University of Pennsylvania

Feasibility and A Stratified Phase II trial of Proton Beam Radiotherapy with Concurrent Chemotherapy and Nelfinavir for Inoperable Stage III NSCLC followed by subsequent Feasibility Confirmation with Nelfinavir

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List of Abbreviations

AUC	Area under the curve
bid	Twice a Day
CGE	Cobalt Gray Equivalent
CR	Complete Response
CT	Computed tomography
CTC	Common Terminology Criteria
CTRT	Chemotherapy-Sensitized Radiation Therapy
CTV	Clinical Target Volume
DIBH	Deep Inspiration Breath Hold
EBRT	External beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
FDG-PET	Fludeoxyglucose-Positron Emission Tomography
GTV	Gross Tumor Volume
Gy	Gray
ITV/iCTV	Internal Target Volume / Imaging Clinical Target Volume
LET	Linear Energy Transfer
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dosage
NSCLC	non-small cell lung cancer
OAR	Organ at risk
OER	Oxygen Enhancement Ratio
PD	Progressive Disease
PO	By Mouth, Orally
PR	Partial Response
PTV	Planning Target Volume
RBE	Relative Biologic Effectiveness
RC	Range Compensator
RPTD	Recommended Phase II Dose
RTOG	Radiation Therapy Oncology Group
PBSTV	Pencil Beam Scanning Target Volume
SD	Stable Disease
SOBP	Spread Out Bragg Peak
SWOG	Southwest Oncology Group

Study Summary

Title	Feasibility and Stratified Phase II trial of Proton Beam Radiotherapy with Concurrent Chemotherapy and Nelfinavir for Inoperable Stage III NSCLC followed by subsequent Feasibility Confirmation with Nelfinavir
Short Title	Stratified Phase II of Proton Radiotherapy with Concurrent Chemotherapy for Stage III NSCLC
Protocol Number	UPCC# 01510; IRB # 811186 IDS # 03771
Phase	Feasibility and Phase II
Methodology	Open
Study Duration	6.5 years
Study Center(s)	University of Pennsylvania
Objectives	Primary Objectives Feasibility Study: 1. To establish the feasibility and safety of proton beam radiotherapy with cisplatin/etoposide for stage III NSCLC. 2. To establish the feasibility and safety of proton beam radiotherapy with carboplatin/paclitaxel for stage III NSCLC. Phase II: 1. To determine the rates of acute esophagitis toxicity in strata defined by chemotherapy regimen and proton beam. Nelfinavir Feasibility Study: 1. To establish the feasibility of the treatment regiment with the addition of standard dose of Nelfinavir. Secondary Objectives 1. Investigate biomarker, as they become available. 2. To determine clinical efficacy, as defined by metabolic response, sites of recurrence (e.g., local, regional, distant) and progression-free and overall survival.
Number of Subjects	130 subjects
Diagnosis and Main Inclusion Criteria	Stage III NSCLC

Introduction

1.1   Background

Disease Background
Lung cancer remains the leading cause of cancer death in the United States[1], approximately 75- 80% of all cases are non-small cell lung cancer (NSCLC). Of these, 30-40% are considered locally advanced comprising both Stage IIIA and IIIB in the current AJCC staging system. Using cancer incidence data from 2009, we can predict that there will be approximately 219,440 cases of lung cancer this year, therefore between 50,000 and 60,000 patients will be diagnosed with locally-advanced NSCLC[1].

Rationale for Proposed Therapeutic Study
RTOG 7301 established 60Gy in 30 daily fractions as the standard of care for locally advanced inoperable NSCLC.[2] It has since been shown that combined modality therapy with platinum-based induction chemotherapy followed by definitive radiotherapy in unresectable Stage III and medically inoperable stage II NSCLC results in a statistically significant improvement in overall survival. The Cancer and Leukemia Group B (CALGB) showed in a Phase III trial that median survival was improved with induction chemotherapy followed by conventional RT than RT alone (13.7 vs. 9.6 mos).[3] The RTOG duplicated these results in a separate phase III trial clearly establishing the combined modality as the standard of care in the management of locally advanced inoperable NSCLC.[4] [4-8]

Optimizing Combined Modality Therapy
The EORTC performed a phase III randomized trial comparing concurrent cisplatin based chemoradiation to radiotherapy alone and demonstrated a clear survival benefit to this approach.[5] Of note, there was no difference in rate of distant metastases and therefore the authors concluded that the benefit in overall survival was due to an improvement in local control secondary to enhanced radiosensitization of the tumor by cisplatin. Additionally, initial phase II trials suggested that concurrent chemoradiotherapy may be an even more effective treatment than sequential chemoradiotherapy.[9] Therefore, Furuse et al. performed a phase III randomized trial comparing concurrent chemoradiotherapy to sequential chemoradiotherapy. They demonstrated a statistically significant survival advantage to the concurrent approach (median survival of 16.5 months vs 13.3 months).[10] The RTOG 9410 study compared two different concurrent regimens (cisplatin and vinblastine with conventional radiotherapy or cisplatin and oral etoposide with hyperfractionated radiotherapy) with a sequential regimen of cisplatin followed by conventional radiotherapy. Again, median survival times improved (17 vs. 14.6 mos) with an increase in acute toxicities. (RTOG 9410 abstract) A third and smaller randomized trial did not show a significant survival advantage, however there was a significant improvement of 2-year survival with concurrent over sequential chemoradiation (35 vs. 24%).[11]

In an attempt to resolve this controversy, a meta-analysis was recently performed by Auperin and colleagues that analyzed individual patient data of 1104 patients enrolled in randomized clinical trials. With a median follow-up of 5 years, they found a statistically significant absolute survival benefit of 6.6% at 3 years (24.8% vs 18.2%). The HR for death with concurrent chemoradiation was 0.83 (p=0.0026). Concurrent chemoradiotherapy decreased loco-regional progression (HR=0.76; p= 0.011). There was no difference in distant progression between concurrent and sequential chemoradiation. The authors therefore concluded that it was due to a decrease in loco-regional progression that was driving the survival benefit observed in these patients.[12] This survival advantage is not unaccompanied by an increase in toxicity, especially acute esophagitis.

The optimal chemotherapeutic platform for concurrent therapy
At present the optimal chemotherapeutic platform for concurrent chemoradiotherapy remains to be determined. In the absence of randomized data, the best survival to date in stage III NSCLC comes from the SWOG 9504 trial, which investigated the role of consolidative chemotherapy after concurrent chemoradiotherapy with cisplatin and etoposide in the phase II setting. Gandara and colleagues demonstrated a promising overall survival of 26 months in stage III patients treated with this approach and a 3-year survival of 37%.[13] This remains the best available data to date for concurrent chemoradiotherapy. The value of consolidative chemotherapy was subsequently tested in a phase III trial performed by

Hanna and colleagues in the Hoosier Oncology Group. The median survival time was no different between the two arms with 21.6 months in the consolidation arm vs. 24.2 months in the observation arm (p=0.94).There was also a significant increase in toxicity, with a 5.5% death rate attributable to docetaxel and 28.8% of hospitalized rate during docetaxel administration, as opposed to only a 8.1% hospitalization rate of patients in the observation arm. [14] The authors concluded that consolidation chemotherapy does not improve overall survival. This suggests that more perhaps is not always better and that before more aggressive therapies, particularly escalation of radiation dose toxicity reduction is critical in order to improve the therapeutic ratio.

The cisplatin-based regimens used in the previously cited randomized trials are less commonly employed in primary chemoradiation therapy regimens today. This is because of the added toxicity associated with these regimens allows for this to be employed with the 'fittest' stage III patients. Another common platform for concurrent treatment is carboplatin and paclitaxel with extensive data from phase II studies.[15-17] This regimen was perceived to be more effective and less toxic than the older regimens. Unfortunately, in the only phase III study to date evaluating carboplatin and paclitaxel with radiation, the median survival time was only 11.4 months. In addition, the toxicity profile appears no safer as the reported grade 3/4 esophagitis and pneumonitis rates are 26-46% and 17-22%, respectively, when carboplatin/paclitaxel therapy is used concurrently with RT. Nevertheless, phase II studies from the RTOG (0117), CALGB (Arm 1 of 30105), and North Carolina University groups are showing encouraging median survival times of approximately 24 months using these agents concurrently with 74 GY(RBE).[25-27] Since weekly administration of carboplatin and paclitaxel was given concurrently with thoracic irradiation in above studies, we will utilize these agents for patients who are not candidates for cisplatin based chemotherapy in the same fashion for this Phase I trial.

Promises and technical challenges of dose escalation for improving survival of NSCLC

Evidence suggests that there is a direct relationship between escalation of radiation dose and tumor control. Perez et al. analyzed the patterns of failure in patients with unresectable NSCLC treated with definitive radiotherapy. The failure rate within the irradiated volume decreased from 53 to 58% at 40 Gy to 35% at 60 GY(RBE)GY(RBE)[2]. Consequently, dose escalation has been investigated as a method to improve overall survival in patients with NSCLC. Recent evidence suggests that for small tumors, dose escalation can significantly improve tumor control[18-20], and there is data to suggest that a subset of patients with large-volume locally advanced tumors may also potentially reap a survival benefit from escalation of dose[21-23]. However, there are fundamental limitations to dose escalation using X-ray beam (photon)

radiation. Due to the physical characteristics of the beam, X-rays deposit dose from the point of entry into the patient until the point of exit (Figure 1). This means that all normal tissue that lies proximal or distal to the tumor will receive dose when being treated with X-rays. Although technological advances have allowed for improved delivery of X-rays to the target, the aforementioned physical characteristics of the X-ray beam have generally impeded the ability to safely escalate the dose of radiation for the majority of NSCLC patients with larger tumors and/or locally advanced disease[22,24-26]. Consequently, these patients have largely been excluded from studies examining radiation dose escalation or included but escalated to an attenuated dose [27-30]. This is primarily due to the exquisite sensitivity of lung tissue to radiation. Even moderate doses of radiation will render uninvolved lung tissue inflamed (pneumonitis) or functionally incompetent (fibrosis) within months after treatment[31,32]. As a result, despite evidence supporting the effectiveness of radiation dose escalation, it is difficult to deliver high doses of radiation to patients with locally advanced NSCLC without damaging a sufficient volume of healthy lung that could render the patient a

Figure 1: Dose deposition profile of various energies of photon (X-ray) beam radiotherapy when treating a hypothetical patient with a tumor. Note that dose deposition continues from point of entry until exit from the patient.

pulmonary cripple. Thus, it remains possible that any benefit of dose escalation with X-ray beam radiotherapy for patients with locally advanced NSCLC is offset by concurrent toxicity.
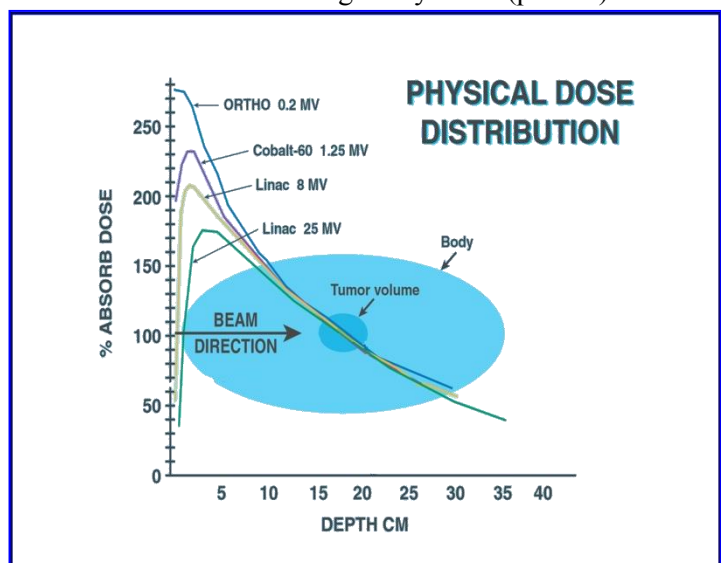
Dose Escalation in Combined Modality Therapy

The emergence of concurrent chemoradiation as the standard treatment approach for patients with locally advanced NSCLC has called into question the need for additional escalation of radiation dose beyond 60Gy, given the very real concerns of excessive toxicity to the patient. However, local control in NSCLC still remains poor. Le Chevalier observed that the 1-year local control rate was only 15% for patients with unresectable NSCLC treated to 65 GY(RBE).[33] A relationship has been shown between local failure and the subsequent appearance of distant metastases.[34] Furthermore, improved local control has been shown to result in a significant improvement in overall survival.[35] In the CHART trial, hyperfractionated radiotherapy resulted in improved local control and survival.[36] A similar correlation between improved local control and survival was seen in the EORTC study comparing concurrent chemoradiation versus radiation alone for locally advanced NSCLC. 2-year local control improved from 19% to 31% with the addition of concurrent daily cisplatin. 2-year overall survival increased from 13% to 26% in the concurrent daily cisplatin arm. Of note, there was no difference in the rate of distant metastases between the chemoradiotherapy and the radiotherapy alone arms in this trial, leading the authors to conclude that it was an improvement in local control that drove the improvement in overall survival observed in this study.[5]

he 60 GY(RBE) dose level was established in the pre-computed tomography era, and therefore its relevance to current modern radiotherapy planning and treatment delivery techniques can be questioned.[2] Rosenman and co-workers reported the results of a single institution phase I dose escalation study with concurrent chemoradiation with a stepwise escalation of dose from 60 to 74GY(RBE) without significant toxicity.[37] The median survival of 24 months and 5-year survival of 25% in this study were provocative, however single-institution data must be interpreted with caution. More recently, Socinski and co-workers reported the results of CALGB 30105, a multi-institutional randomized phase II trial of induction chemotherapy followed by concurrent chemoradiotherapy. Patients with stage IIIA/B NSCLC were randomly assigned to induction chemotherapy with either carboplatin/paclitaxel or carboplatin/gemcitabine. Patients randomized to arm A received weekly carboplatin/paclitaxel while patients treated on arm B received biweekly gemcitabine concurrently with

74 Gy utilizing three-dimensional treatment planning. The primary endpoint was a median survival of at least 18 months. Arm B was closed due to excessive pulmonary toxicity, however arm A met its primary endpoint with an estimated median survival of 24.3 months.[38] These promising results support the need for a multi-institutional randomized phase III study comparing high dose concurrent chemoradiotherapy to the standard of 60GY(RBE). Towards that end, the RTOG, in conjunction with the NCCTG and CALGB have planned a phase III randomized trial of 60Gy with concurrent chemotherapy versus 74GY(RBE) with concurrent chemotherapy (RTOG 0617/NCCTG N0628/CALGB 30609). The radiotherapy in this trial will be delivered with modern 3D-conformal treatment techniques. The results of this study should address the impact of dose and treatment delivery techniques on the efficacy and tolerability of high dose combined modality concurrent chemoradiotherapy.

Figure 2: Dose deposition profile of proton beam radiotherapy (red line) when compared to various energies of photon beam radiotherapy. Note decreased entry dose in front of tumor and NO exit dose beyond tumor with proton beam when compared with photons.

It is unclear as to whether all patients can benefit from higher doses. Some have questioned the value of this dose escalation for patients with large volume tumors.[39] The volume of disease appears to have an impact on survival in patients treated with definitive radiotherapy. Bradley, et al. examined 207 patients with inoperable NSCLC and demonstrated by multivariate analysis that gross tumor volume was the variable most predictive of overall and cause-specific survival.[40] Etiz et al. identified a direct correlation between smaller tumor volume and prolonged survival in patients with NSCLC.[41] Willner, et al. examined the impact of tumor volume on local control and demonstrated that patients with small volume tumors (<100 cc) treated to doses greater than 60 GY(RBE) had a significant improvement in local control when compared with patients treated to 60 GY(RBE) or less (p=0.0003).[20] However, they found that higher dose levels did not improve local control for large volume tumors (>100
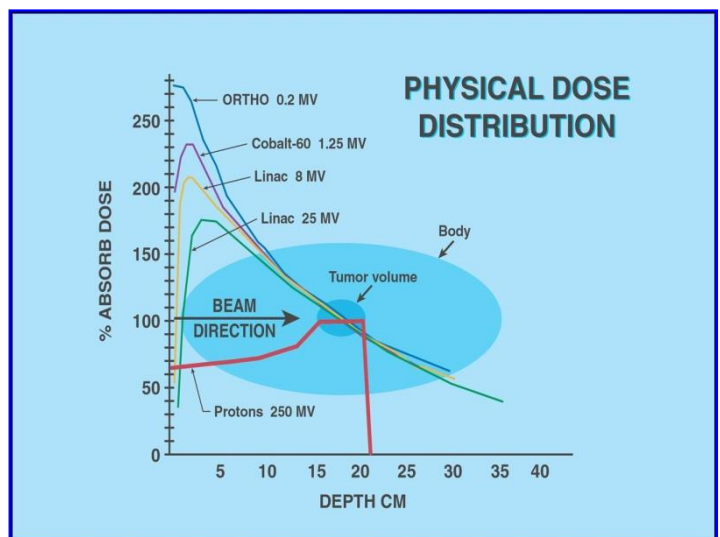
cc). In contrast, Rengan and colleagues examined the value of dose escalation in patients with large volume stage III disease and found that even in patients with large tumor volumes, local failure rates were significantly reduced when treated to 64GY(RBE) or higher.[21] These data highlight an area of controversy in radiotherapeutic management of NSCLC. Specifically, can all patients benefit from dose escalation? If not, which patients should be selected for this aggressive and potentially significantly more toxic treatment approach? As of July 2008, the open phase III dose escalation study, (RTOG 0617/NCCTG N0628/CALGB 30609), does not exclude nor stratify patients based upon tumor volume. Therefore, it is unlikely that this trial will resolve this question definitively.

In 2006, the RTOG opened a 2x2 phase III randomized trial to simultaneously examine the question of 60Gy vs 74Gy and concurrent chemoradiotherapy with or without cetuximab for patients with inoperable stage III NSCLC. After a planned interim analysis, the high dose radiation therapy (74 Gy) arms of RTOG 0617 were closed to accrual effective 6/17/11. In a communication to all RTOG trial investigators, Dr. Bradley stated that the "high dose arms crossed a futility boundary, meaning that high dose radiation therapy cannot result in a survival benefit with further accrual or follow up of patients on these 2 arms".(234) At the 2011 ASTRO annual meeting, the initial results of this trial were presented, actually demonstrating a statistically significant detriment to survival with 74 Gy (p=0.02). The interim analysis did not identify patient safety concerns and gave no indication of a statistical difference in high-grade toxicity between arms, nor any clear explanation for the observed decrement in survival. Regardless, the 74Gy arm for this trial has been closed and 60Gy remains the standard dose in all RTOG lung cancer trials going forward.(235). **Although proton beam radiotherapy may be an appropriate vehicle for dose-escalation in locally advanced disease, due to the results of RTOG 0617, dose-escalation will not be pursued in the context of this clinical trial.**

Proton beam radiation for improving the therapeutic ratio through toxicity reduction for locally advanced NSCLC

In order to improve the ability to deliver definitive doses of radiation to the tumor while at the same time minimizing toxicity to surrounding healthy tissue, clinical research has recently focused on the utility of delivering radiation using a proton beam rather than the more traditional X-ray, or photon beam. One of the major theoretical advantages of using proton beam radiotherapy is that the physical characteristics of the beam eliminate exit dose, or the dose deposited in normal tissue after the beam has penetrated the tumor (Figure 2). As a result, the elimination of exit dose dramatically limits the overall volume of normal tissue exposed during treatment[42,43]. It is important to note that the biological mechanism of tumor cell kill by proton beam radiation is identical to that of photon beam radiation. The only difference lies in the dose deposition profile due to the aforementioned physical characteristics of the beam. Although the use of proton beam radiation is not expected to eliminate toxicity, the favorable physical characteristics of protons compared with photons, is expected to allow for unprecedented dose escalation. Furthermore, due to the favorable toxicity profile of protons, treatment with this modality will allow for greater integration of systemic chemotherapy to be delivered concurrently with proton beam radiation. This may particularly benefit the patient with LA-NSCLC for whom treatment with concurrent chemoradiotherapy represents the greatest chance for cure.[10] However, due to the significant toxicity of this approach, it can only be utilized in the fittest patients. Due to the reduced radiation dose to normal tissues, proton beam radiotherapy will allow for the more effective concurrent regimen to be used for a greater proportion of patients, and also will allow for integration of more aggressive chemotherapeutic regimens that cannot be currently employed with photon beam radiotherapy.[44]

Mechanisms of Radiosensitization: The rationale for Nelfinavir

Inhibition of the Akt phosphorylation results in significant radiosensitization in preclinical studies.[45] However, the drugs used in preclinical studies to inhibit the phosphorylation of Akt *in vitro*, including wortmannin and LY294002, are excessively toxic in vivo and cannot be used clinically.[46] Although inhibition of upstream modulators such as EGFR can result in decreased levels of p-Akt, they do so less efficiently than direct inhibition of PI3K, suggesting that alternative pathways to PI3K and Akt phosphorylation may exist and that direct inhibition of Akt phosphorylation may result in more efficient radiosensitization than inhibition of upstream modulators.[46] Once Akt is phosphorylated, it is known to affect several downstream molecules including mammalian target of rapamycin (mTOR) that play a role in cell cycle regulation, cell proliferation, and apoptosis.[47] The exact mechanism by which inhibition of p-Akt results in radiosensitization is not known, however recent evidence suggests a possible role for VEGF and HIF 1-α.[48]

Nelfinavir is a first generation protease inhibitor used in the treatment of HIV and is known to result in the development of insulin resistance and diabetes in some patients.[49,50] Akt, especially the Akt2 isoform, has been shown to play a role in the coordinated regulation of growth and metabolism by the insulin/IGF-signaling pathway.[51] Because of this link, Nelfinavir, along with 4 other first generation protease inhibitors were tested for their ability to inhibit the PI3k-Akt signaling pathway in preclinical studies.[52] Three of these five protease inhibitors, including Nelfinavir, were shown to result in significant reduction in levels of p-Akt expression in cell lines with mutations in EGFR and H- and K-ras at serum concentrations that are achieved at doses regularly given to HIV patients. Of these three protease inhibitors, Nelfinavir and amprenavir were found to be tolerated well by cell cultures *in vitro* and also resulted in radiosensitization *in vivo* both through clonogenic assays and tumor regrowth assays of xenograft mouse models.[52] These results were consistent with previously reported data that sequinavir, one of the protease inhibitors tested, resulted in radiosensitization in tissue culture.[53] Nelfinavir showed consistent inhibition and radiosensitization in these preclinical studies and is FDA-approved in oral form for the treatment of HIV.[48,52] Because Nelfinavir has been given to a number of patients in the setting of HIV, it is a good candidate inhibitor of Akt phosphorylation that can be tested in the clinic.[54] However, the safety, tolerability, and maximally tolerated dose of Nelfinavir in the setting of concurrent thoracic chemoradiation have never been studied. In the preclinical studies of Nelfinavir in mouse models, no additional toxicity was noted sixty days after irradiation in mice treated with Nelfinavir and radiation compared to unirradiated mice or mice receiving radiation only.[52] One long term goal of radiosensitization with Nelfinavir is to produce added clinical efficacy without significant increases in acute toxicities.

We have recently completed a phase I trial (closed to accrual) of Nelfinavir with concurrent chemoradiotherapy for patients with LA-NSCLC patients. The median follow-up is 13 months for survivors. We have enrolled 16 and have treated 12 patients and one patient has experienced locoregional failure at 9 months. In terms of survival, 8 are alive and being followed. Survival times range from 6+ to 25+ months. No dose limiting toxicities with Nelfinavir have been observed thus far, although toxicity analysis is ongoing. No grade 5 toxicities have been observed. Two patients experienced Grade 3-4 esophageal toxicity. There were no other Grade 3-4 non-hematological toxicities observed. All 12 treated patients had evaluable post-treatment PET/CT at three months after completion of therapy with response as follows: Overall response: 12/12 (100%); Complete metabolic response: 7/12 (58%); partial metabolic response 5/12 (42%). These results compare favorably with previously published results of a complete metabolic response rate of 23% in a patients receiving definitive radiotherapy for NSCLC without concurrent Nelfinavir administration.[55] Additionally, we have only one patient who has experienced local failure to date with a median follow-up of 13 months (Crude local control of 92%). These data suggest that Nelfinavir has promising activity in pts with LA-NSCLC without a dose-dependent increase in chemoradiotherapy-associated toxicities.[56] The clinical trial proposed herein would be a first step to a randomized phase II trial of chemoproton beam radiotherapy +/- Nelfinavir.

The need for integrating predictive markers in dose escalation studies for NSCLC
Although the availability of proton radiation gives us the unprecedented ability to escalate radiation dose, as with new molecularly targeted pharmacological agents, the appropriate selection of patients for dose escalation using this modality will be a critical step in realizing potential improvements in disease outcome. Ideally, treatment intensification using proton beam radiotherapy would be reserved for patients with tumors resistant to standard therapy. In this way, observing the benefit of dose escalation is not diluted by patients that are curable with standard doses or offset by unnecessarily imposing the increased toxicity of dose escalation on patients that can be cured with standard treatment.

Given these considerations and others[57], it becomes apparent that the clinical management of NSCLC would be greatly aided by biomarkers that can predict at the time of diagnosis, whether a patient has cancer that is either resistant or sensitive to standard treatment. Such forecasting can be accomplished by using predictive markers. In contrast to prognostic markers, which assess risk of disease progression independent of therapy, predictive markers identify patients that are sensitive or resistant to treatment. The majority of standard clinicopathological factors and recent genomics-based assays are principally prognostic markers. Thus, the identification of useful predictive markers remains a challenge, particularly for NSCLC. The discovery of a clinically useful predictive marker would greatly benefit the study and use of intensified regimens for patients with resistant disease. One candidate predictive marker for resistance to chemoradiotherapy has been recently characterized in breast cancer. This chemotherapy/ radiation signature consists of 49 genes and is denoted the Interferon Related DNA Damage Resistance Gene Signature, or IRDS.[58] As its name implies, the IRDS is regulated by interferon signaling and mediates both radiation and chemotherapy resistance in mouse models

for cancer. Clinically, the IRDS is expressed among a wide variety of common human cancers, including breast, head and neck, prostate, brain, and lung cancer . Analysis of breast cancer patients reveals that the IRDS can predict which patients are resistant to adjuvant radiation therapy and also identify those patients with microscopic metastasis that will fail chemotherapy. Consistent with the IRDS being a predictive marker rather than a prognostic marker, the IRDS does not track with outcome among patients that do not receive radiation and/or chemotherapy. To-date, analysis of other cancer types also includes high grade gliomas. Similar to breast cancer, high grade gliomas that express the IRDS also show evidence for resistance to post-operative radiation. As with breast cancer and high grade gliomas, the IRDS is expressed in approximately half of patients with NSCLC. However, whether the IRDS also can predict resistance to chemotherapy and radiation for NSCLC remains unknown.

Rationale for Proton Therapy:
The goal of radiation therapy is to deposit most of the dose to the target while minimizing the dose to the surrounding normal tissues. Conventional photon radiotherapy deposits its dose along the entire beam path to the tumor or target volume as well as beyond the depth of the target. Techniques to minimize the dose to surrounding tissues such as using multiple beam angles, modulating the intensity of the radiation delivered through each beam have been utilized, however, these techniques still entail both entrance dose to normal tissue as it penetrates to reach a tumor at depth in tissue, and an exit dose as it exits the body in a straight path beyond the tumor. Proton radiotherapy differs from photon radiotherapy in that most of the energy is deposited at a specific depth known as the Bragg peak. The dose immediately beyond the Bragg peak is essentially zero, which allows tissues on the posterior side of the tumor to be spared. The clinical application of protons provides an improvement over photons in its ability to deliver a high-dose-volume to any configuration within an anatomical site while maintaining lower doses to surrounding normal tissues, resulting in decreased short and long-term morbidity, due to the unique Bragg Peak phenomenon of the dose distribution of protons. Theoretically, this should ease the current limitation of normal tissue tolerance as a dose-limiting factor particularly for larger tumors as well as allow greater dose to be delivered to the tumor/target volume. The current protocol proposes to allow the use of protons (which is approved by the U.S. Food and Drug Administration) for the treatment of Locally Advanced Non Small Cell Lung Cancer

Protons have a similar biologic effect to photons against tumors. The biological effect of radiation is dependent on its linear energy transfer (LET). LET is defined as the rate of energy transferred by ionizing radiation per unit path length. To compare different types of radiation, we use the relative biologic effectiveness (RBE), which is defined as the ratio of the dose of particle radiation to the dose of 60Co radiation producing the same biological endpoint. Standard photon radiation therapy has a RBE of 1.0; the RBE of protons is thought to be between 1.05 to 1.25[59-61]. A recent review of in vivo and in vitro experiments concluded that RBE varies with dose or dose per fraction and increases with an increasing depth in the spread out Bragg Peak (SOBP) and is most significant at the distal edge of the SOBP. Overall though, based on the data to date, an average RBE of approximately 1.1 in the entrance of the SOBP is reasonable to assume[62]. The clinical advantage of proton beam radiotherapy over standard photon radiation results from the more favorable dose distributions achievable with its particular physical properties as previously described. The advantage of protons has been demonstrated for medulloblastoma and, prostate cancer, and comparative treatment planning using protons versus photons have shown a clear advantage to protons in terms of dose distribution[63-68].

2   Study Objectives

This study will be done in two phases. In the first phase, feasibility will be established using the primary objectives set below. The first 12 patients in each chemotherapy arm (Cisplatin/Etoposide or Carbplatin/Taxol) will be enrolled onto the feasibility portion. The second phase will begin no earlier than 30 days after the last patient in the initial phase has completed chemoradiation. The secondary objectives will serve as the objectives for the second phase of the study.

Primary Objective

The primary objective of this study is feasibility.

Feasibility study:
1.   To establish the feasibility and safety of 66.6 GY(RBE) protons in NSCLC patients treated with either cisplatin/etoposide or carboplatin/taxol.

Phase II study:
1.   To determine the rates of acute esophagitis toxicity in strata defined by chemotherapy regimen and proton beam.

Nelfinavir Feasibility study:
1.   To establish feasibility of the treatment regimen with the addition of standard dose Nelfinavir.

All patients will be planned with both a proton plan and a backup photon plan. All enrolled patients will be prescribed to receive 100% of their treatments with proton beam radiotherapy. However, most proton beam facilities, including ours, have an average downtime of 20%. Therefore, patients can either experience a 20% longer treatment time course if they are to receive 100% of their treatments with protons. Or, if any treatment delays are unacceptable due to concern about loss of efficacy, patients can expect to receive up to 20% of their treatment with a backup photon beam plan. Patients planned to be treated with a combination photon-proton plan are ineligible for this trial. However, it may be required for patients to be treated with the backup photon plan for a number of reasons (including but not limited to proton beam downtime, delay of treatment, patient inability to tolerate positioning for proton beam treatment, etc). Patients who receive greater than 35% of their total treatment with photon beam radiotherapy (using the backup photon plan) will be counted as an infeasible patient.

This will be evaluated at the end of radiation treatment course.

The study will be deemed infeasible if greater than 10% of patients experience one of the following:
a.   Patients who receive greater than 35% of their total treatment (for any reason-unable to set patient up within acceptable limits of tolerance, patient unable to tolerate treatment position or immobilization for duration of treatment) with photon beam radiotherapy (using the backup photon plan) will be counted as an infeasible patient.
b.   Patient is unable to complete all of his/her treatments within 10 days of estimated date of treatment completion or requires a treatment break greater than 5 days. This only applies to patients who are able to complete all of their treatments in the opinion of their treating physician. Patients who discontinue treatment due to disease progression, performance status deterioration, or who are discontinued by the treating physician for any reason are not considered an infeasibility based upon this criteria.

c. Additionally, if greater than 60% of patients experience grade 3 or higher (probably or definitely radiation related) non-hematologic acute toxicity except esophagitis and pneumonitis as defined by the Common Toxicity Criteria v 4.0, the study will be deemed infeasible. *Grade 4 toxicity that is considered probably or definitely related to the radiation will continue to be evaluated for toxicity and survival but during the feasibility study, will be counted as infeasible*

Secondary Objective
1. Investigate novel biomarkers, as they become available.
2. To determine clinical efficacy, as defined by metabolic response, sites of recurrence (e.g., local, regional, distant) and progression-free and overall survival.

3   Subject Selection and Withdrawal

This study plans to enroll up to 130 subjects over 6.5 years (24 patients on feasibility, 82 additional patients on stratified phase II, 24 on Nelfinavir feasibility). In the feasibility study, 24 patients will be enrolled; 12 on carboplatin/taxol and 12 on cisplatin/etoposide. These patients may undergo proton therapy with either scattering or pencil beam scanning (PBS). Then a stratified phase II study will be initiated with 4 treatment strata, using a Simon 2-stage design: carboplatin/taxol with scattering (n=34), carboplatin/taxol with PBS (n=15), cisplatin/etoposide with scattering (n=39) or cisplatin/etoposide with PBS (n=18). The 24 patients on the feasibility study will be included in the stratified phase II study and assigned to the appropriate stratum. Thus, a total of 82 additional patients will be enrolled in the stratified phase II study. Once the phase II study is completed for a particular stratum, 6 additional patients will be treated with the assigned treatment regimen plus Nelfinavir at the standard dose of 1250mg po BID. Thus 24 additional patients will be recruited to evaluate Nelfinavir.

This protocol will be conducted in conjunction with the Department of Defense Oncology practices. We anticipate that they will accrue approximately 10 patients per year to this study, while Penn will enroll approximately 10 patients per year. We plan to enroll male and female subjects of all races.)

3.1   Inclusion Criteria
- Histologically confirmed diagnosis of NSCLC.
- Stage IIIA or IIIB NSCLC.
- Patients must have no evidence of metastatic disease based on routine imaging.
- Patients must have an ECOG Performance Status 0-2.
- Age $\geq$ 18.
- Patients must be able to provide informed consent.
- Adequate bone marrow function: WBC $\geq$ 4000/mm^3, platelets $\geq$ 100,000 mm^3.
- Adequate renal function for cisplatin or carboplatin as determined by the medical oncologist: Usually Calculated creatinine clearance (CrCl) $\geq$ 45 mL/min or serum creatinine level $\leq$ 1.5 x institutional ULN.
- Patients must have bilirubin $\leq$ 1.5 mg/dl.
- Women of child-bearing potential as long as she agrees to use a recognized method of birth control (e.g. oral contraceptive, IUD, condoms or other barrier methods etc.). Hysterectomy or menopause must be clinically documented.

3.2   Exclusion Criteria
- Prior or simultaneous malignancies within the past two years (other than cutaneous squamous or basal cell carcinoma or melanoma in situ).
- Pregnant women, women planning to become pregnant and women that are nursing.
- Actively being treated on any other therapeutic research study.
- *For the Nelfinavir phase of the trial only:*

o   Patients receiving the following drugs that are contraindicated with NFV will be excluded.

Drugs That Should Not Be Coadministered With VIRACEPT	
Drug Class: Drug Name	**Clinical Comment**
Antiarrhythmics: amiodarone, quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to VIRACEPT or other coadministered antiretroviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to VIRACEPT or other coadministered antiretroviral agents.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Proton Pump Inhibitors	Omeprazole decreases the plasma concentrations of nelfinavir. Concomitant use of proton pump inhibitors and VIRACEPT may lead to a loss of virologic response and development of resistance.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

o   Patients receiving the following drugs will be clinically evaluated as to whether dosage/medication can be changed to permit patient on study:

Anti-Convulsants: carbamazepine phenobarbital	☐ nelfinavir	May decrease nelfinavir plasma concentrations. VIRACEPT may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly.
Anti-Convulsant: phenytoin	☐ phenytoin	Phenytoin plasma/serum concentrations should be monitored; phenytoin dose may require adjustment to compensate for altered phenytoin concentration.
Anti-Mycobacterial: rifabutin	☐ rifabutin ☐ nelfinavir (750 mg TID) ☐ nelfinavir (1250 mg BID)	It is recommended that the dose of rifabutin be reduced to one-half the usual dose when administered with VIRACEPT; 1250 mg BID is the preferred dose of VIRACEPT when coadministered with rifabutin.
PDE5 Inhibitors: sildenafil vardenafil tadalafil	☐ PDE5 Inhibitors	Concomitant use of PDE5 inhibitors and VIRACEPT should be undertaken with caution. If concomitant use of PDE5 inhibitors and VIRACEPT is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours, or tadalafil at a single dose not

		exceeding 10 mg dose in 72 hours, is recommended.
HMG-CoA Reductase Inhibitor: atorvastatin rosuvastatin	☐ atorvastatin ☐ rosuvastatin	Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with VIRACEPT.
Immunosuppressants: cyclosporine tacrolimus sirolimus	☐ immuno-suppressants	Plasma concentrations may be increased by VIRACEPT.
Narcotic Analgesic: methadone	☐ methadone	Dosage of methadone may need to be increased when coadministered with VIRACEPT.
Oral Contraceptive: ethinyl estradiol	☐ ethinyl estradiol	Alternative or additional contraceptive measures should be used when oral contraceptives and VIRACEPT are coadministered.
Macrolide Antibiotic: azithromycin	☐ azithromycin	Dose adjustment of azithromycin is not recommended, but close monitoring for known side effects such as liver enzyme abnormalities and hearing impairment is warranted.
Inhaled/nasal steroid: fluticasone	☐☐ fluticasone	Concomitant use of fluticasone propionate and VIRACEPT may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
Antidepressant: trazodone	☐☐ trazodone	Concomitant use of trazodone and VIRACEPT may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as VIRACEPT, the combination should be used with caution and a lower dose of trazodone should be considered.

Note: Patients with the following conditions are deemed unsuitable for cisplatin-based chemotherapy (and will be treated with carboplatin):
- **Hearing impairment/peripheral neuropathy Grade 1 or less at baseline**
- **Symptomatic/uncontrolled congestive heart failure (unable to tolerate volume load with pre- and post-cisplatin hydration)**

3.3 Subject Recruitment and Screening

Patients will be referred by their physicians. Subjects will be recruited from either the Department of Radiation Oncology at the University of Pennsylvania or the Department of Defense Oncology practices. The treating radiation oncologist will determine if the patient is a potential research candidate and has the capacity to consent. The treating radiation oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating radiation oncologist will contact a qualified member of the research team in the Radiation Oncology department at the University of Pennsylvania and request availability for enrollment. A qualified member of the research team will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form (ICF). The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study if necessary before making their decision to sign the informed consent document. If a decision to participate is made, the ICF is signed after which any screening procedures will be performed. A series of questions will be asked by the person obtaining consent to verify patient eligibility based upon the criteria outlined in Sections 3.1 and 3.2. After the eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator. All members of the research team will have successfully completed patient oriented research training. **Subjects will receive all radiation treatment in the Radiation Oncology clinic of the University of Pennsylvania.**

Subjects will not be paid for participating in the study.

At the University of Pennsylvania, we see approximately 50 cases of stage IIIA/IIB NSCLC per year. We anticipate that with the availability of proton radiotherapy, these numbers may increase. We estimate an annual accrual of 17 subjects per year combining Department of Defense Oncology practice and Penn patients. Proton radiotherapy will be listed on our web site as a formal protocol and information of its availability will be made known to treating professionals throughout our satellites and referring physicians.

3.4   Early Withdrawal of Subjects

3.4.1   When and How to Withdraw Subjects

- Recurrent or Progressive Disease: Subjects who have clinical or radiologic evidence of recurrent disease will undergo an evaluation to document the nature of the abnormality. If recurrent or progressive cancer is diagnosed, the subject will be considered off study at that time.
- PI Decision: Subjects may be withdrawn at any time during the study if the PI believes it is in the subject's best interest. In this event, the reasons for withdrawal will be documented.
- Toxicity: Grade 4 toxicity that is considered probably or definitely related to the study will continue to be evaluated for toxicity and survival but during the feasibility study, will be counted as infeasible.

- Subject Participation: Refusal to continue treatment, follow-up, comply with the protocol or withdrawal of consent. In this event, the reasons for withdrawal will be documented.
- Adverse Event (including intercurrent illness, unacceptable toxicity).

Once the subject has discontinued treatment, the primary reason for discontinuing treatment must be clearly documented in the subject's records and on the CRF. The investigator will assess each subject for response at the time of withdrawal.

Every effort will be made to follow all subjects off study for toxicity and survival unless subject withdraws consent. If subjects withdraw from the study at any time, we may ask for his/her written permission to continue to access medical records for toxicity gathering/evaluation and overall survival. Acute toxicities will be assessed for 90 days from the start of treatment. Survival will be followed for a minimum of 5 years.

4   Radiation Therapy

4.1   Treatment Planning, Imaging and Localization Requirements

All subjects will be immobilized in a custom designed device in the appropriate position using immobilization devices which will be located outside of the treatment beam. Arms should be in an up position in order to eliminate CT scan artifacts from the humerus and be located outside of the treatment beam

4.1.1   All CTs scans (freebreathing, 4D and breatholding) or the PET/CT employed for dose calculation during the treatment planning process should be acquired without contrast, All scans which require contrast to define gross target volume (GTV) and clinical target volume (CTV). have to be acquiered after the planning CT was obtained. All CT scan (or PET/CT) should be acquired with the subject in the same position and using the same immobilization device as for treatment. Treatment planning will be done using a 3D based CT treatment planning system. All tissues to be irradiated must be included in the CT scan. Planning CT scan will be done at the interval specified by the Proton CT protocol from encompassing the region of interest with sufficient margin for treatment planning and most importantly encompassing the entire lung volumes if possible. At the minimum a biweekly CT will be performed for treatment plan robustness evaluation purposes. A weekley CT scan may be performed during the course of radiotherapy if necessary along with MRI or PET/CT if indicated by the treating physician. Imaging including FDG-PET/CT and/or maybe fused with the planning CT images to better visualize the anatomy when indicated.

4.2   Target Contouring

Target contouring will be performed on the 4DCT data set. If the target motion exceeds 10 mm, an active motion management strategy should be considered. Targets situated near the diaphragm require special attention for any amplitude of motion and along with high amplitude moving targets (>10mm) require Physics evaluation. Based on this evaluation the target will be contoured using the departmental proton simulation and planning protocol.

4.2.1   Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT, MRI, clinical information, and/or endoscopic findings. The GTV will consist of the primary parenchymal tumor as visualized on the 4DCT and PET.

4.2.2   Mediastinal Gross Tumor Volume (GTV_med) This will consist of the ipsilateral hilum and bilateral mediastinum up to the thoracic inlet. The contralateral hilum and supraclavicular fossae will not be irradiated.

4.2.3   Internal Gross Tumor Volume (IGTV) is defined as the GTV0 +GTV50 **plus** an additional margin based upon the 4DCT image sets verification to account for tumor motion.
Mediastinal Internal Gross Tumor Volume (IGTV_med) is defined as the GTV0 +GTV50 **plus** an additional margin based upon the 4DCT image sets verification to account for tumor motion **if necessary.**

4.2.4   Clinical Target Volume (CTV0) is defined as the GTV0plus areas that are considered to contain potential microscopic disease on the T0 fase CT data set.

4.2.5   Clinical Target Volume (CTV50) is defined as the GTV50plus areas that are considered to contain potential microscopic disease on the T50 fase CT data set.

4.2.6   Internal Target volume(ITV)-Lung in lung will be determined as a boolean of the CTV0 and CTV50 of the lung on the average CT data set.Alternatively a 8 to 10mm margin can be added to the IGTV to account for microscopic extension of tumor or can be manually edited by the treating physician based on the 4DCT data sets available or the average CT data set. The ITV corresponds to the Imaging CTV (iCTV).pg.13, 4.2.6 and 4.2.7

4.2.7   Internal Target volume(ITV) in_Med in Mediastinum will be determined as a boolean of the CTV0 and CTV50 of the mediastinumon the average CT data set Alternatively a 3-5mm margin can be added to the IGTV_med to account for microscopic extension of
or can be manually edited by the treating physician based on the 4DCT data sets available. The ITV corresponds to the Imaging CTV (iCTV).pg.13, 4.2.6 and 4.2.7

Planning Target Volume(PTV) will be defined as a 5mm uniform expansion of the iCTV to account for lateral uncertainties and set-up variations. As per ICRU 78 the true PTV for proton therapy is beam orientation dependent and it is established by the planning team if deemed necessary.

4.3.1   Organ at risk volume (OAR) is contoured as visualized on the planning CT data sets(,4D CT or MR scan). Planning PAR is the OAR expanded for setup uncertainty or organ motion should be created as necessary . The physician will contou**r** the OAR. The dosimetrist may create the PAR by expanding the OAR by 2-3 mm, depending on the situation.This will have to be clearly stated in the treatment intent by the treating physician.

> The following structures will be contoured:
> **Lung/thorax:** lung (right/left), spinal cord, esophagus, heart, brachial plexus, carina, diaphragm, liver, stomach.

Note: All foreign objects (devices, wires, etc) within the CT data set will be identified at the time of contouring and HU will be assigned as necessary in consultation with the Physicist.

4.3   Dose fractionation and specification

The prescription dose per fraction to the ITV/iCTV or CTV will be 1.8 Gy(RBE)/day. Patients will be treated with daily fractionated radiotherapy without a planned treatment break. The carina will be contoured for all patients and the isocenter will be placed at mid-carina for all patients, however its location will change for treatment planning and delivery purposes..

The total dose for dose level one will be 66.6 Gy(RBE) over 37 fractions.

4.4   Treatment Planning

Dose specfications:
Dose Constraints for normal tissues and for PTV and ITV/iCTV. A 95% of the ITV/iCTV will be encompassed by 95% of the prescription dose. The PTV will be evaluated (95% of the PTV should be encompassed by 90% of the prescription dose). ITV/iCTV coverage should be reviewed beam-by-beam in order to ensure the robustness of the plan and applay an equivalent methodology for the PTV evaluation. Distal, proximal, and lateral margins should be observed for the particular beam direction; however, beam parameters should not be altered without consultation with Physics to reduce apparent "hot" or "cold" spots. Hot and cold spots are mostly the result of smearing effect and are expected to be smeared out in the presence of setup uncertainties and organ motion. The above criteria can be altered by the treating Physician in consultation with Physics. For pencil beam scanning treatment planning, a PBSTV will be employed for treatment planning optimization purposes.

Normal tissue constraints: Dose-volume histograms should be performed for spinal cord, lungs, and heart. The maximal spinal cord dose should not exceed 50 Gy(RBE). No more than 40% of the total lung volume should receive greater than 20 Gy(RBE). No more than 50% of the total cardiac volume should receive greater than 40 Gy(RBE). Additional normal structures constraints can be specified in the treatment intent by the treating physician.

4.5   Treatment Duration
Proton radiation therapy will in most instances be completed within nine weeks of the start of treatment. This may be extended if subjects require a break from treatment. Criteria for break would include any **Grade 3 non-hematologic toxicity at PI discretion, Grade 4 hematologic toxicity at PI discretion, or Grade 4 non-hematalogic toxicity.** Further treatment plans will be decided at the discretion of their treating physician.

4.6   External Beam Equipment and Beam Delivery

Protons: A high energy proton beam will be used. Treatments will be administered at the University of Pennsylvania Roberts Proton Facility. All charged particle treatment will be given with the patient in the appropriate immobilization device. Film or digital images will be taken prior to the initial treatment to verify the position of the patient and the aperture and as appropriate. A radiation oncologist will check the first film on all fields. A radiation therapist will check subsequent films taken before treatment. All set-up films will be permanently filed for all subjects. Subjects may be treated with motion management techniques such as respiratory gating, deep inspiration breath hold (DIBH), etc..
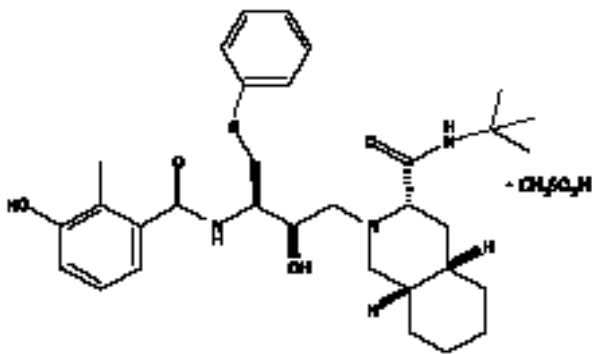
4.7   Quality Assurance

Daily portal films, and/or daily online radiographic imaging will be performed during therapy. Fiducials will help reproduce daily set up and minimize set-up variations as appropriate.

5   Study Drug (Only applies to Nelfinavir portion of the trial)

There are ample data available regarding the use of NFV in humans [37]. The following is an excerpt of the key features.

VIRACEPT® (nelfinavir mesylate) is an inhibitor of the human immunodeficiency virus (HIV) protease. VIRACEPT Tablets are available for oral administration as a light blue, capsule-shaped tablet with a clear film coating in 250 mg strength (as NFV free base) and as a white oval tablet with a clear film coating in 625 mg strength (as NFV free base). Each tablet contains the following common inactive ingredients: calcium silicate, crospovidone, magnesium stearate, hypromellose, and triacetin. In addition, the 250 mg tablet contains FD&C blue #2 powder and the 625 mg tablet contains colloidal silicon dioxide. VIRACEPT Oral Powder is available for oral administration in a 50 mg/g strength (as NFV free base) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor. The chemical name for nelfinavir mesylate is [3S-[2(2S*, 3S*), 3a,4ab,8ab]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4- (phenylthio)butyl]-3-isoquinoline carboxamide mono-methanesulfonate (salt) and the molecular weight is 663.90 (567.79 as the free base). Nelfinavir mesylate has the following structural formula:

Nelfinavir mesylate is a white to off-white amorphous powder, slightly soluble in water at pH 4 and freely soluble in methanol, ethanol, 2-propanol and propylene glycol.

Pharmacokinetics

The pharmacokinetic properties of NFV were evaluated in healthy volunteers and HIV-infected patients; no substantial differences were observed between the two groups.

Absorption: Pharmacokinetic parameters of NFV (area under the plasma concentration-time curve during a 24-hour period at steady-state [AUC24], peak plasma concentrations [Cmax], morning and evening trough concentrations [Ctrough]) from a pharmacokinetic study in HIV-positive patients after multiple dosing with 1250 mg (five 250 mg tablets) twice daily (BID) for 28 days (10 patients) and 750 mg (three 250 mg tablets) three times daily (TID) for 28 days (11 patients) are summarized in Table 1.

Table 1
Summary of a Pharmacokinetic Study in HIV-positive Patients with Multiple Dosing of 1250 mg BID for 28 days and 750 mg TID for 28 days

Regimen	AUC_{24} mg•h/L	C_{max} mg/L	C_{trough} Morning mg/L	C_{trough} Afternoon or Evening mg/L
1250 mg BID	52.8 ± 15.7	4.0 ± 0.8	2.2 ± 1.3	0.7 ± 0.4
750 mg TID	43.6 ± 17.8	3.0 ± 1.6	1.4 ± 0.6	1.0 ± 0.5

data are mean ± SD

The difference between morning and afternoon or evening trough concentrations for the TID and BID regimens was also observed in healthy volunteers who were dosed at precisely 8- or 12-hour intervals. In healthy volunteers receiving a single 1250 mg dose, the 625 mg tablet was not bioequivalent to the 250 mg tablet formulation. Under fasted conditions (n=27), the AUC and Cmax were 34% and 24% higher, respectively, for the 625 mg tablets. In a relative bioavailability assessment under fed conditions (n=28), the AUC was 24% higher for the 625 mg tablet; the Cmax was comparable for both formulations. In healthy volunteers receiving a single 750 mg dose under fed conditions, NFV concentrations were similar following administration of the 250 mg tablet and oral powder.

Effect of Food on Oral Absorption: Food increases NFV exposure and decreases NFV pharmacokinetic variability relative to the fasted state. In one study, healthy volunteers received a single dose of 1250 mg of VIRACEPT 250 mg tablets (5 tablets) under fasted or fed conditions (three different meals). In a second study, healthy volunteers received single doses of 1250 mg VIRACEPT (5 x 250 mg tablets) under fasted or fed conditions (two different fat content meals). The results from the two studies are summarized in Table 2 and Table 3, respectively.

Table 2
Increase in AUC, C_{max} and T_{max} for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)

Number of Kcal	% Fat	Number of subjects	AUC fold increase	C_{max} fold increase	Increase in T_{max} (hr)
125	20	n=21	2.2	2.0	1.00
500	20	n=22	3.1	2.3	2.00
1000	50	n=23	5.2	3.3	2.00

Table 3
Increase in Nelfinavir AUC, C_{max} and T_{max} in Fed Low Fat (20%) versus High Fat (50%) State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)

Number of Kcal	% Fat	Number of subjects	AUC fold increase	C_{max} fold increase	Increase in T_{max} (hr)
500	20	n=22	3.1	2.5	1.8
500	50	n=22	5.1	3.8	2.1

NFV exposure can be increased by increasing the calorie or fat content in meals taken with VIRACEPT. A food effect study has not been conducted with the 625 mg tablet. However, based on a cross-study comparison (n=26 fed vs. n=26 fasted) following single dose administration of NFV 1250 mg, the magnitude of the food effect for the 625 mg NFV tablet appears comparable to that of the 250 mg tablets. VIRACEPT should be taken with a meal.

Distribution: The apparent volume of distribution following oral administration of NFV was 2-7 L/kg. NFV in serum is extensively protein-bound (>98%).

Metabolism: Unchanged NFV comprised 82-86% of the total plasma radioactivity after a single oral 750 mg dose of 14C-NFV. *In vitro*, multiple cytochrome P-450 enzymes including CYP3A and CYP2C19 are responsible for metabolism of NFV. One major and several minor oxidative metabolites were found in plasma. The major oxidative metabolite has *in vitro* antiviral activity comparable to the parent drug.

Elimination: The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87%) of an oral 750 mg dose containing 14C-NFV was recovered in the feces; fecal radioactivity consisted of numerous oxidative metabolites (78%) and unchanged NFV (22%). Only 1-2% of the dose was recovered in urine, of which unchanged NFV was the major component.

Special Populations

Hepatic Insufficiency:	The multi-dose pharmacokinetics of NFV have not been studied in HIV-positive patients with hepatic insufficiency.
Renal Insufficiency:	The pharmacokinetics of NFV have not been studied in patients with renal insufficiency; however, less than 2% of NFV is excreted in the urine, so the impact of renal impairment on NFV elimination should be minimal.
Gender and Race:	No significant pharmacokinetic differences have been detected between males and females. Pharmacokinetic differences due to race have not been evaluated.

5.1   Treatment Regimen

 The standard dose of Nelfinavir will be evaluated in each treatment stratum at 1250 mg PO bid. All patients will begin taking daily oral nelfinavir 7 to 14 days prior to the start of CTRT. Nelfinavir will be continued during the complete course of concurrent CTRT. The 7 days of nelfinavir prior to CTRT are based on the known pharmacokinetics of the drug that has shown suppression of p-Akt within three days after the administration of nelfinavir (see background information). Subjects will be asked to maintain a drug diary to assess compliance with administration of nelfinavir.

5.2 Evaluation of Nelfinavir Feasibility

If 1 or fewer dose limiting toxicities are observed in 6 patients treated on a particular stratum, then Nelfinavir will be considered feasible. If 2 or more dose limiting toxicities are observed in 6 patients treated on a particular stratum, then Nelfinavir will be reduced to 625 mg po BID and 6 additional patients will be treated and evaluated for feasibility. Dose limiting toxicities will be scored for 90 days from start of radiotherapy.

6   Chemotherapy

For cisplatin candidates (all enrolled patients who are cisplatin candidates as deemed by the treating medical oncologist will be treated with this regimen):

Chemotherapy for all cisplatin candidates (as deemed by the treating physician) will consist of cisplatinum and etoposide that will be administered as concurrent therapy with radiation. This is the same regimen as was used in SWOG 8805[69] and the Intergroup 0139 trials[70].

- o   Cisplatinum 50 mg/m^2 will be administered on days 1, 8, 29 and 36, with pretreatment and post treatment hydration and a polyantiemetic regimen.
- o   Etoposide 50 mg/m^2 will be administered days 1 to 5 and 29 to 33.

The second cycle (day 29) will be started if:

- ■   the absolute neutrophil count (ANC) is more than 1,000/μL,
- ■   the platelet count is more than 100,000/μL, and if
- ■   the creatinine clearance is > 50 mL/min.

If any one of these criteria is not met, then treatment will be delayed 1 week. If renal insufficiency does not recover, cisplatinum will be withheld. The dose of etoposide for the second cycle will be reduced if febrile neutropenia occurs during the first cycle. Development of severe dysphagia, dehydration, orthostasis, neuropathy or other unforeseen grade 4 toxicity is potential grounds for discontinuation of treatment if therapy is delayed longer than 1 week to permit recovery. The patient may be taken off study at PI discretion if discontinuation of therapy is required. Should a holiday, hospital closing or other extenuating circumstance interfere with the above detailed chemotherapy administration schedule, the medical oncologist will adjust each subjects administration as they see medically appropriate.

For carboplatin candidates (ie non-cisplatin candidates as deemed by the treating medical oncologist):

Carboplatin and paclitaxel will be given weekly during radiotherapy. The dosing will consist of carboplatin (AUC=2) and paclitaxel (45 mg/m^2) being administered on days 1, 8, 15, 22, 29, 36, and 43.

- o Carboplatin dose should be calculated using the Calvert formula (Carboplatin dose = AUC x (CrCl + 25)). The maximum CrCl used should be 150 ml/min.
- o The Cr Cl should be calculated using the Cockroft-Gault equation:
  CrCl (ml/min) = (140-age) (Actual weight in kg) x 0.85 (females only) 72 x serum Creatinine (mg/dl)
  A measured CrCl from a 24 hour urine collection may also be used.

Should a holiday, hospital closing or other extenuating circumstance interfere with the above detailed chemotherapy administration schedule, the medical oncologist will adjust each subjects administration as they see medically appropriate.

Note: For subsequent weekly doses, a >10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose. All drugs will be administered intravenously by intravenous drip. The paclitaxel will be given over 1 hour with standard premedication consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel. The carboplatin will be given after the paclitaxel over 30 minutes with standard antiemetics.

7   Study Procedures

	Baseline/ Eligibility	Weekly on treatment	First follow up (approx 90 days from start of tx)	Follow-up Months* (Approximately) 3, 6, 9, 12, 15, 18, 21, 24,	Follow-Up Months* (Approximately) 30, 36, 42, 48, 54, 60	Year "X" or "Survival"
Tests and Observations						
[1]History and PE	X			X	X	X
[1]ECOG score	X					
[2]FDG PETor CT or MRI	X			X	X	X[C]
Biopsy	X					
Laboratory						
CBC w/diff, Hgb, Platelets…	X[b]	X			X[C]	X[C]
CMP	X[b]	X			X[C]	X[C]
Pregnancy Test	X[a]					
Toxicity Assessment	X	X	X	X	X	X[C]

X[a]- If pre-treatment is 30 days from eligibility, you should repeat a pregnancy test within 24 hours of treatment initiation.
X[b]- Measurements cannot be more than 4 weeks from the beginning of treatment.
X[C]- As clinically indicated.
[1]- Within 4 weeks of consent.
[2]- No more than 90 days prior to consent.
*follow up visits occur at time points from the end of treatment.

7.1   Post-treatment Evaluation and follow-up

All subjects will be evaluated prior to initiation of treatment, weekly during the course of the protocol and every three months from the last dose of radiation therapy either by the treating radiation oncologist or a referring physician for two years, and every 6 months thereafter for 3 years, and then annually as long as subject wishes to be followed for survival with the provision that if subjects are no longer in the local area, communications such as a telephone call or letter will be sent as follow up. Patients will be treated and followed for a minimum of 90 days from the start of radiation treatment to determine feasibility and safety (acute toxicity) for the initial phase of the study before moving to the second phase of the study. Each follow-up examination will consist of interval history and physical examination, toxicity assessment. Laboratories and Assessment of the disease by CT will be performed at the above intervals.

7.2   Assessment of Tumor Response

7.2.1   Tumor Response (RECIST criteria): (if measurable disease)

Target Lesions:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of target lesion, taking as reference the baseline sum of the longest diameters.

Progressive Disease (PD): At least a 20% increase in the LD of the target lesions, taking as reference the smallest sum of the LD recorded since the treatment started or the appearance any new lesion(s)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Non-Target Lesions:

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions or any new lesion(s)

7.2.2   Confirmation of Response

To assign a PR or CR, changes in tumor measurement must be confirmed by repeat assessments no less than 4 weeks after the criteria for response are first met.

To assign SD, measurements must have met the stable disease criteria at least once after study entry at "X" interval (*as defined by protocol*).

7.2.3   Failure

Local failure is defined as: evidence of tumor growth in any direction beyond that present of the pre-treatment imaging studies or the appearance of tumor in tissues previously scored as sites of subclinical disease. The imaging studies are to be comparable in technical factors.

Marginal failure is defined as appearance of tumor growth at the margin of the target volume

Nodal Failure: Failure in regional lymph nodes.

Distant failure is defined as appearance of tumor at sites beyond regional nodal and marginal site.

Overall Survival: Duration measured from date of first treatment until death or censored at date of last follow-up for patients still alive.

8.   STATISTICAL PLAN.

8.1 STUDY DESIGN.

This is a study of definitive proton radiotherapy for inoperable Stage III NSCLC. The study will be conducted in two phases, first a feasibility study and then, a Phase II study. Since proton is a new treatment modality at PENN, the first proton trial conducted in <u>each</u> cancer site will be a feasibility study, in order to gain experience on both the logistics of proton planning, dosimetry, scheduling and delivery and patient safety issues. Patients receive concurrent chemotherapy and will be stratified by their chemotherapy regimen; either cisplatin/etoposide or carboplatin/taxol. Only patients who are <u>not</u> candidates for cisplatin/etoposide will be treated with carboplatin/taxol.

Initially, this study was designed to establish feasibility and safety of 74 Gy of protons when administered with concurrent chemotherapy. But recent results of RTOG 0617 showed that 74 Gy is inferior to 60 Gy. Because 74Gy was inferior, we have now modified this trial to treat patients at the Departmental standard of 66.6 Gy. Also, this **study was originally designed to conduct a Phase I dose escalation study after completion of the feasibility study. This is no longer possible. We will instead conduct a stratified Phase II study, to investigate acute esophagitis toxicity. We will also confirm feasibility of Nelfinavir administration once the phase II study is completed.**

This study plans to enroll up to 130 subjects over 6.5 years (24 patients on feasibility, 82 additional patients on stratified phase II, 24 patients on Nelfinavir feasibility). In the feasibility study, 24 patients will be enrolled; 12 on carboplatin/taxol and 12 on cisplatin/etoposide. These patients may undergo proton therapy with either scattering or pencil beam scanning (PBS). Then a Simon 2-stage stratified phase II study will be initiated with 4 treatment strata: carboplatin/taxol with scattering (n=34), carboplatin/taxol with PBS (n=15), cisplatin/etoposide with scattering (n=39) or cisplatin/etoposide with PBS (n=18). The 24 patients on the feasibility study will be included in the stratified phase II study and assigned to the appropriate stratum. Thus, a total of 82 additional patients will be enrolled in the stratified phase II study. Once the phase II study is completed for a particular stratum, 6 additional patients will be treated with the treatment regimen with the addition of Nelfinavir at the standard dose of 1250mg po BID. Thus 24 additional patients will be recruited to evaluate Nelfinavir.

In the feasibility study, 12 evaluable patients will be enrolled in each chemotherapy stratum. Subjects will be considered evaluable if they remain on study up until their first follow-up visit after radiotherapy. We expect to screen/enroll 18 subjects to attain 12 evaluable. [Note: A subject WILL be considered evaluable if they willingly remain on the study up until their first follow up visit or if they meet any of the infeasibility criteria detailed in section 2.0 as this is critical to determining feasibility]. Once feasibility and safety are established, the phase II study will begin.

In the Phase II study, patients will be stratified by chemotherapy regimen and type of proton beam (scattering or pencil beam scanning, PBS). Patients from the feasibility study will be included in the phase II study and assigned to the appropriate stratum. Because reduced toxicity is anticipated with proton therapy, we will test the hypothesis that the rate of acute esophagitis will be lower than that reported for photons.

Once the phase II study is completed for a particular stratum, standard dose Nelfinavir will be added and 6 additional patients will be enrolled to establish feasibility. In a phase II study, nelfinavir has already been successfully added to photon chemoradiotherapy in NSCLC with few acute toxicities experienced.

8.2 OBJECTIVES.
8.2.1 Primary objectives

> **Feasibility study:** To establish the feasibility and safety of 66.6 GY(RBE) protons in NSCLC patients treated with either cisplatin/etoposide or carboplatin/taxol.

> **Phase II study:** To determine the rates of acute esophagitis toxicity in strata defined by chemotherapy regimen and proton beam.
> **Nelfinavir Feasibility study**: To establish feasibility of the treatment regimen with the addition of standard dose Nelfinavir.

8.2.2 Secondary objectives
1. To investigate novel biomarkers, as they become available.
2. To determine clinical efficacy, as defined by metabolic response, sites of recurrence (e.g., local, regional, distant) and progression-free and overall survival.

8.3 ENDPOINTS.

Feasibility will be based on multiple radiation planning and treatment parameters. Any patient who is enrolled and not felt to have a dosimetric benefit from protons or a patient who would require a combination photon-proton plan would be a screen failure rather than an "infeasible" patient. A subject is considered infeasible if they experience any of the following events:

a) Patients who receive greater than 30% of their total treatment (for any reason-unable to set patient up within acceptable limits of tolerance, patient unable to tolerate treatment position or immobilization for duration of treatment) with photon beam radiotherapy (using the backup photon plan) will be counted as an infeasible patient.
b) A subject is unable to complete all of his/her treatments within 10 days of estimated date of treatment completion or requires a treatment break of greater than 5 days (due to non-hematologic toxicities).

Acute toxicity or dose limiting toxicity is defined as any treatment related Grade 4 hematologic toxicity requiring a break in therapy of greater than 14 days or Grade 3 or higher non-hematologic toxicity (probably or definitely radiation related), except esophagitis and pneumonitis, which is observed within 90 days from start of radiotherapy and which is probably or definitely related to treatment. All toxicities will be graded by NCI CTCAE Version 4.0.

Late toxicity is defined as any treatment related to Grade 3 (probably or definitely radiation related) or higher non-hematologic toxicity, except esophagitis and pneumonitis, which is observed later than 90 days from start of radiotherapy and which is probably or definitely related to radiation treatment. Late toxicities will be graded according to the CTCAE Version 4.0. The time frame for late toxicity is open-ended and late toxicities have been known to occur a year or more after therapy. Follow-up for late toxicity will cease when a patient experiences disease progression, since 2nd line therapies may then be initiated.

Clinical efficacy is defined as metabolic response (complete, partial or less than partial) based on PET/CT imaging. Patients are followed for disease recurrence and site (local, regional, distant). Progression-free and overall survival are defined as from start of treatment to first documented recurrence (for PFS), date of death or last patient contact alive.

Biomarkers will be evaluated on tumor tissue, as the methods for measurement become available. For example, the radiation resistance biomarker, IRDS (Interferon Related DNA Damage Resistance Gene Signature), will soon be under prospective validation in NSCLC. Similar biomarker discoveries will be considered during the course of this 4 ½ year trial.

8.4 EARLY TERMINATION AND ESCALATION RULES.
8.4.1 Feasibility study.
Bayesian probability calculations will be employed to define rules of early termination and end of trial evaluation for feasibility and safety. The tables below indicate termination rules after groups of 3 patients have been treated. Hundreds of patients with certain types of cancer have undergone radiation therapy with protons. Thus, we will assume some "prior" feasibility and safety data for protons delivered at the standard radiation dose for our Bayesian calculations. We will assume prior information equivalent to that of 6 treated patients, which is commonly required to establish feasibility and safety in a standard 3+3 phase I trial design.

Feasibility

We will assume a beta (5,1) prior, which is information equivalent to feasibility established in 5 of 6 treated patients. A feasibility rate > 90% is considered acceptable. If the number of patients deemed feasible is less than or equal to the number in the table below then termination will be considered as it is highly unlikely that the feasibility rate is > 90%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Feasibility				
Patients treated	3	6	9	12
Patients who are feasible	1	4	6	9
Posterior Prob[feasibility rate >90%]	0.04	0.09	0.04	0.08
Action	Terminate enrollment			

Acute Toxicity

We will assume a beta (4,2) prior, which is information equivalent to unacceptable toxicity in 4 of 6 treated patients. An acute toxicity rate < 60% is considered acceptable. If the number of patients with unacceptable toxicity is greater than or equal to the number in the table below, then termination will be considered as it is likely that the toxicity rate is > 60%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Acute Toxicity				
Patients treated	3	6	9	12
Patients who experience acute toxicity	3	5	7	10
Posterior Prob[acute toxicity rate >60%]	0.89	0.88	0.88	0.95
Action	Terminate enrollment			

8.4.2 Phase II study.
8.4.2.1 Simon 2-Stage design to assess acute esophagitis
A Simon 2-stage optimal design will be employed to evaluate Grade 3 or higher acute esophagitis. Patients will be stratified by chemotherapy regimen and proton beam. Historical esophagitis rates are based on CALGB or RTOG trials. A decrease in Grade 3 or higher esophagitis is expected with protons and a more dramatic decrease is expected with PBS protons. After enrollment in stage 1 is complete, the particular stratum will be suspended for 90 days from start of treatment, in order to score the acute toxicity.

IF ENROLLMENT TO STAGE 1 IS COMPLETED FOR A PARTICULAR STRATUM *DURING THE FEASIBILITY STUDY*,THEN ENROLLMENT TO THAT STRATUM MUST BE SUSPENDED UNTIL ACUTE ESOPHAGITIS IS GRADED AND THE SIMON 2-STAGE DESIGN RULE IS APPLIED. FOR EXAMPLE, FOR THE CARBO/TAXOL/PBS STRATUM, STAGE 1 IS EVALUATED IN 7 (n1) PATIENTS. IF 7 SUCH PATIENTS ARE ENROLLED DURING THE FEASIBILITY STUDY, THEN THIS STRATUM MUST BE SUSPENDED PENDING REVIEW OF ESOPHAGITIS TOXICITY (i.e., STOP if 2+ PATIENTS EXPERIENCE TOXICITY). THIS REVIEW IS INDEPENDENT OF THE BAYESIAN EVALUATION OF OTHER ACUTE TOXICITIES IN THE FEASIBILITY STUDY WHICH IS BASED ON 2 PATIENTS TREATED WITH CARBO/TAXOL AND ANY BEAM TYPE.

If the number of patients with Grade 3 or higher esophagitis, deemed related to protons by the PI, equals or exceeds r_1 then enrollment to the stratum is terminated. At the end of the trial, if the number of patients with Grade 3 or higher esophagitis equals or exceeds r then a reduced rate of esophagitis was not established.

Regimen	Proton beam	Historical rate on photons	Expected rate on protons	Simon's 2-stage rule for 10% type I and II error rates				Probability of early termination
				r_1	n_1	r	n	
Carboplatin/Taxol	Scattering	35%	15%	5	15	9	34	0.65
Carboplatin/Taxol	PBS	35%	5%	2	7	3	15	0.77

| Cisplatin/Etoposide | Scattering | 45% | 25% | 10 | 23 | 14 | 39 | 0.64 |
| Cisplatin/Etoposide | PBS | 45% | 15% | 3 | 7 | 6 | 18 | 0.68 |

r_1 = number of patients in stage 1 with Grade 3 or higher acute esophagitis
n_1 = number of patients in stage 1
r = total number of patients with Grade 3 or higher acute esophagitis
n = total number of patients in study

8.4.3 Nelfinavir feasibility study

Nelfinavir will only be added assuming that the Simon 2-stage termination rules are not invoked for a particular stratum. If 1 or fewer dose limiting toxicities are observed in 6 patients treated on a particular stratum, then Nelfinavir will be considered feasible while if 2 or more dose limiting toxicities are observed, then Nelfinavir will be reduced to 625 mg po BID and 6 additional patients will be treated and evaluated for feasibility. Dose limiting toxicities will be scored for 90 days from start of radiotherapy.

8.5 STATISTICAL ANALYSES.

8.5.1 Feasibility study.
The feasibility rate and exact 90% CI will be computed. The reasons why patients were not feasible will be tabulated. Acute and late toxicities will be graded by CTC Version 4.0 and tabulated. Estimation of Event Rates. The table below displays the 90% exact binomial confidence intervals based on 12 patients treated.

No. of Events	%	90% exact CI	No. of Events	%	90% exact CI
0	0.0	17.5*	7	58.3	31.5 , 81.9
1	8.3	.43 , 33.9	8	66.7	39.1 , 87.7
2	16.7	3.0 , 43.8	9	75.0	47.2 , 92.8
3	25.0	7.2 , 52.7	10	83.3	56.1 , 97.0
4	33.3	12.3 , 60.9	11	91.7	66.1 , 99.6
5	41.7	18.1 , 68.5	12	100.0	82.5*
6	50.0	24.5 , 75.5	* 90% 1-sided CI		

8.5.2 Phase II study.

Acute and late toxicities will be graded by CTC Version 4.0 and tabulated for each stratum. Esophagitis rates and 95% confidence intervals will be calculated for each stratum. Metabolic response (CR, PR, <PR) will be scored and tabulated for each stratum. Site of recurrence will be similarly tabulated. PFS and OS will be estimated for each statum using Kaplan-Meier analysis, as a preliminary evaluation of outcome for patient treated with protons plus chemoradiotherapy. Biomarkers will be scored as present/absent and will be cross tabulated with toxicity and metabolic response.

8.5.3 Nelfinavir feasibility study
Acute and late toxicities will be graded by CTC Version 4.0 and tabulated for the 6 subjects enrolled to each stratum.

8.6 SAMPLE SIZE AND TRIAL DURATION.

With an annual accrual of approximately 20 patients, this study plans to enroll up to 130 subjects over 6.5 years (24 on feasibility, 82 additional on stratified phase II, 24 on Nelfinavir feasibility).

9   Safety and Adverse Events

The investigator or research staff will be responsible for detecting, documenting and reporting all events that meet the definition of an AE or SAE as defined in this protocol.

9.1   Definitions

Adverse event

An *adverse event* (AE) is any unfavorable and unintended sign, symptom, sign (including abnormal laboratory findings), illness/disease (new or exacerbated) or experience that develops or worsens in severity temporally associated with the use of the investigational agent/device/procedure. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a Serious Adverse Event (SAE)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

AEs Not to Include:
  o Medical or surgical procedures (e.g. endoscopy, appendectormy); the condition that leads to the procedure is an AE.
  o Situations where an untoward medical occurrence did not occur (elective and/or convenience admission to a hospital).
  o Anticipated day-to-day fluctuation of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen in grade or severity.
  o The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A *Serious Adverse Event* is any medical occurance that at any dose:

- fatal
- life-threatening
  Note: (Subject was at risk of death at the time of the event, not events that hypothetically might have caused death if it were more severe)
- hospitalization or prolongs hospital stay (hospitalization signifies in general, the subject has been detained [at least an overnight stay] at the hospital or emergency department for observation/treatment that would not have been appropriate in a physician's office or outpatient setting).
  Note: Hospitalization for elective treatment, diagnostic purposes or a pre-existing condition that did not worsen from baseline in not considered an AE or SAE. Hospitalization/prolong hospitalization to allow for study efficacy assessment is not an SAE.
- results in persistent or significant disability or incapacity.
  Note: A substantial disruption of a person's ability to conduct normal life functions. Not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient

hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***adverse events (AEs)*** *per protocol definition.*

Clinical Laboratory and Other Safety Assessments
Any abnormal laboratory test result as compared to baseline (.e.g. hematology, clinical chemistry, urinalysis) or other safety assessment (e.g. vital signs), that meet the definition of an AE or SAEs as defined by the CTCAE Version 4.0 are to be recorded as AEs or SAEs.
The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. This assessment will be documented on the lab report or in a timely clinic/progress note.

Disease Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs
An event that is part of the natural course of the disease (e.g. disease progression) does not need to be reported as an SAE. Progression of the subject's cancer will be clearly recorded in the clinic/progress note. Death due to progressive disease is not an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject or if the investigator considers that there was a causal relationship between the investigational agent/treatment/device and the disease progression, then this must be reported as an SAE. Any new cancer must be reported as an SAE.

Preexisting Condition
A preexisting condition is one that is present at the start of the study, prior to administration or exposure to any protocol agents/treatments/devices. A preexisting condition should be recorded as Medical History and becomes an adverse event if the frequency, intensity, or the character of the condition worsens during the study period as defined by the protocol.

Radiation Effect
Radiation side effects are typically divided into those that occur acutely and those that occur later. Common acute radiation side effects include fatigue, skin irritation or erythema, cough, and esophagitis. Typically, these side effects can be controlled with medication. Late side effects that are unlikely to occur are paralysis or cardiac complications. Another rare but serious late side effect is the development of second tumors. It is hoped that proton radiation will substantially reduce both acute and late side effects by reducing the amount of normal tissue that is irradiated.

Acute radiation effect and late radiation effects will be evaluated using the CTCAE 4.0.

Assessment of Causality
The investigator must assess the relationship between the investigation aspect of the protocol and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational aspect of the protocol should be considered and investigated.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

9.2   Assessing and Recording Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning, examination and review of clinical documentation (e.g. lab reports, radiology reports). Information on all adverse events, as defined by the protocol, should be recorded immediately in the source document and also on the adverse event Case Report Form (CRF). It is preferred that events are recorded by diagnosis (where applicable) instead of through signs/symptoms/test results. For example, shortness of breath, chest pain and nausea may have been confirmed as a myocardial infarct through lab test and an ECG, therefore, "MI" or "myocardial infarct" or "heart attack" should be recorded instead of all of the signs/symptoms.

All adverse events meeting the protocol definition, occurring during the study period must be recorded. Full documentation of an event includes start/stop dates, event, grade, expectedness, attribution and outcome. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

All Adverse and Serious Adverse Events will be assessed using NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0).

9.3   Reporting of Serious Adverse Events

9.3.1 Adverse Event Reporting Period

The study period during which Adverse Events must be collected and Serious Adverse Events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. This protocol will begin assessment of AEs and SAEs following the first dose/treatment with any experimental aspect of the protocol. Therefore, only treatment emergent events will be evaluated. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

9.3.2 IRB Notification by Investigator

All events meeting the Penn IRB SOP for Unanticipated Events posing risks to subjects or others will be reported to the IRB as follows:

Unanticipated problems are:
(1) Unforeseen; and
(2) indicate that participants are at increased risk of harm.

The IRB requires investigators to submit reports of the following problems within 10 working days **with one exception**. The one exception for prompt reporting within 10 days applies to death of a research participant as noted below.

Adverse Event (regardless of whether the event is serious or non-serious, onsite or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is both unexpected and related to research procedures.

Note: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts); An event is "related to the research procedures" if the event is deemed probably or definitely related.

If the adverse event involved death as unforeseen and indicates participants or others are at increased risk of harm, report in **three days**.

Unanticipated adverse device effect: Any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, if that effect, problem, or death was not previously identified in

nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects). Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:

- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.

Any adverse event that represents a serious unexpected problem that is rare in absence to drug exposure (agranulocytosis, hepatic necrosis, or Stevens-Johnson syndrome).

Withdrawal from marketing for safety of a drug, device, or biologic used in a research protocol.

Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.

Event that requires prompt reporting to the sponsor (*where applicable*).

Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

Violation, meaning an accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk, or has the potential to occur again.

Breach of confidentiality must also be reported to the institutional Office of Research Compliance and Integrity.

Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

9.3.3 Data and Safety Monitoring Committee (DSMC) Notification by Investigator

All Serious Adverse Events (SAEs), regardless of grade, expectedness or attribution must be reported to the DSMC within **30 days**. Deaths that are possibly, probably or definitely related to the protocol treatment/experience must be reported within **24 hours**. SAEs should be reported to the DSMC for **six months from the date the last subject was treated**.

9.4   Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, rules should be developed that clarify the circumstances and procedures for interrupting or stopping the study. If a central Data and Safety Monitoring Board (DSMB) or Committee (DSMC) is set up for the study, the stopping rules should be incorporated into their safety analysis plan as well.

9.5   Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 11 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The Medical Monitor will be " Dr. David Henry" (a physician who is not directly involved in the trial and is not collaborating with the sponsor/investigator in any other trial). Because of Dr. Henry's background and experience in medical oncology/he is an appropriate Medical Monitor (MM) for this study. In the role, he will review all AEs including grading, toxicity assignments, dose modifications, appropriateness of dose escalation

and all other safety data and activity data observed in the ongoing clinical trial along with discussing relevant animal and toxicology studies and similar investigational agents. The MM may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The investigator will meet with the MM approximately every six months assuming subjects are active on study. Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of MM activity will be maintained in the study specific Regulatory Binder. Copies of an MM report requiring action on the part of the PI to protect subject safety or study integrity must be submitted to the DSMC within 10 business days.

9.5.1   Internal Safety and Compliance

The Abramson Cancer Data and Safety Monitoring Committee is charged with the responsibility of reviewing all SAEs, deviations, Medical/Safety Monitoring reports for all cancer based protocols conducted at the University of Pennsylvania. The DSMC reviews these document and data on a monthly basis and makes recommendation necessary to ensure subject safety and study integrity. Additionally, the DSMC monitors and audits the progress and conduct of all cancer based studies in accordance with their NCI approved Institutional Data and Safety Monitoring Plan.

Protocol Deviations/Exceptions

Occasionally, the investigator may need to deviate from the approved protocol. Deviations are categorized as reportable and non-reportable. Reportable deviations may be urgent or not. Urgent deviations may occur on the spot as necessary to protect the safety of a study subject and do not allow enough time for reporting in advance. However, they must be reported as soon as possible.

All deviations from the study protocol will be handled as follows:

Eligibility - Deviations from established eligibility criteria will not be allowed. If the investigator believes that a subject would truly benefit from the protocol therapy and there are no other viable options, then the protocol should be amended to reflect the change in restrictions. There may be situations where the deviation from eligibility may not warrant a study amendment (e.g. a necessary test/procedure being a few days outside of the eligibility window, subject taking a concomitant medication within recent timeframe etc.). These deviations must still be reviewed and approved in advance of enrolling the subject.

The IRB must be notified of the planned deviation and a copy of all applicable amended study documents must be sent to the IRB. The planned deviation must also be submitted to the DSMC for evaluation. The DSMC does not approve deviations but rather provides and unbiased assessment of the appropriateness of the request. Both committees must be given sufficient time to review the request, gather additional information as necessary and make a decision.

Other Reportable - Deviations that affect the protocol treatment administration (i.e. dose administered, route/method of administration etc.), dose adjustment schema, stopping rules, modification to follow-up, removal of safety assessments/follow-up visits, accrual goal or any deviation that may affect the study outcome analysis or study integrity must be approved by the IRB and reviewed by the DSMC.

Non-Reportable - During the course of a study, there may be times when deviations are outside of the control of the investigator (i.e. subject not showing up for a study visit, lab errors, subject confusion etc.). These type of deviations are not reportable (unless they occur at a level that impacts any of the reportable categories) but must be documented in a timely manner to show the impact of the deviation and corrective/follow-up actions that were taken. Documentation can be in the clinic/progress notes or note/memo to file. Notes/memos should be signed and dated.

Reporting Deviations/Exceptions

All deviations/exceptions will be reviewed and approved by the study Medical Monitor before being sent to the IRB and DSMC. Reports to the IRB and DSMC will be done via the DSMC website www.ctsrmc.org. Reportable deviations must also be sent to the study Medical Monitor (if applicable).

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subject(s) in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.1.1 Unintentional Disclosure:

Upon discovering that PHI may have been or has been disclosed to anyone not specified in the HIPAA disclosure consent, the investigator will report the disclosure to the Institutional Officer in the Office of Research Compliance and Integrity. The report should contain details about the type of data disclosed and the extent of the disclosure (number of subjects, who received it etc.).

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a research study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents and may be paper, electronic or a combination of both. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". If the item is unknown, write "UNK". All entries should be **PRINTED** legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above/next to the item, then initial and date it. Do not backdate changes.

10.4 Records Retention

The DHHS regulation (45 CFR 46.115) states that records relating to research conducted or supported by any Federal department or agency shall be retained for at least 3 years after completion of the research.

The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research for these same types of studies.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 3 years from the date of full study terminations. If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

HIPAA Retention Period (45 CFR164.530(j):
Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 6 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain 6 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will maintained for 6 years after the research is fully terminated.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan
The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

Auditing and Inspecting
The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations
This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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Attachments - none