with BRCA1 and BRAC2 mutations is fairly modest pointing to combination therapy as the most promising direction for the use of PARPi. In general tumor cell death achieved through the interaction of PARP inhibition with chemotherapy and radiotherapy is proposed to occur through mitotic (necrotic) or apoptotic cell death. A novel set of data underpinning our proposal is that inhibition of PARP combined with radiotherapy and chemotherapy also accelerates senescence and might provide an alternative pathway to achieve anti-tumor effects especially in tumor cells resistant to necrotic or apoptotic death. We propose that accelerating DNA damage induced senescence by PARPi may be a novel approach to cancer therapy. The hypothesis is that the addition of a PARP inhibitor (ABT-888) to induction chemotherapy for LAHNC will be feasible and lead to measureable differences in clinical outcome parameters, especially complete (or near complete) response rate, as well as correlate with expression of cellular targets and potential biomarkers.

2.8 Correlatives Studies Background

PARP is a nuclear enzyme that recognizes DNA damage and facilitates DNA repair.[26,46,47] Activation of PARP-1 and PARP-2 enzymes is an essential step in the recognition of DNA damage that results in the poly(ADP-ribosyl)ation of many nuclear target proteins, including those that facilitate DNA repair. DNA repair pathways can be divided into those that involve single-stranded DNA breaks and those that involve double-stranded DNA breaks. PARP activity is essential for the repair of single-stranded DNA breaks through the Base Excisional Repair (BER) pathways.[18,30,48] PARP activity also has been demonstrated to be an important modulator of the nonhomologous end-joining and homologous recombination double-stranded break repair pathways. Consequently, inhibition of PARP should enhance the effects of DNA-damaging

agents, including alkylators, platinums, topoisomerase poisons, and radiation therapy. Higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress.[14,15,20,49] Therefore, PARP inhibitors are proposed as sensitizing agents for a variety of DNA-damaging agents.

A novel set of data underpinning our proposal is that inhibition of PARP combined with radiotherapy and chemotherapy also accelerates senescence and might provide an alternative pathway to achieve anti-tumor effects especially in tumor cells resistant to necrotic or apoptotic death. We thus propose that accelerating DNA damage induced senescence by PARPi may be a novel approach to cancer therapy.

As such, this study will be amended after phase 1 is completed to ask patients to undergo research tumor biopsy prior to induction chemotherapy and during carboplatin-paclitaxel administration in order to optimize measurements of the interaction of ABT-888 with carboplatin-paclitaxel chemotherapy and its effects on tumor cells on-treatment, biopsies will be obtained on day 4 of the carboplatin-paclitaxel chemotherapy administration during cycle 1. The investigators believe that day 4 biopsy will be able to demonstrate DNA damage, activation of P21 and P16 pathways, and γH2Ax. The investigators expect that the peak without PARP inhibitors will have passed at day 4. The reason for biopsying at day 4 is to see if in the presence of PARP inhibitors, the DSDNA breaks persist longer than without ABT 888.

γ-H2AXand poly (ADP-ribose) as suggested by Redon et al., 2010**:** tumor cells are often deficient in DNA damage response (DDR) pathways, and anticancer therapies are commonly based on genotoxic treatments using radiation and/or drugs that damage DNA directly or interfere with DNA metabolism, leading to the formation of DNA double-strand breaks (DSB), and ultimately to cell death. Because DSBs induce the phosphorylation of histone H2AX (γH2AX) in the chromatin flanking the break site, an antibody directed against γH2AX can be employed to measure DNA damage levels before and after patient treatment. Poly(ADP-ribose) polymerases (PARP1 and PARP2) are also activated by DNA damage, and PARP inhibitors show promising activity in cancers with defective homologous recombination (HR) pathways for DSB repair.

Other markers of value in SCCHN or determinants of sensitivity to PARP inhibitors, including testing for EGFR, MET and p16 (HPV) expression and analysis of PTEN, P16 and BRCA1 mutations will also be analyzed.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria for Phase 1 Component

3.1.1 Documentation of Disease: Patients who are treatment naïve, high risk, stage IVa/IVb (all other sites) and histologically proven squamous cell carcinoma of the head and neck (SCCHN) with no definitive evidence of metastatic disease, excluding patients with oropharynx HPV-positive tumors.

In summary, those patients eligible are newly diagnosed and treatment naive:

- Stage IVa-b Squamous Cell Carcinoma other than Oropharyngeal Cancer (OPC), OR
- Oropharyngeal Cancer (OPC) HPV-negative, Stage IVa-b

3.1.2 Measurable Disease: Patients must have at least one measurable site of disease according to RECIST criteria. i.e., patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan MRI, or calipers by clinical exam. See Section 11.2 for the evaluation of measurable disease.

3.1.3 ECOG performance status 0-1.

3.1.4 Age ≥18 years.

3.1.5 Patients must be able to swallow the drug.

3.1.6 Ability to understand and the willingness to sign a written informed consent document.

3.1.7 Required Lab Values:

leukocytes	≥ 3,000/mm^3
absolute neutrophil count	≥ 1,500/ mm^3
platelets	≥ 100,000/ mm^3
total bilirubin	≤ 1.5 Institutional upper limit of normal (ULN)
SGOT(AST) and SGPT(ALT)	≤ 2.5 X institutional ULN
creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above ULN*

* As calculated by Cockcroft-Gault.

3.1.8 Patients who are receiving any other investigational agents are not eligible**.**

3.1.9 Patients with active seizure or a history of seizure are not eligible.

3.1.10 Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to ABT-888 or other agents used in study, including cremophor, carboplatin, paclitaxel, cisplatin, 5-fluorouracil, hydroxyurea, or any compounds of similar chemical or biologic composition are not eligible.

3.1.11 Patients with impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of ABT-888 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection) are not eligible to participate in this study.

3.1.12 Patients with 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 are not eligible to participate in the study.

3.1.13 **Pregnant women are not eligible to participate in this study**. NOTE: Women of child bearing potential must have a negative serum or urine pregnancy test within 7 days prior to treatment. ABT-888 is a PARP inhibitor with the potential for teratogenic or abortifacient effects.

- Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ABT-888, breastfeeding should be discontinued if the mother is treated with ABT-888. These potential risks may also apply to other agents used in this study.

3.1.14 HIV-positive patients on combination antiretroviral therapy are not eligible because of the potential for pharmacokinetic interactions with ABT-888.

3.1.15 Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent are not eligible to participate in this study. Topical or inhaled corticosteroids are allowed.

3.1.16 Patients with other malignancies within the past 2 years, except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin or surgically treated early stage solid tumors are ineligible to participate in this study.

3.2 Eligibility Criteria for Phase 2 Component

3.2.1 **Documentation of Disease:** Patients who are treatment naïve, high risk, stage IVa/IVb (all other sites) histologically proven Squamous Cell Carcinoma of the Head and Neck (SCCHN) with no definitive evidence of metastatic disease**.**

In summary, those patients eligible are:

- Stage IVa-b SCCHN other than oropharyngeal Cancer (OPC), OR
- OPC, HPV-negative, IVa-b, OR
- OPC, HPV positive, with greater than 10 pack-year smoking history and N2b-N3 disease

3.2.2 **Measurable disease:** Patients must have at least one measurable site of disease according to RECIST criteria. i.e., patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan MRI, or calipers by clinical exam. See Section 11.2 for the evaluation of measurable disease.

3.2.3 **ECOG performance status 0-1.**

3.2.4 Age ≥18 years.

3.2.5 Patients must be able to swallow the drug**.**

3.2.6 Ability to understand and the willingness to sign a written informed consent document.

3.2.7 Required Lab Values:

leukocytes	≥ 3,000/mm^3
absolute neutrophil count	≥ 1,500/ mm^3
platelets	≥ 100,000/ mm^3
total bilirubin	≤ 1.5 Institutional upper limit of normal (ULN)
SGOT(AST) and SGPT (ALT)	≤ 2.5 X institutional ULN
creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above ULN*

* As calculated by Cockcroft-Gault.

3.2.8 Patient History: Patients who are receiving any other investigational agents are not eligible**.**

3.2.9 Patients with active seizure or a history of seizure are not eligible.

3.2.10 Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to ABT-888 or other agents used in study, including cremophor, carboplatin, paclitaxel, cisplatin, 5-fluorouracil, hydroxyurea, or any compounds of similar chemical or biologic composition are not eligible.

3.2.11 Patients with impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of ABT-888 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection) are not eligible to participate in this study.

3.2.12 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 are not eligible to participate in this study.

3.2.13 Pregnant women are not eligible to participate in this study. NOTE: Women of child bearing potential must have a negative serum or urine pregnancy test within 7 days prior to treatment. ABT-888 is a PARP inhibitor with the potential for teratogenic or abortifacient effects.

- Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ABT-888, breastfeeding should be discontinued if the mother is treated with ABT-888. These potential risks may also apply to other agents used in this study.

3.2.14 HIV-positive patients on combination antiretroviral therapy are not eligible because of the potential for pharmacokinetic interactions with ABT-888.

3.2.15 Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent are not eligible to participate in this study. Topical or inhaled corticosteroids are allowed.

3.2.16 Patients with other malignancies within the past 2 years, except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin or surgically treated early stage solid tumors are ineligible to participate in this study.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION/RANDOMIZATION PROCEDURES AND STRATIFICATION

Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form are required.

Registration must occur prior to the initiation of therapy.

OPEN Access Requirements

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment holds should be discussed with the Study Chair.

4.1 Phase I Patient Registration

4.1.1 OPEN Registration Procedures

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

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 (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for A091101 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- Study Chair approval

Institutional Participation Requirements

Institutions: Institutions listed on the protocol cover page may participate in this study.

Conference Calls: One representative from each participating institution must participate in a conference call every 2 weeks for the Phase I portion. Institutions with patients enrolled to the Phase I portion **must** participate in this call. Institutions not participating in this conference call may be denied future registration to this study. A representative from CTEP may also take part in these calls.

Dose Level Confirmation: During the Phase I portion of the trial, patient enrollment will be facilitated using the **CTSU Slot Reservation** System in conjunction with the Oncology Patient Enrollment Network (OPEN). **Prior to discussing protocol entry with prospective patients**, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot for the study is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll patients to this study. Please note that a slot reservation will only be held for up to seven calendar days. After 7 calendar days, the slot reservation may only be renewed once for an additional 7 calendar days.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.2 Phase II Patient Registration

4.2.1 Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated the applicable consent.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site

Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3 Stratification Factors

Randomization will be stratified by:

1) Tumor nodal status:
   - •T1-3, N0-N2a versus
   - •N2b, N2c-N3 and /or T4
2) Oropharyngeal disease/ HPV status:
   - •non-oropharyngeal disease versus
   - •oropharyngeal disease with HPV positive status versus
   - •oropharyngeal disease with HPV negative status
3) Institution

* Note: stratification by institution implicitly stratifies by concomitant CRT, as it is planned that concomitant CRT will be an institution-level choice.

5.0 TREATMENT PLAN

Study Overview

Phase I portion: This will be a dose-escalation scheme to determine the MTD of ABT-888. Induction chemotherapy will be followed by one of 2 options of concomitant chemoradiotherapy, as described in Section 5.1.2.

Phase II portion: Patients will be randomized in a 1:1 manner to receive induction chemotherapy with or without ABT-888 at the dose determined during Phase I. Randomization will be stratified by tumor/nodal status (T1-3, N0-N2a versus N2b-N3 and/or T4), oropharyngeal disease/ HPV status and institution (and implicitly, institutional-chosen concomitant CRT) as described in Section 2.5. Induction chemotherapy will be followed by one of 2 options of concomitant chemoradiotherapy, as described in Section 5.1.2. Treatment assignment will be double-blinded. Induction chemotherapy will be administered on an outpatient basis. Exceptions can be made if patients need hospitalization for any reason, which should not delay treatment. Chemoradiotherapy can be administered on an inpatient or outpatient basis. Expected AEs and appropriate dose modifications for carboplatin, paclitaxel and 5-fluorouracil, hydroxyurea, and radiation are described below. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1 Phase I

5.1.1 Induction Chemotherapy

There will be 2, three-week cycles (6 weeks total) in the induction chemotherapy portion of Phase I. ABT-888 will be administered PO twice daily for the first 7 days of Cycle 1 and 2 (starting on Day 1). This will be combined with a chemotherapy regimen of carboplatin and

paclitaxel. Carboplatin will be administered on Day 1 of each 21 day cycle and paclitaxel will be administered on Days 1, 8, and 15 of each 21 day cycle.

This will be a dose-escalation scheme to determine the MTD of ABT-888. Patients will be placed in one of the dose cohorts of ABT-888 listed below, using a conventional 3+3 design. Only the first cycle will be used to determine dose level. Two 3-week cycles of induction chemotherapy will be followed by one of two options for concomitant chemoradiotherapy.

Dose Levels

ABT-888 doses will be given at 200 mg bid for 7 days in combination with paclitaxel 100 mg/m^2 and carboplatin AUC 6. Please see the table below for dose cohorts that are planned for the study design.

Dose Cohort	**ABT-888**	Paclitaxel (weekly)	Carboplatin (every 3 weeks)
-3	**50 mg BID x 7 days**	100 mg/m^2	6 AUC
- 2	**100 mg BID x 7 days**	100 mg/m^2	6 AUC
-1	**150 mg BID x 7 days**	100 mg/m^2	6 AUC
*0B	**200 mg BID x 7 days**	100 mg/m^2	6 AUC
1	**250 mg BID x 7 days**	100 mg/m^2	6 AUC
2	**300 mg BID x 7 days**	100 mg/m^2	6 AUC
3	**350 mg BID x 7 days**	100 mg/m^2	6 AUC

* starting dose

Drugs are given sequentially; start next drug after completion of previous one.

ABT-888 PO twice daily on days 1-7, every three weeks for 2 cycles. Dose according to assigned cohort.

Paclitaxel: 100 mg/m^2 IV infusion (on Day 1), every week on days 1, 8, and 15 for 2 cycles, followed by….

Carboplatin: AUC 6, every 3 weeks for 2 cycles. Carboplatin will be administered as an intravenous infusion over 30 minutes. The carboplatin dose will be calculated using the Calvert formula using AUC of 6 as follows:

$$\text{Carboplatin dose in mg}^* = 6 \times (\text{GFR} + 25)$$

* Calculated total dose is in mg, not mg/m^2

The Creatinine Clearance (to replace GFR) will be calculated for each treatment course using the formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight in kg.} \times (0.85 \text{ only if female})}{72 \times \text{serum creatinine}}$$

Note: The GFR (calculated by Cockcroft-Gault) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min (i.e., maximum carboplatin dose is 900mg).

At this time, there is no data for ABT-888 administration through PEG-tube. Therefore, patients who are unable to swallow capsules at baseline need to be excluded. Patients who develop dysphagia during treatment may not be able to complete the planned doses of ABT-888. Given the plan is to give this induction regimen for 2 cycles and 7 days of ABT-888, a significant number of missed doses of ABT-888 due to dysphagia is not expected.

Nevertheless, if patients missed planned doses during cycle 1 of the phase I trial, they will be replaced. If they miss doses during cycle 2, they will not be given later doses, and the patients will not be replaced during the phase I portion of this study.

5.1.1.1 Definition of Dose-Limiting Toxicity – Phase 1

In the Phase 1 portion, DLTs will be assessed during the first cycle of induction chemotherapy.

Dose Limiting Toxicity (DLT) will be defined as follows, during the first cycle of induction chemotherapy:

- Hematological toxicities:
  - Grade 4 neutropenia (ANC < 500) lasting more than 14 days
  - Febrile neutropenia
  - Grade 4 thrombocytopenia
  - Dose delay of greater than 3 weeks due to failure to recover counts.
- Non-hematological toxicities:
  - Study treatment-related grade 3 or grade 4 non-hematological toxicity (excluding alopecia, fatigue, hypersensitivity reaction, nausea, vomiting, constipation, diarrhea, hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia, and grade 3 hypertension).
  - Dose delay of greater than 3 weeks for non-hematological toxicity despite replacement of electrolytes, maximum treatment for diarrhea, nausea, vomiting, and hypertension.
- Any drug-related death.

Management and dose modifications associated with the above adverse events are outlined in Section 6.0.

5.1.1.2 Dose Escalation

Dose escalation will proceed according to the following scheme.

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 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 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.1.2 Concomitant Chemoradiotherapy Regimen Options

Following induction chemotherapy, patients will be placed into one of 2 regimens of radiation and chemotherapy, based on the guidelines of the institution where they are being treated. It is expected that the institutional choice of concomitant CRT will apply to all patients enrolled at that institution.

OPTION 1: Concomitant Chemoradiotherapy with Cisplatin

5.1.2.1 Cisplatin Treatment during concurrent cisplatin/radiation treatment

Cisplatin, 100 mg/m^2, IV on days 1 and 22 (cisplatin may be given within 24 hours of days 1 and 22).

Adjustment for actual or ideal body weight is per institutional standard.

High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly emetogenic regimens should be followed. In the absence of such guidelines, see Section 5.3.

Hydration and diuresis: per institutional guidelines.

5.1.2.2 Dose Specifications for 3D Radiotherapy during concurrent cisplatin/radiation treatment

The initial target volume encompassing the gross and subclinical disease sites will receive 1.8 Gy per fraction, five fractions a week to 54 Gy in 30 fractions over 6 weeks. The boost volume covering gross tumor and clinically/radiologically involved nodes will receive boost irradiation of 1.5 Gy/Fx delivered as a second daily fraction (with at least a six-hour interval) for a total of 12 treatment days (18 Gy total). The boost irradiation should commence during week 4 of the large field irradiation at the latest at 32.4 Gy/18 Fx of the initial target volume (i.e., latter part of week 4). All treatment times must be documented on the treatment record. The primary tumor and clinically/radiologically-involved nodes (PTVHD) will thus receive 72 Gy in 42 fractions over 6 weeks, and uninvolved upper neck nodes (PTVED) will receive an elective dose of 54 Gy in 6 weeks.

When desired, PTVINT can receive a total dose of 63 Gy, i.e., by delivering 9 fractions of 1.5 Gy to PTVINT before making a second cone down to PTVHD. Clinically/radiologically negative posterior neck should receive a minimum dose of 50.4 Gy at 3 cm.

The uninvolved lower neck nodes will receive 1.8 Gy per fraction at 3-cm depth to a total dose of 50.4 Gy in 28 fractions in 5.6 weeks through a matching AP or AP/PA lower neck field. Involved lower neck nodes can receive a total dose of up to 69-72 Gy when it is possible to limit the dose to the brachial plexus to ≤ 60 Gy. If this is not possible, the total dose can be limited to 60 Gy, in which case, neck dissection is mandatory regardless of the response.

Technical Factors

- Photon beams of ≥4 MV and/or electron beams from 6-25 MeV are required.
- Treatment distance must be ≥ 80 cm SAD for isocentric techniques.

Immobilization

Although a thermoplastic head mask may suffice for conformal radiotherapy, the use of a head and shoulder mask is recommended for better reproducibility

Planning CT scan

A treatment planning CT scan is mandatory for defining target volumes CT scan thickness should be at most 0.5 cm for conformal radiotherapy or 0.3 cm for IMRT. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be include in the CT scan.

Treatment Planning/Target Volumes

- CT based treatment planning is mandatory for every patient.
- Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.
- Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTV1 represents GTV plus a margin of generally 1 cm and CTV2 represents GTV with a margin of about 2 cm and nodal regions to receive elective irradiation. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose (e.g., 59-63 Gy) to a volume (CTVINT) that is slightly larger than CTV1. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues.
- Planning Target Volume (PTVHD and PTVED) represents an additional margin around CTV1 and CTV2 to compensate for the variability of treatment set up and internal organ motion. A minimum margin of 0.5 cm around the CTV is required in all directions to define each respective PTV, except for situations in which the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously. A minimum margin of 3 mm can be used in all directions as long as an institution implements a study to define the appropriate magnitude of the uncertain components of the PTV. Careful consideration should be made when defining the superior and inferior margins in three dimensions.
- The density corrected dose distributions shall be calculated and the dose prescription is to be based on a dose distribution corrected for heterogeneities.

Critical Structures

- Spinal cord: A margin of 0.5-1cm around the spinal cord may be added to create a Planning Organ at Risk Volume (PRV). The dose to any point within the spinal cord should not exceed 48 Gy to any volume larger than 0.03 cc (approximately equivalent to a 3x3x3 mm cube).
- Glottic larynx: In patients with oropharyngeal carcinoma without extension to the larynx, placing the isocenter just above the arytenoids and irradiating the lower neck with an anterior matching field with larynx block can minimize the dose to the glottic larynx. Alternatively, the dose to the larynx should be kept <45 Gy whenever feasible.
- Brachial plexus: The dose to the brachial plexus must be limited to ≤ 60 Gy in patients with level IV node(s).
- Unspecified tissue outside the target volumes: ≤ 100% of the dose prescribed to CTV1. No more than 5% of the non-target tissue can receive greater than the dose to CTV1.

Compliance Criteria

- Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Missed treatments due to holidays or logistic reasons can be compensated for by delivering additional BID treatments with a minimum interfraction interval of 6 hours.
- Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and ideally, should not exceed 5 treatment days at a time and 10 treatment days in total. Any treatment break(s) exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.
- Plan normalization should provide coverage of 95% of the volume of the PTV of the GTV (PTVHD) with the prescribed dose of 69.96 Gy. No more than 1% of the volume of the PTVHD should receive less than 64 Gy. Additionally, no more than 20% of the PTV of the GTV should receive more than 76 Gy, and no more than 5% of this volume should receive more than 79 Gy. These numbers describe the DVH shown in the figure below with the diamond shaped symbols. Obviously, better DVHs (i.e., with smaller amounts of either underdose or overdose) are preferable.
- A region of "minor deviation" is also defined in the figure as the DVH represented by the square symbols. Deviations of this magnitude are not desirable, but will be deemed acceptable. That is, a DVH with at least 97% of the volume receiving 64 Gy is acceptable as a minor deviation. Additionally, as a minor deviation for the overdose region, as much as 40% of the PTVHD volume can receive 76 Gy and up to 20% of this volume can receive 79 Gy. DVHs for the PTVHD falling outside the limits for a minor deviation (i.e., increased under or overdose) will be scored as unacceptable "major deviations."
- The DVHs for the other target regions should deliver the prescribed dose, as much as possible, to at least 95% of the volume of that PTV.

Overall Evaluation	**Radiotherapy Prolongation**	**Total Dose Variation 3-D RT**	**Total Dose Variation IMRT****
Per Protocol	≤ 5 days	≤ 4% deviation from prescribed dose	See parameters in the figure and table below
Minor Variation (Acceptable)	6-10 days	> 4% to ≤ 9%	See parameters in the figure and table below
Major Deviation (Unacceptable)	> 10 days	> 9%	Deviations greater than presented in the figure/table below

*****These criteria are to be reassessed based on the results of the recently completed RTOG trial, 0129.

****Note:** For IMRT, prescription dose is the isodose surface that encompasses at least 95% of the planning target volume (PTV) with no more than 20% of any PTV_{HD} receiving ≥

110% of the prescribed dose and no more than 1% of any PTV_{HD} and PTV_{ED} receiving ≤ 93% of the prescribed dose.

Dose (Gy)	Per Prescription	Minor variation
65	99%	97%
70	95%	95%
77	20%	40%
80	5%	20%

OPTION 2: Concomitant Chemoradiotherapy with TFHX

5.1.2.3 Chemotherapy should be administered during all 5 weeks of radiotherapy. If less than 3 days of radiation therapy (RT) are required during Week 5, chemotherapy may be omitted. Repeat every 14 days for a total of 5 cycles.

P.M.: **hydroxyurea** 500 mg PO q 12 hours for 11 doses beginning the evening before radiotherapy start. During radiotherapy, the morning dose of hydroxyurea is given 2 hours prior to the first fraction of daily radiotherapy.

6:00 P.M.: **5-FU** 600 mg/m2/day IV infusion over 120 hours beginning the evening before radiotherapy starts. Total dose 3000mg/m^2 per cycle. (**5-FU** may begin in the morning prior to the first daily radiotherapy fraction)

Paclitaxel 100 mg/m2 IV infusion on the first day of radiotherapy. Premedication for paclitaxel according to institutional procedures.

Radiation therapy is administered twice daily for 5 days (Mon- Fri) at 150 cGy per fraction.

Chemoradiotherapy cycles are repeated every 14 days until the completion of radiotherapy.

5.1.2.4 Radiotherapy Guidelines for concurrent TFHX treatment

1. All patients will have a complete dental evaluation prior to the start of radiation therapy, ideally prior to the start of chemotherapy.

2. Prior to the initiation of induction chemotherapy, all patients will be properly immobilized and simulated in the treatment position with a contrast enhanced CT scan for planning purposes. Additionally, after the completion of induction chemotherapy and prior to the initiation of concurrent chemoradiotherapy, all patients will undergo a second planning CT scan. The pre- and post-chemotherapy scans will be fused to define the targets below. Slice thickness for all planning CT scans should optimally be 3mm and no greater than 5 mm.

3. Target volume definition: Three volumes will be defined on each planning CT slice where appropriate. Gross disease based on all available imaging and clinical information will be designated as gross tumor volume (GTV). Planning target volume 1 (PTV1) will include the GTV + a 1.5 cm margin for set-up uncertainty, organ motion, and microscopic extension. High risk microscopic disease (PTV2) will include the entirety of PTV1 and will also include the nodal stations at risk for microscopic spread.

- Contouring the primary and involved neck nodes (GTV) will be performed per consensus recommendations [Salama JK, Haddad RI, Kies MS, Busse PM, Dong L, Brizel DM, Eisbruch A, Tishler RB, Trotti AM, Garden AS. Clinical Practice Guidance for Radiotherapy Planning After Induction Chemotherapy in Locoregionally Advanced Head-and-Neck Cancer. *Int J Radiat Oncol Biol Phys*. 2009 Apr 11.] In general, the pre-induction chemotherapy scan is used to define the primary tumor GTV and the post-induction chemotherapy volume is used to define the nodal volume GTV.
- PTV1 will be created by uniformly expanding the GTV by 1.5 cm.
- PTV2 will include all of PTV1 as well as the next regional nodal not involved with pathologic lymphadenopathy. Anatomic guidelines for lymph node stations will be defined using the RTOG Head and Neck Atlas Guidelines for delineation of the Nodal CTV.

Additionally site by site guidelines are provided below.

i. Guidelines for definition of PTV2:

- PTV2 is defined as the entirety of PTV1 as well as the next nodal station at risk.
- For example, a patient have an ipsilateral level 2 LN involved as GTV, PTV2 will encompass ipsilateral level 3.
- PTV2 may not differ significantly from PTV1 if the required GTV expansion includes the next nodal station at risk.
- For tumors that cross midline in the oral cavity or oropharynx, PTV 2 may include contralateral level 2 LN. An example would be a soft palate tumor or a base of tongue tumor that crosses midline.
- PTV1 and PTV2, can be modified at the discretion of the treating physician for the constraints of normal tissue tolerance and to avoid extension beyond the skin. Variations in anatomy and tumor size make it necessary for the radiation oncologist to carefully define the PTV on each individual CT slice. Reasonable attempts should be made to provide an adequate treatment volume without encroaching on critical organs (e.g. spinal cord) or extending to the skin.

4. Radiotherapy Techniques Allowed: Either 3-D CT based treatment planning or Intensity Modulated Radiation Treatment (IMRT) techniques will be acceptable.

- Planning Goals: In both instances the physician will attempt to deliver an even dose to the target tissue and minimize doses to surrounding normal structures.
- Blocking will be individualized for each patient. Either custom Cerrobend blocks or mutileaf collimation will be acceptable.
- Field Size: Appropriate field sizes will be determined at the time of simulation to treat gross disease and areas of potential microscopic disease. Initial field size and arrangement will be at the discretion of the attending radiation oncologist. The optimal field arrangement will be determined based on the treatment planning techniques employed. All fields must be treated during each treatment session.

5. 3D Conformal technique and prescription:

i. The neck should be treated with opposed lateral fields using a half-field technique.

ii. In general, the lower neck should be treated with an anterior field to a depth of 3 cm. Opposed fields for the lower neck are permitted in order to improve PTV coverage and increase homogeneity.

iii. Wedges, tissue compensators or segmented fields should be used to insure uniformity of PTV coverage.

iv. Electron fields of the posterior neck are permitted to limit the spinal cord dose.

v. A cord block is permitted on the anterior or lateral fields provided it does not cover tumor

vi. A moving match line is permitted in cases where a cord block would cover tumor.

vii. Acceptable plans will encompass the PTV within the 95% isodose line.

viii. The dose variation in the PTV will be +7% and -5% of the prescription point dose.

ix. Electron fields shall be prescribed to the depth of maximum dose with the energy and field size chosen so that the target volume is encompassed within 90% of the prescribed dose.

6. IMRT technique and prescription

i. Optimal IMRT planning will depend on the planning system employed.

ii. We anticipate that the optimal plan will use 7 to 11 gantry positions.

iii. Acceptable plans will encompass the PTV with the 95% isodose line.

iv. No more than 1% of the PTV should receive less than 1% of the prescribed dose.

v. Plans should be reviewed to ensure that any part of the PTV getting less than 95% of the prescription dose is at the edge of the volume.

vi. In no situation should a central area of the PTV receive less than 95% of the prescribed dose.

vii. No more than 1% of the PTV should receive 110% of the prescription dose.

Radiation Dose: each cycle of treatment will consist of 5 consecutive days of hyperfractionated radiation with 150 cGy given bid with a 6 hour interval between radiation fractions (300 cGy per day and 1500 cGy per week) in conjunction with chemotherapy.

i. The dose for PTV1 will be 70-75 Gy.

ii. The dose for PTV2 will be 45-54 Gy

iii. In the case of mechanical failure or a holiday, one day of BID radiotherapy can be replaced with a single QD fraction of 200cGy. Accordingly, the final cumulative dose will be slightly less.

The dose limit to the spinal cord will vary depending upon the technique used. Attempts should be made to limit the spinal cord dose to < 40 Gy with conventional 3D radiation treatment. Doses should be limited to 46 Gy with IMRT techniques and reduced fraction size to the spinal cord.

Countouring Atlas for Head and Neck:

http://www.rtog.org/atlases/hnatlas/tableneck.html

Detailed Site by Site Instructions for Nodal Planning Target Volume 2 Delineation:

Base of Tongue: Lateralized

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												

Ipsilateral	IB, II	IA, II	IB, III	II, IV	II,III	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	II	IB	II, IV	II, III	II, III

Base of Tongue: Crosses Midline

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II,III	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	---	II	II	II	II	IB	II	IB, III	II, IV	II, III	II, III

Soft Palate:

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	II	IB, III	II, IV	II,III	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	IA(?), II	IB, III	II, IV	II, III	II, III

Tonsil: No BOT invasion

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II,III	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	---	---	---	---	---	IB	IA(?), II	IB, III	II, IV	II, III	II, III

Tonsil: BOT Invasion

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V

PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II,III	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	---	II	II	II	II	IB	II	IB, III	II, IV	II, III	II, III

Larynx: T1-2

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	III	II, IV	II,III	II, III	IA, IB, II	II	II	III	III	II
Contralateral	IA	---	II	II	II	II	IB	II	III	II, IV	II, III	II, III

Larynx: T3-4

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	III	II, IV	II,III	II, III	IA, IB, II	II	II	III	III	II
Contralateral	IA	---	II	II	II	II	IB	II	III	II, IV	II, III	II, III

Hypopharynx

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	II, III,	III,IV	II, IV	II,III	II, III,IV	IA, IB, II	II	II	III	III	II
Contralateral	IA	---	II, III	II, III	II, III	II,III	IB	II	III	II, IV	II, III	II, III

Lower Gingiva

	Adenopathy Level											
	Ipsilateral						Contralateral					

Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB,II, IV	IB, IA, II,III	IA, IB, II, III	IA, IB	IA ,II	IA, IB, II,	IA, IB, II	IA, IB, II,	IA, IB, II,
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IA, IB, III	IB, IA, II, IV	IA, IB, II, II, III	II, III

Retromolar Trigone

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IB, III	IB,II, IV	IB, II,III	IB, II, III	IA, IB	IA ,II	IB, II,	, IB, II	IB, II,	IB, II,
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IB, III	IB, II, IV	IB, II, II, III	II, III

Oral Tongue: Lateralized

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB,II, IV	IB, IA, II,III	IA, IB, II, III	IA, IB, II	IA ,II	IA, IB, II,	IA, IB, II	IA, IB, II,	IA, IB, II,
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IA, IB, III	IB, IA, II, IV	IA, IB, II, II, III	II, III

Oral Tongue: Crosses Midline

	Adenopathy Level											

	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB,II, IV	IB, IA, II,III	IA, IB, II, III	IA, IB, II	IA ,II	IA, IB, II,	IA, IB, II	IA, IB, II,	IA, IB, II,
Contralateral	IA, IB	IA, IB	IA, IB	IA, IB	IA, IB	---	IB, II	IA, II	IA, IB, III	IB, IA, II, IV	IA, IB, II, II, III	II, III

Floor of Mouth

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved nodes:	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV 2 includes:												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB,II, IV	IB, IA, II,III	IA, IB, II, III	IA, IB, II	IA ,II	IA, IB, II,	IA, IB, II	IA, IB, II,	IA, IB, II,
Contralateral	IA, IB	IA, IB	IA, IB	IA, IB	IA, IB	---	IB, II	IA, II	IA, IB, III	IB, IA, II, IV	IA, IB, II, II, III	II, III

Changes to the proposed schedule are to be discussed with Dr. Daniel Haraf [(773) 702-5976, dharaf@radonc.bsd.uchicago.edu].

Missed treatments due to holidays or logistical reasons can be compensated for by delivering additional BID treatments with a minimum interfraction interval of 6 hours or by treating on a Saturday or Sunday.

5.1.3 Duration of Follow up

See Section 5.5 for clinical and survival follow-up schedule.

5.2 Phase II

Patients will be randomized in a 1:1 manner to receive induction chemotherapy **with or without ABT-888** at the dose determined during Phase I. Within 10 days after the completion of induction chemotherapy (i.e., week 6, day 7) patients will begin one of 2 options of concomitant chemoradiotherapy (as described in Section 5.1.2). It is expected that the institutional choice of concomitant CRT will apply to all patients enrolled at that institution. Treatment assignment will be double-blinded.

5.2.1 Carboplatin-Paclitaxel Induction Chemotherapy-Repeat every 3 weeks for 2 cycles

The doses of carboplatin and paclitaxel will remain the same during the phase I and II induction chemotherapy (refer to Section 5.1.1) Dose delays and dose modifications should take place as described below. **The total duration of induction chemotherapy should be 6 weeks and not exceed 8 weeks.**

ABT-888/placebo Twice daily at the dose determined in phase I, on days 1-7 (for a total of 7 days and 14 doses).

Paclitaxel: 100 mg/m^2 IV infusion over 60 minutes on Days 1, 8, and 15

Carboplatin: AUC 6, every 3 weeks for 2 cycles. Carboplatin will be administered as an intravenous infusion over 30 minutes. The carboplatin dose will be calculated using the Calvert formula using AUC of 6 as follows:

Carboplatin dose in mg* = 6 X (GFR + 25)

* Calculated total dose is in mg, not mg/m^2

The Creatinine Clearance (to replace GFR) will be calculated for each treatment course using the formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \text{ X weight in kg. X (0.85 only if femail)}}{72 \text{ X serum creatinine}}$$

Note: The GFR (calculated by Cockcroft-Gaul) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min (i.e., maximum carboplatin does is 900mg).

5.2.2 Concomitant Chemoradiotherapy

Concomitant chemoradiotherapy will start **within 10 days** from the completion of cycle 2 of carboplatin-pactlitaxel induction chemotherapy (as the cycles are 21 days long, patients should start concomitant therapy by day 31 of cycle 2). It is expected that the institutional choice of concomitant CRT will apply to all patients enrolled at that institution.

OPTION 1: Concomitant Chemoradiotherapy with Cisplatin as described in **Cisplatin**, 100 mg/m^2, IV on days 1 and 22 (cisplatin may be given within 24 hours of days 2 and 23).

Adjustments for actual or ideal body weight is per institutional standard.

High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly emetogenic regimens should be followed. In the absence of such guidelines, see Section 5.3.

Hydration and diuresis: per institutional guidelines.

For dose specifications for 3D Radiotherapy refer to Section 5.1.2.2.

OR

OPTION 2: Concomitant Chemoradiotherapy with TFHX

Chemotherapy should be administered during all 5 weeks of radiotherapy. If less than 3 days of radiation therapy (RT) are required during Week 5, chemotherapy may be omitted. Repeat every 14 days for a total of 5 cycles.

P.M.: hydroxyurea 500 mg PO q 12 hours for 11 doses beginning the evening before radiotherapy start. During radiotherapy, the morning dose of hydroxyurea is given 2 hours prior to the first fraction of daily radiotherapy.

6:00 P.M.: 5-FU 600 mg/m2/day IV infusion over 120 hours beginning the evening before radiotherapy starts. Total dose 3000mg/m^2 per cycle. (5-FU may begin in the morning prior to the first daily radiotherapy fraction)

Paclitaxel 100 mg/m2 IV infusion on the first day of radiotherapy. Premedication for paclitaxel according to institutional procedures.

Radiation therapy is administered twice daily for 5 days (Mon- Fri) at 150 cGy per fraction.

Chemoradiotherapy cycles are repeated every 14 days until the completion of radiotherapy.

For dose specifications for 3D Radiotherapy refer to Section 5.1.2.4.

5.3 Concomitant Medication and Supportive Care Guidelines

5.3.1 Supportive care for Carboplatin-Paclitaxel Induction

Pre-medications, hydration, and antiemetics should be given according to institutional procedures.

- Breakthrough nausea and vomiting and delayed nausea and vomiting should be managed aggressively according to institutional procedures.
- Colony stimulating factors should be given as described in Section 6.0.

5.4 Duration of Therapy

The total duration of induction chemotherapy should be 6 weeks, and not exceed 8 weeks. In no case should the duration of induction chemotherapy exceed 8 weeks or 2 cycles. In the absence of treatment delays due to adverse event(s), treatment may continue for 2 cycles or until one of the following criteria applies:

Disease progression,

Unacceptable adverse event(s),

Patient decides to withdraw from the study, or

General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

5.5.1 Clinical Follow-Up

Medical Oncology and/or Radiation Oncology: A brief history and physical by a medical oncologist and/or radiation oncologist must be done at 2 weeks, 1 month and 3 months from the end of chemoradiotherapy treatment, then every 3 months through year 2, every 6 months in year 3 and annually in years 4 and 5.

ENT or Head and Neck Surgeon: An examination by an ENT or Head and Neck Surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), must be completed at months 1 and 3 from the end of chemoradiotherapy treatment, then every 3 months through year 2, every 6 months in year 3, and annually in years 4 and 5.

Imaging: 3, 6, 12, 18, 24, 30, 36, 48, and 60 months following the end of CRT, any of the following options: a) CT scan of the neck (with contrast) and a chest CT scan (with or without contrast); b) MRI of the neck and a chest CT scan (with or without contrast); c) CT scan of the neck and a PET/CT of neck and chest (with or without contrast).

5.5.2 Survival Follow-up

Patients who have progressed will be followed every 6 months through year 5.

5.6 Criteria for Removal from Study

Patients will be removed from study treatment when any of the criteria listed in Section 5.4 applies.

6.0 DOSE MODIFICATIONS FOR PHASE I ONLY

Please note, the dose modifications for the phase II portion will be determined once the dose of ABT-888 is known for the phase II portion. When we reach the phase II portion, an amendment will detail the new dose modifications.

General rules for dose modification:

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed.
- Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Paclitaxel will not be re-escalated once reduced
- If dose reductions beyond dose level -1 is required induction will be discontinued, and patient will move to concurrent chemoradiotherapy
- If treatment is held 21 days or more, patient will move on to concurrent chemoradiotherapy
- CTEP-AERS reporting may be required for some adverse events (See Section 7.0)

Growth Factors:

In general, patients will NOT receive prophylactic filgrastim (G-CSF), tbo-filgrastim, PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience treatment delays, dose omissions, or recurrent neutropenic complications after treatment modifications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, patients may also receive growth factors for management of neutropenic complications in accordance with clinical treatment guidelines.

When GCSF is utilized, given the weekly chemotherapy doses, it is recommended that filgrastim, tbo-filgrastim or sargramostim (dosed according to institutional standard) will be administered daily subcutaneously starting 24-72 hours after the last dose of weekly paclitaxel.

As a reminder, dose cohorts for the phase I trial are:

Dose Cohort	**ABT-888**	Paclitaxel (weekly)	Carboplatin (every 3 weeks)
-3	**50 mg BID x 7 days**	100 mg/m^2	6 AUC
- 2	**100 mg BID x 7 days**	100 mg/m^2	6 AUC
-1	**150 mg BID x 7 days**	100 mg/m^2	6 AUC
*0B	**200 mg BID x 7 days**	100 mg/m^2	6 AUC
1	**250 mg BID x 7 days**	100 mg/m^2	6 AUC
2	**300 mg BID x 7 days**	100 mg/m^2	6 AUC
3	**350 mg BID x 7 days**	100 mg/m^2	6 AUC

* starting dose

6.1 Dose Reduction and Delays during Induction

Dose modification tables for phase I induction by cohort:

Cohort 0B:

Dose level	ABT-888	Carboplatin	Paclitaxel
0 (starting dose)	200 mg bid x 7 days	6 AUC	100 mg/m^2
-1	150 mg bid x 7 days	5 AUC	80 mg/m^2

Cohort 1:

Dose level	ABT-888	Carboplatin	Paclitaxel
0 (starting dose)	250 mg bid x 7 days	6 AUC	100 mg/m^2
-1	200 mg bid x 7 days	5 AUC	80 mg/m^2

Cohort 2:

Dose level	ABT-888	Carboplatin	Paclitaxel
0 (starting dose)	300 mg bid x 7 days	6 AUC	100 mg/m^2
-1	250 mg bid x 7 days	5 AUC	80 mg/m^2

Cohort 3:

Dose level	ABT-888	Carboplatin	Paclitaxel
0 (starting dose)	350 mg bid x 7 days	6 AUC	100 mg/m^2
-1	300 mg bid x 7 days	5 AUC	80 mg/m^2

Cohort -1:

Dose level	ABT-888	Carboplatin	Paclitaxel
0 (starting dose)	150 mg bid x 7 days	6 AUC	100 mg/m^2
-1	100 mg bid x 7 days	5 AUC	80 mg/m^2

Cohort -2:

Dose level	ABT-888	Carboplatin	Paclitaxel
0 (starting dose)	100 mg bid x 7 days	6 AUC	100 mg/m^2
-1	50 mg bid x 7 days	5 AUC	80 mg/m^2

Cohort -3:

Dose level	ABT-888	Carboplatin	Paclitaxel
0 (starting dose)	50 mg bid x 7 days	6 AUC	100 mg/m^2
-1	Discontinue ABT-888	5 AUC	80 mg/m^2

6.1.1 Dose Modifications for Hematologic Toxicity During Induction

For grade 2 neutropenia on day 1, proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 at same dose. For grade 3 or 4 neutropenia on day 1, delay day 1 until grade ≤ 2, then proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 1 dose level decreased. For febrile neutropenia on day 1, delay day 1 until recovery, then proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 1 dose level decreased.

For grade 4 neutropenia on day 8, omit paclitaxel on day 8, and upon reaching day 1 proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 at same dose on day 1. For grade 4 neutropenia on day 15, omit paclitaxel on day 15, and upon reaching day 1 proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 at same dose on day 1.

For grade 1 thrombocytopenia on day 1, proceed with carboplatin at 1 dose level decreased, paclitaxel at same dose, and ABT-888 at same dose. For grade 2 thrombocytopenia on day 1, delay day 1 until grade ≤ 1, then proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 at same dose. For grade 3 thrombocytopenia on day 1, delay day 1 until grade ≤ 1, then proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 at 1 dose level decreased. For grade 4 thrombocytopenia on day 1, delay day 1 until grade ≤ 1, then proceed with carboplatin 1 dose level decreased, paclitaxel 1 dose level decreased, and ABT-888 at 1 dose level decreased.

For grade 3 or 4 thrombocytopenia on day 8, omit paclitaxel on day 8, and upon reaching day 1 proceed with carboplatin 1 dose level decreased , paclitaxel at same dose, and ABT-888 at 1 dose level decreased on day 1. For grade 3 or 4 thrombocytopenia on day 15, omit paclitaxel on day 15, and upon reaching day 1 proceed with carboplatin 1 dose level decreased, paclitaxel at same dose, and ABT-888 at 1 dose level decreased on day 1.

6.1.2 Dose Modifications for Neurotoxicity (CTCAE Nervous System Disorders) during Induction

- For any grade seizure, discontinue ABT-888. Continue carboplatin and paclitaxel at same dose.
- For grade 2 peripheral motor or sensory neuropathy, decrease paclitaxel by one dose level. Continue carboplatin and ABT-888 at the same dose.
- For grade 3 or 4 peripheral motor or sensory neuropathy, delay all subsequent protocol-directed therapy for a maximum of three weeks until grade ≤ 2, then decrease paclitaxel and carboplatin by one dose level for the next cycle and give ABT-888 at the same dose.
- If induction (cycle 2) is delayed for more than three weeks, proceed to chemoradiotherapy.

6.1.3 Musculoskeletal and Connective Tissue Toxicity During Induction

- For grade 3 or 4 arthralgia, delay all subsequent protocol-directed therapy for a maximum of three weeks until grade ≤ 2, then decrease paclitaxel by one dose level for the next cycle, and give carboplatin and ABT-888 at the same dose.
- If Induction (cycle 2) is delayed for more than 2 weeks for arthralgia or myalgia, proceed to chemoradiotherapy.

6.1.4 Fatigue (CTCAE General Disorders and Administration Site Conditions) during Induction

- For grade 3 or 4 fatigue, delay all subsequent protocol-directed therapy for a maximum of three weeks until grade ≤ 2, then decrease paclitaxel by one dose level for the next cycle, and give carboplatin and ABT-888, at the same dose.
- If Induction (cycle 2) is delayed for more than three weeks for fatigue, proceed to chemoradiotherapy.

6.1.5 GI Toxicity During Induction

- For grade 2 mucositis, oral, decrease paclitaxel by one dose level for the next cycle, and give carboplatin and ABT-888 at the same dose.
- For grade 3 or 4 mucositis, oral, delay all subsequent protocol-directed therapy for a maximum of three weeks until grade ≤ 2, then decrease paclitaxel and carboplatin by one dose level for the next cycle, and give ABT-888 at the same dose.
- For grade 3 or 4 nausea or vomiting, delay all subsequent protocol-directed therapy for a maximum of three weeks until grade ≤ 2, then decrease carboplatin 1 dose level, and give paclitaxel and ABT-888 at the same dose.
- If Induction (cycle 2) is delayed for more than three weeks for mucositis, nausea, or vomiting, proceed to chemoradiotherapy.

6.1.6 Dose Modifications for Liver Function During Induction

- For grade 3 or 4 ALT, or AST, or alkaline phosphatase increase (CTCAE version 4.0, investigations section), delay all subsequent protocol-directed therapy for a maximum of three weeks until recovered until ALT, AST, and alkaline phosphatase improve to grade ≤ 2, then decrease paclitaxel and carbolatin by one dose level for the next cycle, and give the ABT-888 at the same dose.
- For grade > 1 blood bilirubin increase, delay all subsequent protocol-directed therapy for a maximum of three weeks until recovered until bilirubin level improved to grade ≤ 1, then decrease paclitaxel and carboplatin 1 dose level and give ABT-888 at the previous dose.
- If Induction (cycle 2) is delayed for more than three weeks for abnormal liver function tests, proceed to chemoradiotherapy.

6.1.7 Allergic Reactions

- For grade 4 allergic reactions, or anaphylaxis, stop the infusion(s). Manage the reaction according to institutional procedure. Discontinue all protocol therapy.

6.1.8 Other non-Hematologic Toxicity During Induction

- For grade 3 or 4 other non-hematologic toxicity considered at least possibly related to treatment, delay all subsequent protocol-directed therapy for a maximum of three weeks until recovered to grade ≤ 1, then decrease the suspected drug(s) by one dose level for the next cycle.
- If Induction (cycle 2) is delayed for more than three weeks, proceed to chemoradiotherapy.

6.2 Dose Modifications during Chemoradiotherapy, Option 1 (cisplatin) for phase I

6.2.1 Hematologic Toxicity During Chemoradiotherapy

- For grade 3 or 4 decrease in neutrophil count, delay cisplatin until ANC < grade 2, then give cisplatin at the planned dose (i.e., no dose reduction). If ANC does not improve to < grade 2 within 2 weeks, skip cisplatin. Continue radiotherapy.
- For febrile neutropenia grade 3 or 4, wait for resolution before proceeding, and decrease cisplatin to 75mg/m^2 for the next dose.
- For grade > 2 platelet count decrease; delay cisplatin until platelets improve to grade < 1, then give cisplatin at the planned dose (i.e., no dose reduction). If thrombocytopenia does not improve to < grade 1 within 2 weeks, skip cisplatin. Continue radiotherapy.
- For any grade platelet count decrease associated with bleeding, decrease cisplatin to 75mg/m^2 for the next dose.

6.2.2 GI Toxicity during Chemoradiotherapy

- For grade 3 or 4 nausea or vomiting during cisplatin, hold next cycle until grade 2 or less, then give next cycle cisplatin 75mg/m^2
- For grade 3 or 4 mucositis, continue cisplatin at same dose with no delays
- For grade 3 or 4 dysphagia, continue cisplatin at same dose with no delays

6.2.3 Skin Toxicity during Chemoradiotherapy

For all grades radiation dermatitis, do not change dosing and do not delay cisplatin.

6.2.3 Neurotoxicity during Chemoradiotherapy

- For grade 2 neurotoxicity decrease cisplatin to 75mg/m^2. Start/continue radiotherapy.
- For grade 3 or 4 neurotoxicity, discontinue cisplatin. Continue radiotherapy.

6.2.4 Ototoxicity

- For grade 2 hearing impairment or grade 2 tinnitus, decrease cisplatin to 50mg/m^2.
- For grade 3 hearing impairment or grade 3 tinnitus, discontinue cisplatin.
- For patients with hearing impairment, audiogram is encouraged.

6.2.5 Nephrotoxicity during Chemoradiotherapy

- For CRCL 40-50 mL/min, decrease cisplatin to 50 mg/m^2 for that dose only.
- For CRCL <40mL/min, discontinue cisplatin. Continue radiotherapy.

6.3 Dose modifications during Chemoradiotherapy, Option 2 (hydroxyurea/5FU/paclitaxel) for phase I

Dose levels for chemotherapy during chemoradiotherapy

	Hydroxyurea	5-FU	Paclitaxel
Dose Level			
0	**500 mg every 12 hr. x 11 doses**	**600 mg/m^2/day**	**100 mg/m^2**
–1	**500 mg every 24 hr. x 6 doses**	**500 mg/m^2/day**	**75mg/ m^2**

6.3.1 Hematologic toxicity

- For grade 3 neutrophil count decreased on days of treatment in any cycle, decrease hydroxyurea by one dose level for this and all subsequent cycles. Continue paclitaxel, 5-FU and radiotherapy at the planned doses.
- For grade 4 neutrophil count decrease on days of treatment in any cycle, skip hydroxyurea for this cycle, and decrease hydroxyurea by one dose level for all subsequent cycles. Continue paclitaxel, 5-FU, and radiotherapy at the planned doses.
- For grade 2 platelet count decrease on days of treatment in any cycle, decrease hydroxyurea by one dose level for this and all subsequent cycles. Continue paclitaxel, 5-FU and radiotherapy at the planned doses.
- For grade 3 or 4 platelet count decrease on days of treatment in any cycle, skip hydroxyurea for this cycle and decrease paclitaxel and 5-FU by one dose level for the remainder of this cycle. Decrease hydroxyurea by one dose level for all subsequent cycles. Continue radiotherapy at the planned dose.
- For > grade 2 neutrophil count decreased on any day of treatment with TFHX, administer filgrastim (or sargramostim per institutional procedures) SQ daily for 7 days, beginning at least 24 hours after the completion of 5-FU in this and all subsequent cycles.

6.3.2 GI Toxicity During Chemoradiotherapy

- For grade 4 mucositis, oral, lasting > 7 days or present on day 1 of any cycle, decrease 5-FU by one dose level for this and all subsequent cycles. Continue hydroxyurea, paclitaxel, and radiotherapy at the planned doses.
- For grade 4 diarrhea lasting > 7 days or present on day 1 of any cycle, decrease 5-FU by one dose level for this and all subsequent cycles. Continue hydroxyurea, paclitaxel, and radiotherapy at the planned doses.
- For grade 4 dysphagia lasting > 7 days or present on day 1 of any cycle, decrease 5-FU by one dose level for this and all subsequent cycles. Continue hydroxyurea, paclitaxel, and radiotherapy at the planned doses.

6.3.3 Skin Toxicity during Chemoradiotherapy

For grade 4 radiation dermatitis (CTCAE Injury, poisoning, and procedural complications) lasting > 7 days or present on day 1 of any cycle, decrease 5-FU by one dose level for this and all subsequent cycles. Continue hydroxyurea, paclitaxel, and radiotherapy at the planned doses.

6.3.4 Neurotoxicity during Chemoradiotherapy

- For grade 2 peripheral neuropathy during chemoradiotherapy, decrease paclitaxel by one dose level and do not delay treatment. If neuropathy improves to grade 1 or less, can return to original dose level. Continue hydroxyurea and 5-FU at same dose.
- For grade 3 or 4 peripheral neuropathy, discontinue paclitaxel. Continue hydroxyurea and 5FU at same dose.

6.3.5 Nephrotoxicity During Chemoradiotherapy

- For grade 2 nephrotoxicity, decrease hydroxyurea by one dose level for this cycle only. Do not change dose of paclitaxel or 5FU.
- For grade 3 or 4 nephrotoxicity, skip hydroxyurea for this cycle only. Do not change dose of paclitaxel or 5FU.

6.3.6 Dose Modifications for Liver Function during Chemoradiotherapy

For grade 3 or 4 ALT or AST or alkaline phosphatase increase (CTCAE version 4.0, Investigations section), skip hydroxyurea for this cycle only.

6.3.7 Other non-Hematologic Toxicity during Chemoradiotherapy

For grade 3 or 4 other non-hematologic toxicity considered at least possibly related to treatment, hold the suspected drug ONLY until toxicity improves to grade < 1, then add back and decrease the suspected drug(s) by one dose level for the next cycle. Do not make any changes in drugs that are not related to the toxicity, and do not delay any cycles due to toxicity.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform

presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information.

For protocols with CAEPRs not including a "SPEER" category, protocol-specific exceptions to the CTEP-AERS reporting table can be found in the CAEPR's "ASAEL" category instead. This protocol-specific exception is limited to Grade 1 and Grade 2 ASAEL events, *i.e.* Grade 3 through Grade 5 ASAEL-listed events are NOT exceptions to CTEP-AERS reporting.

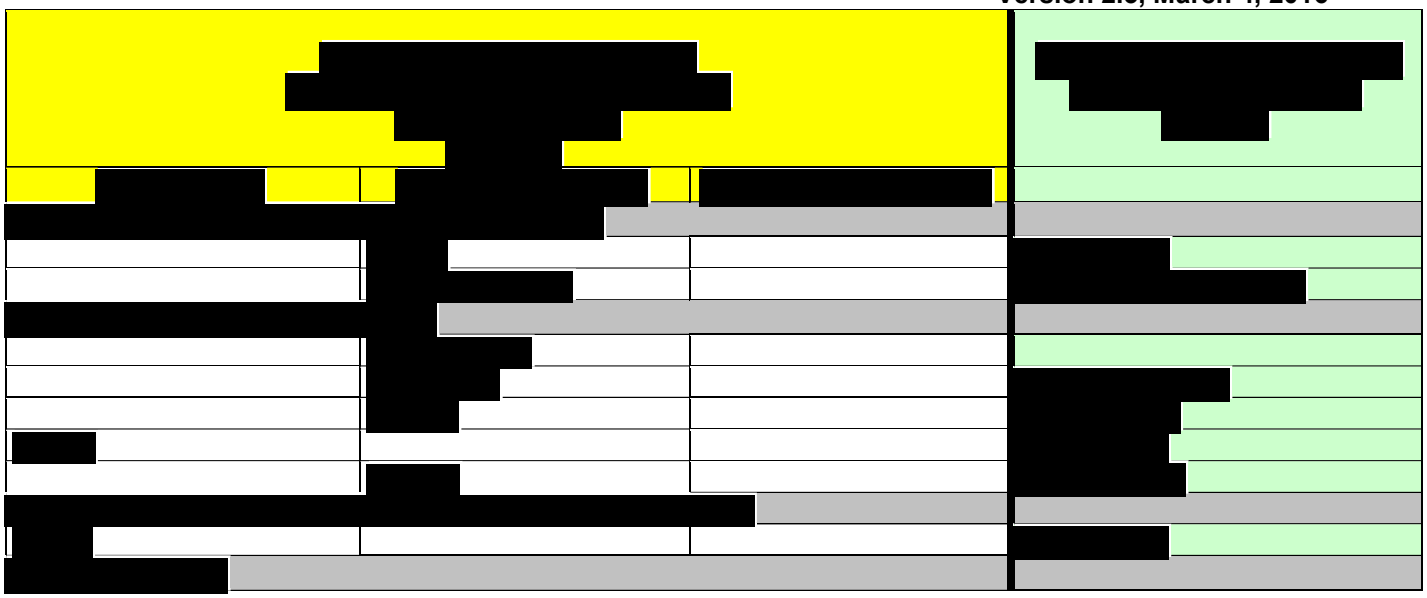
7.1.1 CAEPR for ABT-888

Comprehensive Adverse Events and Potential Risks list (CAEPR) For ABT-888 (Veliparib, 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]



[redacted]

[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.

[redacted]

7.1.2 Radiation

Radiation to the head and neck will cause skin irritation, dry mucous membranes due to salivary gland dysfunction, mucositis and stomatitis. The concomitant administration of chemotherapy will aggravate these side effects. Long-term side effects include myelitis, osteoradionecrosis, hoarseness, hypothyroidism, trismus, swallowing dysfunction, and fibrosis of soft tissues.

7.1.3 Radiation Adverse Events

Grade 3-4 therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations provided in Appendix VI), and cervical myelopathy (<1% with restriction of spinal cord dose to ≤ 45 Gy).

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for both routine and expedited AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For expedited reporting purposes only:

AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.3.3.

7.3 Expedited Adverse Event Reporting

Investigators are required by federal regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Investigational Drug Branch, the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. The descriptions and severity grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for reporting. All treatment areas should have access to a copy of the CTCAE version 4.0. It can be downloaded from the CTEP website (http://ctep.cancer.gov). Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table. Note that the additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supercede the table.

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3). In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Protocol Coordinator, Study Chair, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided. Use the

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

A091101: Expedited Reporting Requirements for Adverse Events that occur on studies under and IND within 30 Days of the last administration of the Investigational Agent/Intervention[1]

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	

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 treatment 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 that are at least possibly related to treatment

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization, and that are at least possibly related to treatment

Effective Date: May 5, 2011

Additional instructions or exclusions to CTEP-AERS expedited reporting requirements for Alliance A091101:

Treatment expected adverse events include those listed in Section 8.0 and in the package inserts for carboplatin, cisplatin, 5-FU, hydroxyurea, paclitaxel, and in the CAEPR for ABT-888. Note that in the CAEPR, the ASAEL has been replaced by the Specific Protocol Exceptions to Expedited Reporting (SPEER) list. The SPEER includes "expected" severity grades in addition to event terms. All of these expected adverse events do not require CTEP-AERS reporting

- Grade 3/4 hematosuppression and hospitalization from such do not require CTEP-AERS, but should be reported via routine data submission.
- Grade 3/4 nausea or vomiting from cisplatin or carboplatin, and hospitalization from such do not require CTEP-AERS, but should be reported via routine data submission.
- Grade 3/4 dysphagia during chemoradiotherapy, and hospitalization from such, do not require CTEP-AERS, but should be reported via routine data submission.
- Grade 3/4 dehydration or increased creatinine from cisplatin, and hospitalization from such, do not require CTEP-AERS, but should be reported via routine data submission.
- Grade 3/4 hypersensitivity reactions to carboplatin, cisplatin, or paclitaxel do not require CTEP-AERS, but should be reported via routine data reporting.
- Deaths due to progressive disease do not require CTEP-AERS, but should be reported via routine data submission.
- The reporting of adverse events via CTEP-AERS is in addition to routine data submission, for those events requiring expedited reporting.
- All new malignancies should be reported through CTEP-AERS independent of attribution to treatment. This includes solid tumors (including non-melanoma skin cancers), hematologic malignancies, MOS, AML, and in-situ tumors. In CTCAE, new malignancies (second and secondary) may be reported as one of the following: leukemia secondary to oncology chemotherapy, myelodysplastic syndrome, treatment-related secondary malignancy, or neoplasm other, malignant (grade 3 or 4). Whenever possible, CTEP-AERS reports for new malignancies should include tumor pathology, history of prior tumors, prior treatment/ current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how it was detected, molecular characterization or cytogenetics of the original and new malignancy (if available), and treatment and outcome of the new malignancy, if available.
- All pregnancies and suspected pregnancies occurring in female patients during therapy or within 28 days after completion of therapy should be reported via CTEP-AERS. In CTCAE, pregnancy or suspected pregnancy should be reported as pregnancy, puerperium and perinatal conditions-other: fetal exposure (grade 4).

7.4 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

8.0 PHARMACEUTICAL INFORMATION

8.1 CTEP IND Agent ABT-888 (NSC 737664; IND #77840; veliparib)

Availability

Clinical Supplies: ABT-888 (veliparib, NSC 737664/ IND 77840) and matching Placebo will be provided free of charge by AbbVie and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Phase I Open-label drug orders: No open-label starter supplies will be available for this study. Patient-specific supplies will be sent to the registering investigator at the time of registration and should arrive within 7 to 10 days. Once a patient has been registered, the Alliance Registration/Randomization Office will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the Alliance Registration/Randomization Office the day the patient is registered 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 Ground (up to 5 business days). Shipments to United States sites can be expedited by the provision of an express courier account name and number to the Alliance Registration/Randomization Office at the time the patient is registered/randomized.

Initial supplies for patients registered to All Dose Levels
The request will be for 64 capsule bottles of 50 mg ABT-888, a 2-cycle / 6-week supply at the prescribed dose level given orally BID on days 1 through 7 of each cycle. This supply will be sufficient for the patient to complete the prescribed maximum of two cycles of induction with ABT-888.

Dose Cohort	ABT-888 (veliparib) Dose	Supplies provided (50 mg capsules x 64 capsules/bottles)
-3	50 mg BID x 7 days	1 bottle
-2	100 mg BID x 7 days	2 bottles
-1	150 mg BID x 7 days	2 bottles
*0B	200 mg BID x 7 days	3 bottles
1	250 mg BID x 7 days	3 bottles
2	300 mg BID x 7 days	4 bottles
3	350 mg BID x 7 days	4 bottles

*starting dose level

Note: In order to dispense a single cycle at a time, ABT-888/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).

Note: Partial bottles of patient specific supplies remaining after completion of treatment should be destroyed on-site per institutional policy and be recorded on the patient specific accountability log.

Phase II Blinded drug orders: Once the Phase II dose has been determined, a protocol amendment will be completed to incorporate appropriate ordering instructions.

ABT-888 (veliparib) and matching Placebo will be supplied in bottles containing either 64 – 50 mg capsules ABT-888 (veliparib) or 64 – 0 mg capsules [Placebo for 50 mg ABT-888 (veliparib)] with a child-resistant cap and a tamper-evident seal. Each blinded, patient-specific bottle will be labeled with …

- the protocol number (i.e., "A091101")
- 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.,"9999999", where "9999999" represents the unique patient identifier assigned at registration)
- the patient initials (i.e., first initial, last initial [e.g., "FML"])
- the agent identification [i.e., "ABT-888 (veliparib) 50 mg or Placebo"]
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take __ capsules twice daily.")
- 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. The Julian date should be recorded in the Lot No. field on the drug accountability record (DARF). 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 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., "9999999"') and the patient initials (e.g.,

"FML") 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., "A091101").

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., "9999999") and the patient initials (e.g., "FML") should be entered in the "Lot Number" field. Opened bottles with remaining capsules should be documented in the patient-specific NCI ORAL Investigational Agent Accountability Record (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 ORAL NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575. A separate NCI ORAL Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "9999999") on this protocol (Phase I and Phase II).

Emergency Unblinding Procedures (Phase II only): Unblinding can be done only in cases of an emergency. Follow the directions below to unblind patient treatment. Please note that, if a treatment assignment is unblinded, the patient must discontinue protocol therapy. Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Office on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:
• Alliance study ID (i.e., "A091101")
• Alliance patient ID number (e.g., "9999999")
• Patient initials (e.g., "L,FM")
• Institution name
• Name and telephone number of treating physician
• Name and contact information of person requesting the unblinding procedure
• Name and contact information of person to inform of treatment assignment
• Reason for emergency unblinding
Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation. After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

[redacted]

Administration: ABT-888 is administered orally. It may be taken without regard to meals.

Potential Drug Interactions: Clinical studies evaluating the metabolism of ABT-888 have not been conducted. However, results from the in vitro analysis reveal that this agent is metabolized by multiple isoenzymes – CYP1A1, 2D6, 2C19 and 3A4. ABT-888 is neither a potent inhibitor nor a potent inducer of the CYP-450 isoenzymes. Use caution when concomitantly administered with drugs that are substrate, inhibitor, inducer of CYP1A1, 2D6, 2C19 and 3A4. ABT-888 clears primarily in the urine as intact parent drug along with metabolites suggesting that renal function plays an important role in the drug clearance and its metabolites.

[redacted]

8.2 Commercial Agents

8.2.1 Carboplatin

Please refer to the package insert for full prescribing information.

Availability: Carboplatin is commercially available as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of carboplatin will be used for this study. Carboplatin is also available as an aqueous solution in 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL and 600 mg/60 mL multidose vials.

Preparation: Reconstitute lyophilized powder with Sterile Water, 0.9% Sodium Chloride, or 5% Dextrose Injection with volumes of diluents specified below. The reconstituted solution can be further diluted to a concentration as low as 0.5 mg/mL with 0.9% Normal Saline or 5% Dextrose Injection.

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

Storage and Stability: When prepared as directed, the resultant carboplatin solutions, when protected from light, are stable for 8 hours at room temperature. No antibacterial preservative is contained in the formulation, and therefore, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

NOTE: Aluminum reacts with carboplatin, causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature (59 - 86°F) and protected from light. When prepared,

carboplatin solutions are stable for 8 hours at room temperature. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25º C following multiple needle entries.

8.2.2 Cisplatin

Formulation: Cisplatin is a sterile aqueous solution, each mL containing 1 mg cisplatin and 9 mg sodium chloride. Cisplatin is supplied in multidose vials of 50 mg and 100 mg cisplatin.

NOTE: Aluminum reacts with cisplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

Storage and Stability: Storage Store intact vials at room temperature 15°C to 25°C (59°F to 77°F) and protect from light. Do not refrigerate solution as a precipitate may form. Further dilution stability is dependent on the chloride ion concentration and should be mixed in solutions of NS (at least 0.3% NaCl). After initial entry into the vial, solution is stable for 28 days protected from light or for at least 7 days under fluorescent room light at room temperature.

Adverse effects: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, ocular toxicity, and allergic reactions. Infrequent: cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia, and acute myeloid leukemia.

NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

Severe renal toxicity can largely be avoided by induction of a diuresis before, during and after treatment. Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy according to protocol specifications.

Refer to package insert for complete details.

Availability: Cisplatin is commercially available from Bristol Laboratories Oncology Products.

8.2.3 Fluorouracil

5-Fluorouracil (Adria, OH): commercially available as 10 ml ampules containing 500 mg/10 ml. No dilution is necessary for administration, but it may be further diluted in D5W or normal saline. It is stored at room temperature and is stable for 24 hours. It will be administered by intravenous continuous infusion. Please refer to the package insert for full prescribing information.

8.2.4 Paclitaxel

Paclitaxel: Please refer to the package insert for information on preparation and for full prescribing information.

Drug interactions: There is a potential for interaction with Ketoconazole, which might interfere with paclitaxel metabolism. Contraindications: Known hypersensitivity to either paclitaxel or Cremaphor EL.

8.2.5 Hydroxyurea

Hydroxyurea (Bristol-Myers Squibb, Princeton, NY): commercially available as 500 mg capsules. It is stored at room temperature and will be administered orally. Please refer to

the package insert for solution preparation and expected AE. Please refer to the package insert for full prescribing information.

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.

Geriatric Use: Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

9.0 CORRELATIVE SCIENCE COMPANION STUDY

Description of correlative science sample collection, analysis, and statistical consideration to be added after the completion of the Phase I portion of the study.

10.0 STUDY CALENDAR

Baseline evaluations are to be conducted ≤4 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Treatment	**Treatment**		**Clinical Follow-Up**			
Item	**Pre-therapy**	**Induction chemo-therapy (Wks 1-6)***	**CRT****	**2 wks after CRT**	**1 month after CRT**	**3 mos after CRT**	**Clinical Follow-up*****
History and physical	X	X	X	X	X	X	X
ENT/Surgeon's evaluation[1]	X				X	X	X
Tumor map	X						
Dental assessment	X			X	X		
Barium swallowing assessment[2]	X					X	X
Patient Medication Calendar`		X					
Performance status	X	X	X	X	X	X	X
Concomitant meds assessment[3]	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X
Imaging[4]	A	B				X	X
CBC, diff, platelets	X	weekly	X	X	X	X	X
Electrolytes (Na, K, Cl, bicarb)	X	weekly	X	X	X	X	X
Mg, Ca, Phosphorous	X	weekly	X	X	X	X	C
AST, ALT, Alk. Phos. bili	X	weekly	X	X	X	X	X
Albumin, total protein	X	weekly	X	X	X	X	X
Serum Creatinine	X	weekly	X	X	X	X	X
Creatinine Clearance[5]	X	X					
BUN	X	weekly	X	X	X	X	X
Glucose	X	weekly	X	X	X	X	
TSH, uric acid, PT/INR	As clinically indicated						
mvHPV status in Oropharyngeal tumors	X						
ECG	X						
Pregnancy test	X						
Biopsy	X	As clinically indicated					

* At the beginning of each cycle, unless otherwise noted

** Concurrent CRT therapy is to begin within 10 days following the end of induction therapy. Tests and evaluations are to be done prior to beginning CRT, then weekly.

*** 6, 12, 18, 24, 30, 36, 48, and 60 months following the end of CRT. Patients who progress will move to the Survival Only Follow-up Phase and be followed every 6 months through year 5.

1. An examination by an ENT or Head & Neck Surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure).

2. Barium swallowing assessments should be performed pre-treatment and in Months 10, 16, and 25 from the completion of chemoradiotherapy and as otherwise indicated.

3. Document use of concomitant medications in physician or nursing note.

4. The same imaging method should be used throughout the study.

5. Can be calculated using Cockcroft-Gault formula. Recalculate if creatinine or weight change > 30%. In cases of low Creatinine Clearance or clinic disparities obtain 24-hour urine for CrCl calculation.

6. PT (INR) evaluation will be included at pre-therapy only unless otherwise indicated.

A Pre-therapy imaging **options per physician preference:** a) CT scan of the neck (with contrast) and a chest CT scan (with or without contrast); b) or an MRI of the neck and a chest CT scan (with or without contrast); c) or a CT scan of neck (with contrast) and a PET/CT of neck and chest (with or without contrast) within 4 weeks prior to registration.

B **During the last week of induction chemotherapy (week 6), patients will undergo primary endpoint image assessment. The same evaluation method as pre-treatment imaging must be used.**

C Only calcium and not magnesium and phosphorous need be measured during clinical follow-up.

11.0 TREATMENT EVALUATION USING RECIST GUIDELINE

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.4.4, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[52]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

In order not to delay the start of concurrent CRT, patients should be reevaluated prior to concomitant CRT (during the last week of induction chemotherapy), where the response to induction chemotherapy will be assessed and measured (primary endpoint). The same imaging evaluation method that was used pre-treatment should also be used for imaging during the last week of induction chemotherapy.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

• A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.
• A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
• A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.2.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

• All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
• The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
• Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease:

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, 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 be performed with breath-hold scanning techniques, if possible.

PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.

Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET

scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

c. After concurrent chemoradiotherapy, FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. This post-treatment FDG-PET should be performed within 8-12 weeks after completion of concurrent chemoradiotherapy. The use of FDG-PET in this circumstance has been described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

11.4 Measurement of Effect

11.4.1 Target Lesions & Target Lymph Nodes

• Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.
Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
• Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
• Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
• Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even

if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 11.4.3.

11.4.3 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Evaluation of Target Lesions

Complete Response (CR): All of the following must be true:

a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.4.1).

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR):All of the following must be true:

a. Disappearance of all non-target lesions.

b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.4.3

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the NCCTG protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.4.5 Symptomatic Deterioration

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

as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

Worsening of tumor-related symptoms.

Decline in performance status of >1 level on ECOG scale.

11.5 Formal statistical definitions

Formal statistical definitions of analysis variables involving response and disease progression are contained in **Section 13.0**.

12.0 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Data Submission

This study will use Medidata Rave® for remote data capture (RDC) of all study data. The Rave system can be accessed through the iMedidata portal at https://login.imedidata.com. For additional information regarding account setup or training, please visit the training section of the Alliance website.

Common Terminology Criteria for Adverse Events: This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and adverse event reporting.

12.2 Collaborative Agreements Language

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(s) in this study:

1. Agent(s) may not be used for any purpose 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 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 prior 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 that 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 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.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available 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 Collaborator(s) for Phase 3 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 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:

Email: ncicteppubs@mail.nih.gov

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

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Phase 1

The maximum tolerated dose (MTD) will be determined in the Phase I portion of this trial. Patients will be placed in one of the dose cohorts of ABT-888 listed in Section 5.1.1, using a conventional 3+3 design. All patients will receive concomitant paclitaxel and carboplatin. The initial dose cohort is anticipated to be 30 mg BID (Abbott Personal Communication) and, together with doses for subsequent cohorts will be adjusted at the time of protocol initiation based on available data from other phase I studies in discussion with Abbott Pharmaceuticals and NCI. The Alliance will notify CTEP when the Recommended Phase II Dose (RP2D) is reached, and an amendment will be submitted to open the phase II portion of the study.

13.1.2 Randomized Phase 2

The primary endpoint will be the relative change in tumor size following 2 cycles of induction, rather than a dichotomous objective response rate.[50,51] This trial design is based on the ratio of tumor size measurements (post-treatment/baseline) which has been shown to follow the log-normal distribution; a two-sample *t*-test is then commonly used to compare the log-ratios between treatment arms. Tumor size will be measured using the RECIST criteria (i.e. the sum of the longest diameters of all target lesions will be used). The advantage of using continuous tumor size change is the reduction in sample size relative to a two-arm design with a dichotomous endpoint, which can be 44%-64% under several scenarios considered by Lavin. Furthermore, a single-arm trial will not be appropriate due to the lack of reliable historical data.

Formulated in terms of "good response" rate following induction chemotherapy (defined as $\geq$ 50% reduction in the sum of target lesions), detecting a difference between 20% vs. 40% "good response" rates would be of interest. This difference in proportions corresponds to a difference in log-ratios of -1.091 versus -1.453. Based on the tumor size changes among patients enrolled on the carboplatin-paclitaxel induction regimen in UC protocol 13362B [*A Phase III Randomized Trial of Docetaxel Based Induction Chemotherapy in Patients with N2/N3 Locally Advanced Head and Neck Cancer*], the standard deviation (SD) of the log-ratios of tumor size change was SD=0.616, and the log-normality assumption was satisfied. Because a CR rate of 5-10% is expected based on prior trials with induction chemotherapy at the University of Chicago, the use of a *t*-test would be problematic, given that the log-ratio will be undefined for CR's. Instead, patients with CR will be assigned the lowest rank (lower rank corresponds to better outcome), and treatment arms will be compared using the nonparametric Wilcoxon rank-sum test. Similarly, patients who die during treatment will be assigned the highest rank (corresponding to the worst outcome).

An interim analysis for futility will be performed when half of the patients have completed induction. The trial will be stopped early if the sum of ranks is lower than expected in the placebo arm and the Wilcoxon rank-sum test statistic is $Z<0$, i.e. when the interim analysis does not favor the treatment group.

A simulation study was performed to determine the sample size. Data were generated from a mixture distribution where the outcome was CR with probability p_j, not evaluable (drop-

out or death) with probability d_j, and lognormally distributed with probability (1 - p_j - d_j); j=1,2 denotes placebo and ABT-888 arms, respectively. An early stopping rule was incorporated. The following scenario was considered: CR rates p_1=0.05 and p_2=0.10; drop-our rates d_1=0.10 and d_2=0.07 (assuming fewer deaths in the ABT-888 arm); tumor size log-ratios distributed with $\mu_1 = -1.091$, $\mu_2 = -1.091$ and $\sigma_1 = \sigma_2 = 0.616$ (as described above). Based on R=10,000 simulations, the sample size of 46 patients/arm (92 total) will have 81% power with one-sided α=0.05. Note that the sample size is almost 45% less than 64 patients/arm that would be required for a randomized two-arm trial comparing response rates.

13.2 Sample Size/Accrual Rate

We plan to enroll 18 patients in the Phase 1 portion of the study at an accrual rate of 1 to 4 patients per month. In the Phase 2 portion we plan to enroll 92 patients, at an accrual rate of 5 to 10 patients per month. Study accrual will be monitored and an accrual plan will be instituted if deemed necessary.

TARGETED/PLANNED ENROLLMENT - NUMBER OF SUBJECTS				
Hispanic or Latino Category		Phase I/II Trial – total anticipated sample size is up to 110 subjects (up to 18 subjects to be enrolled in the Phase I portion and 46 patients per induction chemotherapy treatment arm).		
		Sex		
		Female	**Male**	**Total**
Hispanic or Latino		3	7	10
Not Hispanic or Latino		20	80	100
Ethnic Category: Total of All Subjects		**23**	**87**	**110**
Racial Categories				
Others and Mixed		1	2	3
Asian		2	3	5
Black or AA		8	22	30
White or Caucasian		12	60	72
Ethnic Categories: Total of All Subjects		**23**	**87**	**110**

13.3 Stratification Factors

13.3.1 Phase II:

In the Phase II part of this trial, patients will be randomized in a double-blinded fashion to induction therapy with carboplatin and paclitaxel plus ABT-888 or placebo; and the patient's subsequent therapy will be determined by institution guidelines between two options of concurrent chemoradiotherapy options. Randomization will be stratified by tumor/nodal status (T1-3 and N0-N2a versus T4 and/or N2b-N3 respectively), oropharyngeal disease/HPV status (non-oropharyngeal disease versus oropharyngeal disease with HPV positive status versus oropharyngeal disease with HPV negative status) and institution (implicitly stratifies by concomitant CRT, as it is planned that concomitant CRT will be an institution level choice) and permuted blocks will be used to balance patient allocation.

13.4 Analysis of Secondary Endpoints

Secondary endpoints include evaluation and comparison of toxicity rates during induction and overall; time-to-event endpoints [progression-free survival (PFS), disease-free survival (DFS),

time to local or distant progression, disease-specific survival (DSS), and overall survival (OS)]. Toxicity rates will be summarized by group, and compared between groups using the chi-squared or Fisher's exact test. Time-to-event endpoints (PFS, DFS and OS) will be summarized using the method of Kaplan-Meier, and compared between groups using the log-rank test. Multivariate Cox proportional hazards regression models will be used to further explore group differences adjusting for other prognostic factors, as well as to estimate hazard ratios. Cause-specific survival will be summarized using cumulative incidence, and will be compared between groups using Gray's test. Other methods appropriate for the analysis of competing risks data (e.g. Fine-Gray regression models) may also be used.

13.5 Reporting and Exclusions

13.5.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with ABT-888.

13.5.2 Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. The 95% confidence interval will also be provided. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported

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APPENDIX A- PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B - HEAD & NECK STAGING

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PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*

LIP and ORAL CAVITY

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease*
	(lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
	(oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b	Very advanced disease
	Tumor invades masticator space, pterygoid plates or skull base and/or encases internal carotid artery

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

NASAL CAVITY and PARANASAL SINUSES Maxillary Sinus

T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease
	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Very advanced local disease
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx or clivus

Nasal Cavity and Ethmoid Sinus

T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, or clivus

<u>PHARYNX</u> Nasopharynx

T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity with out parapharyngeal extension*
T2	Tumor with parapharyngeal extension*
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.

Oropharynx

T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

*Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

Hypopharynx

T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without

	fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a	Moderately advanced local disease
	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.*
T4b	Very advanced local disease
	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

LARYNX

Supraglottis

T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease
	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease
	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1	Tumor limited to the vocal cord(s) [may involve anterior or posterior commissure] with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation, and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease
	Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease

Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Subglottis

T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease
	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease
	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

REGIONAL LYMPH NODES (N) Excluding Nasopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastases in a lymph node, more than 6 cm in greatest dimension

REGIONAL LYMPH NODES (N) Nasopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING, Excluding Nasopharynx		**STAGE GROUPING Nasopharynx**	
Stage 0	Tis, N0, M0	Stage 0	T*is*, N0, M0
Stage I	T1, N0, M0	Stage I	T1, N0, M0
Stage II	T2, N0, M0	Stage II	T2, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0		
Stage IVA	T4a, N0-1, M0 Any T, N2, M0		
Stage IVB	T4b, Any N, MO Any T, N3, M0		
Stage III	T1-T3, N1, M0 T3, N0, M0		
Stage IVA	T4a, N0-2, M0 T1-3, N2, MO		
Stage IVB	Any T, N3, M0 T4b, Any N, M0		
Stage IVC	Any T, Any N, M1	Stage IVC	Any T, Any N, M1

APPENDIX C - ABT-888 PATIENT MEDICATION CALENDAR

Pill Calendar for ABT-888:
Carboplatin-Paclitaxel Induction chemotherapy and ABT-888 (Veliparib) – a Phase 1/Randomized Phase 2 Study in Patients with Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck

Number of Pills Given:_____ Pill Bottle(s) returned: Circle Yes or No
Total Daily Dose:_____
Number of Pills returned:_____
(To be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS

1. ABT-888 should be taken orally, twice a day, on days 1 through 7 of each induction chemotherapy cycle

CYCLE #: _____

DAY	Medication	DATE	TIME/notes					# of pills/mg taken
Example	ABT-888	*07/01/2012*	*9:00*	*AM*	*9:00*	*PM*		
1	ABT-888							
2	ABT-888							
3	ABT-888							
4	ABT-888							
5	ABT-888							
6	ABT-888							
7	ABT-888							
8								
9								
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18								
19								
20								
21								

Patient Signature: _____Date:_____

Consenting Professional/Research RN Signature: _____Date:_____

Comments:_____