Phase II Study of Accelerated and Adaptive Radiation Therapy for Locally-Advanced NSCLC

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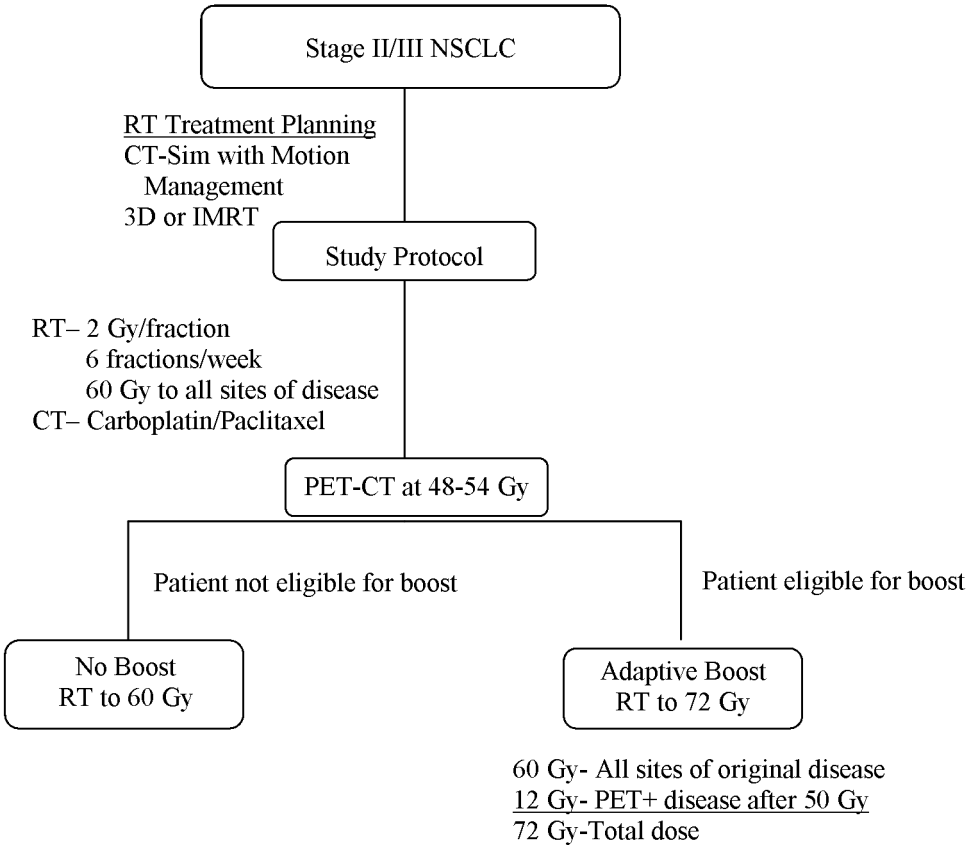
Schema



Eligibility for Boost

Dosimetric criteria (composite of initial and boost plans)

1. Lung V20 ≤ 35%
2. Spinal cord Dmax < 50 Gy
3. Esophageal V60 ≤ 20%
4. Heart V30 ≤ 50%
5. Brachial plexus Dmax ≤ 64 Gy

Clinical criteria

1. No evidence of local, regional, or distant progression on interim PET-CT
2. No grade 3-4 non-hematologic toxicity related to radiation therapy after completing 60 Gy

1.0 Background and Significance

1.1 Rationale for Dose Intensification

Historically, the conventional treatment for locally-advanced non-small cell lung cancer (NSCLC) was RT alone. RTOG 73-01 randomized 383 patients with NSCLC to 40 Gy (split course), or a continuous course of 40 Gy, 50 Gy, or 60 Gy [1]. While local control was improved with 60 Gy, 5-year survival rate was only ~5% and did not differ between treatment arms. Due to improved intrathoracic control with 60 Gy, this became standard. However, local failure still occurred in most patients. In the 1980s-1990s, two approaches were taken to increase the effectiveness of conventional RT: adding chemotherapy to RT (first sequentially then concurrently) and intensifying the radiation therapy (dose escalation and/or altered fractionation).

1.1.1 Chemotherapy with Conventional RT

Several randomized studies compared RT alone (60 Gy) with cisplatin-based chemotherapy followed by RT [2-4]. These studies demonstrated a modest, but statistically significant, improvement in overall survival from ~5% with RT alone to ~10% with sequential chemotherapy. Subsequent randomized studies compared sequential chemotherapy with concurrent chemotherapy and found the latter to be superior[5,6], with 5-year survival reaching 15-20% with concurrent chemotherapy and RT. Unfortunately, even with this approach, local failure occurs in ~50% or more of patients[7,8].

1.1.2 RT Dose Intensification without Chemotherapy (Table 1)

The second approach attempting to improve local control and survival in locally-advanced NSCLC was intensifying the RT. Initial studies did not include chemotherapy. The largest randomized study was performed in the United Kingdom and evaluated continuous, hyperfractionated, accelerated radiotherapy (CHART)[9]. Patients with locally-advanced NSCLC were randomized to conventional RT (2 Gy qd to 60 Gy over 42 days) or CHART (1.5 Gy tid to 54 Gy in 12 consecutive days). CHART was associated with a 21% relative improvement in local control which translated to an improvement in survival (20% vs 13% at 3 years). However, the incidence of grade 3-4 esophagitis was also increased with accelerated treatment (19% vs 3%). This treatment approach has not been incorporated into broad practice for several reasons- lack of chemotherapy, logistical challenges of a tid schedule, and increased rates of esophagitis. Of note, two smaller studies, with different fractionation schedules, failed to demonstrate an advantage with RT intensification[4,10].

1.1.3 RT Dose Intensification with Chemotherapy (Table 1)

As outlined above, chemotherapy improves survival in locally-advanced NSCLC when given with conventional RT. Several studies evaluated RT dose intensification combined with chemotherapy. A randomized study from the Eastern Cooperative Oncology Group (ECOG 2597) compared conventional radiation therapy (2 Gy qd to 64 Gy) with hyperfractionated accelerated RT (1.5 Gy tid to 57.6 Gy)[11]. All patients received sequential chemotherapy with carboplatin and paclitaxel. The study was closed early after enrolling 141 patients for multiple reasons: sequential instead of concurrent chemotherapy, logistical challenges of a tid fractionation schedule, and increased rates of esophagitis. Local control was not reported but survival at 3 years was superior with accelerated RT (34% vs 14%), but this was not statistically significant (p=0.28). Grade 3-4 esophagitis was more common in the experimental arm (25% vs 16%). Two additional randomized studies, one using a hyperfractionated regimen[5] and the other using a split course of RT [12] (which may have decreased the effectiveness of RT), failed to demonstrate a survival advantage with RT dose-intensification.

Multiple phase I/II studies [13,14] have demonstrated that 74 Gy is the maximally-tolerated dose when given with conventionally fractionated (2 Gy qd) with concurrent chemotherapy. These studies provided the basis for the Intergroup randomized study comparing 60 Gy and 74 Gy with concurrent chemotherapy with

carboplatin and paclitaxel on a weekly schedule, and after completion of chemoradiotherapy, two cycles of systemic dose carboplatin and paclitaxel were given (referred to as consolidation therapy). This study randomized patients to conventional dose RT (2 Gy qd to 60 Gy) or high-dose RT (2 Gy qd to 74 Gy). The high-dose arm was discontinued early after an interim analysis demonstrated futility. Median survival was 28.7 months for the conventional dose arm versus 20.3 months for the high-dose arm (p=0.004). This study suggests that dose intensification is not successful when the full dose of radiation therapy is delivered to the entire initial treatment volume. Of note, a secondary randomization to concurrent and adjuvant cetuximab demonstrated no benefit.

Table 1
Randomized Studies Evaluating Altered Fractionation in NSCLC

Study	n	Treatment	Survival	Grade 3-4 Esophagitis
Radiation therapy alone				
Sause[4]	310	RT (60 Gy, 2 Gy qd)	5%	NS
		RT (69.6 Gy,1.2 Gy bid)	6% (5 years)	
Ball[10]	99	RT (60 Gy, 2 Gy qd)	10%	12%
		RT (60 Gy, 2 Gy bid)	13% (5 years)	32%
Saunders[9]	563	RT (60 Gy, 2 Gy qd)	13%	3%
		RT (54 Gy, 1.5 Gy tid)	20% (3 years, p<0.01)	19%
Radiation therapy and chemotherapy				
Belani[15]	119	CT→RT (64 Gy, 2 Gy qd)	14%	16%
		CT→RT (57.6 Gy, 1.5 Gy tid[a])	34% (3 years, p=0.28)	25%
Schild[12]	234	CT-RT (60 Gy, 2 Gy qd)	37%	20%
		CT-RT (60 Gy, 1.5 Gy bid[b])	40% (2 years)	18%
Curran[5]	397	CT-RT (60 Gy, 2 Gy qd)	21%	NS
		CT-RT (69.6 Gy, 1.2 Gy bid)	17% (4 years)	
Bradley[16]	424	CT-RT (60 Gy, 2 Gy qd)	28.7 months	7%
		CT-RT (74 Gy, 2 Gy qd)	20.3 months (median, p=0.004)	15%

NS- not stated; [a]2nd daily fraction 1.8 Gy; [b]split course, which will decrease rates of esophagitis but also decrease local tumor control.
Belani- carboplatin and paclitaxel
Schild- cisplatin and etoposide
Curran- cisplatin and vinblastine
Bradley- carboplatin and paclitaxel

1.1.4 Summary of Rationale for Dose Intensification

Based on RTOG 0617, the current standard of care for locally-advanced NSCLC is concurrent chemotherapy with conventional RT (60-66 Gy). Administering higher doses to all sites of disease appears to be counterproductive. However, despite concurrent chemotherapy and radiation therapy, local failure is common, occurring in ~50%[7,8] or more[2] of patients.

A recent meta-analysis demonstrated a statistically significant improvement in survival with accelerated radiation therapy[17]. We recently completed a phase I study that demonstrated that the dose of RT could be safely escalated to 74 Gy using accelerated RT (6 fractions/week) and concurrent chemotherapy[18]. Another prospective study at our institution demonstrated that adapting the RT using interim PET is feasible[19]. In this study, all patients received a standard dose of RT (60 Gy) to all sites of original disease. A PET was performed at 50 Gy. If dosimetric constraints could be met, and the patient was tolerating treatment well without high-

grade toxicity, a boost dose of 10 Gy (total dose- 70 Gy) was given to residual FDG-avid disease apparent at 50 Gy on the interim PET. The metabolic complete response rate at 50 Gy was 8%.

For this phase II study, we plan to investigate a strategy of accelerated and adaptive RT. Patients with locally-advanced NSCLC will receive RT (6 fractions/week), to a total dose of 60 Gy. Patients will undergo a PET at 50 Gy. In the absence of high-grade toxicity, and if strict normal tissue dosimetric constraints can be met, then a 12 Gy boost will be administered to residual FDG-avid disease to a total dose of 72 Gy. All patients will receive concurrent weekly carboplatin and paclitaxel.

1.1.5 Rationale for Carboplatin and Paclitaxel

Carboplatin and paclitaxel is a widely accepted platinum-doublet chemotherapy regimen that has been studied extensively in the setting of concurrent radiation therapy for locally-advanced non-small cell lung cancer. It is listed as an appropriate chemotherapy regimen when given with concurrent RT by the NCCN and was the chemotherapy backbone for the recently reported RTOG 0617 regimen[16]. Older trials have employed combination chemotherapy with cisplatin and etoposide, cisplatin and vinblastine, and mitomycin, vindesine, and cisplatin (MVP). Due to concerns about the toxicities and tolerability of the cisplatin-based chemotherapy several trials have investigated more recently developed chemotherapy combinations.

A three-arm phase III perform by West Japan Thoracic Oncology Group trial (WTJOG) investigated the combination of weekly carboplatin (AUC=2) and paclitaxel (40 mg/m2) concurrent with thoracic radiation therapy (TRT) followed by systemic dose carboplatin (AUC=5) and paclitaxel (200 mg/m2) or carboplatin (AUC=2) and irinotecan (20 mg/m2) concurrent with RT followed by systemic dose carboplatin (AUC=5) and irinotecan (50 mg/m2 on days 1,8) compared to the standard therapy of mitomycin, vinblastine and cisplatin **(**MVP) concurrent with RT followed by two cycles of MVP[20]. The median survival observed in the MVP arm and carboplatin and paclitaxel arms were 20.5 and 22 months, respectively. The 5-year OS rate in MVP and carboplatin and paclitaxel arms were 17.5% and 19.8%, respectively. The incidence of grade 3 or 4 neutropenia, febrile neutropenia, and gastrointestinal disorders observed on the MVP were statistically significantly higher than the incidence observed on the carboplatin and paclitaxel arm. The number of patients who received 0,1, or 2 cycles of systemic dose chemotherapy in the carboplatin and paclitaxel arm was 30.6%, 19.7%, and 49.7%, respectively; significantly more patients in the carboplatin and paclitaxel arm received two courses of the systemic therapy (p=0.002). The conclusion of the trial was that the combination of carboplatin and paclitaxel had a more favorable toxicity profile and should be considered a standard regimen in the management of locally advanced NSCLC.

A three arm, non-comparative randomized phase II trial investigated the optimal sequencing of carboplatin and paclitaxel with daily thoracic radiation therapy to 63 Gy/7 weeks/34 fractions.32 Patients were randomized to two cycles of induction carboplatin (AUC=6) and paclitaxel (200 mg/m2) followed by TRT alone (arm 1), two cycles of induction carboplatin (AUC=6) and paclitaxel (200 mg/m2) followed by concurrent carboplatin (AUC=2) and paclitaxel (45 mg/m2) with TRT (arm 2), or concurrent carboplatin (AUC=2) and paclitaxel (45 mg/m2) with TRT followed by systemic dose carboplatin (AUC=2) and paclitaxel (200 mg/m2) (arm 3)[11]. The median overall survival observed in arms 1, 2, and 3 was 13.0, 12.7 and 16.3 months, respectively. The rate of grade 3 and 4 esophagitis observed in arms 1, 2, and 3 was 3%, 19%, and 28%, respectively ($p<0.001$); the higher rate of esophagitis in the concurrent chemoradiotherapy. Of the patients enrolled in arm 3, 25% did not receive systemic chemotherapy, 8% received a single cycle, and 67% received two cycles. The conclusion of the authors was the weekly concurrent carboplatin and paclitaxel followed by the consolidation carboplatin and paclitaxel was associated with the best outcome.

The combination of these trials led to the adoption of carboplatin and paclitaxel weekly with concurrent TRT followed by consolidation carboplatin and paclitaxel for two cycles as the chemotherapy platform for the ROG 0617 phase III trial previously discussed. Patients received weekly carboplatin (area under curve (AUC) of 2) and paclitaxel 45 mg/m^2 weekly during concurrent TRT, and followed by two cycles of carboplatin (AUC of 6) and paclitaxel (200 mg/m^2) every 3 weeks for 2 cycles. In the patients assigned to the 60 Gy and 74 Gy arms concurrent chemotherapy was delivered per protocol in 88% and 85% of patients, respectively, and with acceptable variation in additional 6% of patients of both arms. Consolidation chemotherapy was delivered per protocol in the 60 Gy and 74 Gy arms in 70% and 64% of patients, respectively, and with acceptable variation in 5% of patients. Finally, a VA study showed no difference in clinical outcomes, with less toxicity, when carboplatin and paclitaxel are utilized instead of cisplatin and etoposide[21].

Since weekly administration of carboplatin and paclitaxel was given concurrently with thoracic irradiation in above studies, we chose to administer these agents in the same fashion for this phase II trial.

1.1.6 Rational for Primary Endpoint

PERCIST (Positron Emission Tomography Response Criteria in Solid Tumors) provides guidelines on how to report responses to therapy based on PET-CT[22,23]. PET-CT response has been shown to be prognostic in a variety of clinical scenarios in lung cancer including after induction therapy[24]. In one study, PET was performed after neoadjuvant chemoradiotherapy (40-50.4 Gy). Complete or partial metabolic response using PERCIST criteria was predictive of loco-regional, distant, and overall progression-free survival[25]. The complete metabolic response rate was 2%; the partial metabolic response rate was 45%. Interim PET-CT response may provide a more rapid assessment of the efficacy of therapy than conventional clinical endpoints such as progression-free or overall survival.

2.0 Purpose

Despite concurrent chemotherapy and radiation therapy, local/regional failure occurs in ~50% of patients with locally-advanced NSCLC. Clinical studies have demonstrated that accelerated fractionation (giving the same total dose in a shorter period of time) improves outcomes in several malignancies, including lung cancer[17]. Administering higher than conventional doses of RT to all sites of original disease leads to inferior outcomes[16]. Adapting the RT approach, giving a higher dose to slowly responding disease as assessed with interim PET has been shown to be feasible[19]. This is a prospective phase II study designed to study an accelerated and adaptive RT approach for locally-advanced NSCLC.

2.0 Objectives

2.1 Primary Objective

To determine the metabolic complete response rate, assessed using interim PET-CT, in an accelerated fashion (2 Gy/fraction, 6 fractions/week) with concurrent chemotherapy.

Hypothesis- The metabolic complete response rate, assessed using interim PET-CT between 48Gy and 54Gy, will increase from 8% to 20% with RT dose acceleration (6 fractions/week).

2.2 Secondary Objectives

2.2.1 To determine how many patients will be eligible for an RT boost after assessment with an interim PET-CT between 48Gy and 54Gy, delivered in an accelerated fashion (6 fractions/week) with concurrent chemotherapy.

2.2.2 To evaluate clinical outcomes including overall survival, progression-free survival, and local control with an accelerated and adaptive RT approach.

2.2.3 To correlate clinical outcomes (survival, progression-free survival, local control) with interim PET-CT responses using PERCIST criteria.

3.0 Patient Recruitment

This will be a prospective study with all eligible patients offered enrollment prior to their radiation treatment. The subject population (with no gender or minority restrictions) will include adult patients meeting the eligibility criteria. Inclusion of women and minorities will be encouraged. Lung cancer is a diseases of adults- patients under 18 will be excluded from this study. All patients must sign an IRB approved informed consent prior to enrollment

4.0 Eligibility Criteria

Conditions for Patient Eligibility

1. Histologic/cytologic documentation of non-small cell lung cancer (NSCLC)
2. Unresectable stage II-III disease, per AJCC 8th edition
3. Zubrod/ECOG performance status 0-1
4. Weight loss < 10% in preceding 3 months prior to diagnosis
5. Adequate organ function defined as the following
    1. Absolute neutrophil count of ≥ 1,500 and platelet count ≥ 100,000
    2. Cockcroft calculated creatinine clearance of ≥ 45 ml/min or 1.5 x the upper limit of normal (ULN)
    3. A total bilirubin ≤ 1.5 ULN, aspartate aminotransferase (AST) ≤ 2.0 x ULN
6. ≥ 18 years of age.
7. Negative pregnancy test in women of child-bearing potential
8. Signed study-specific informed consent.
9. No prior chemotherapy or radiotherapy for NSCLC
10. No prior mediastinal or thoracic radiation

Conditions for Patient Ineligibility

1. Prior thoracic irradiation.
2. Medical contraindications to thoracic irradiation.
3. Pre-existing sensory neuropathy of grade ≥ 2
4. Pleural effusion: when pleural fluid is visible on both CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative. Patients with effusions that are minimal (i.e. not visible on chest x-ray) or that are too small to safely tap are eligible
5. Patients with contralateral hilar involvement

5.0 Pretreatment Evaluation

1. A complete history and physical to include recent weight loss and performance status
2. Laboratory studies will include a complete blood count (CBC) with differential, complete metabolic panel, and pregnancy test in women of child-bearing potential
3. Baseline staging exams within 8 weeks of signing written consent:
    a. PET-CT (skull-base to mid-thigh)
    b. Brain MRI with contrast (preferred) or head CT scan with and without contrast

6.0 Registration Procedures

Only radiation oncologists listed as Key Personnel for this study by the Duke University Health System (DUHS) IRB and who have completed the DUHS required ethics training may enroll patients on this study. The patient's primary medical oncologist will be apprised of the patient's intent to participate on study. Following verification of eligibility the patient will be assigned a sequential study ID number.

7.0 Protocol Treatment

7.1 Radiation Therapy

Radiation therapy is to be initiated concurrently with the first cycle of chemotherapy. All radiation planning and treatment procedures are standard of care.

Equipment
All patients will be treated using either three-dimensional or intensity modulated (including volumetric modulated arc therapy- VMAT) techniques with a linear accelerator using photon energies of 6, 10, and/or 15 MV.

Treatment Planning
Treatment planning procedures are standard of care. A custom immobilization device will be designed for each patient. Intravenous and oral contrast are recommended but not mandated. A CT-Sim procedure will be performed with respiratory management on all patients. At the discretion of the treating physician, patients may be treated with breath hold techniques if this is deemed appropriate.

Target Volume
The gross tumor volume (GTV) will include the primary tumor (GTV-Lung) as well as PET positive lymph nodes in regional lymph nodes (GTV-LNs). These volumes will be adjusted to account for motion observed on the 4D CT dataset. The GTV-Lung will be expanded by 5 mm to account for possible microscopic extension beyond the visible primary tumor mass. The GTV-LNs will be expanded by 3 mm to allow for microscopic extracapsular extension. The expanded lung and lymph node volumes will be combined to create a clinical target volume (CTV). The CTV will be expanded by 3-5 mm to create a planning target volume (PTV) to account for daily set-up uncertainty and motion that may not have been accounted for in the 4D CT scan. The PTV will be the final target for radiation treatment planning.

Treatment Planning Technique
Patients can undergo three-dimensional or intensity-modulated radiation therapy (including VMAT). An original plan to 60 Gy will be designed.

The following dose constraints are *recommended* per standard of care:

1. Lung V20 (volume of lung receiving 20 Gy or more) ≤ 35%
2. Spinal cord Dmax (maximum point dose) < 50 Gy
3. Heart V30 (volume of heart receiving 30 Gy or more) ≤ 50%
4. Esophagus V60 (volume of esophagus receiving 60 Gy or more) ≤ 20%
5. Brachial plexus Dmax ≤ 64 Gy

RT Treatment

Patients will be set up daily using daily kV imaging +/- cone-beam CT. Typically, radiation will be given with 6 weekly fractions (with two fractions administered once a week, preferably on Fridays, separated by 6 hours). Patients may begin radiation therapy on a day other than Monday. In such cases, they will receive daily radiation treatments and will receive two fractions on one day of that week (preferably Fridays).

During weeks that have holidays, the number of fractions delivered will be at the discretion of the treating radiation oncologist. Any missed treatment(s) during a holiday will be added at the end of radiation.

It will not be considered a protocol deviation if a patient receives less than 6 fractions during a holiday week or during the first week of radiation therapy.

Treatment Interruptions during RT

Treatment breaks due to radiation-induced esophagitis will be given at the discretion of the radiation oncologist. Other (less common) reasons for a treatment break will be:

1. Febrile neutropenia (ANC ≤ 500). RT will be resumed once the ANC is >800 and the patient has been afebrile for at least 24 hours.
2. Grade 3 thrombocytopenia associated with bleeding or grade 4 thrombocytopenia (platelets < 20,000). RT will be resumed once the platelets are > 20,000.
3. Non-hematologic grade 3-4 toxicity if felt by treating radiation oncologist that a break is necessary (i.e. significant skin reaction).

7.2 Chemotherapy

Primarily standard of care concurrent and consolidation chemotherapy is administered using carboplatin and paclitaxel. However, any chemotherapy regimens per the National Comprehensive Cancer Network (NCCN) version 2.2018 issued on December 19, 2017 for non-small cell lung cancer will be acceptable for the concurrent and consolidation phase, at the discretion of the treating physician. Premedication, adjustments to dosing schedules, discontinuation of chemotherapy, and/or dose modifications, and/or alternative systematic therapy will be determined by the treating medical oncologist per clinical assessment. General guidelines for concurrent and consolidation chemotherapy are included in the protocol.

Concurrent Chemotherapy:

Concurrent chemoradiotherapy: given weekly during the duration of thoracic radiation to include boost week.

Treatment administration

Agent	Dose	Infusion time	Days
Paclitaxel	45 mg/m^2	1 hour	Weekly
Carboplatin	AUC=2	30 minutes	Weekly

AUC= area under curve

Consolidation Chemotherapy:
Consolidation chemotherapy: beginning ~4 weeks after completion of concurrent chemoradiotherapy.

Treatment administration

Agent	Dose	Infusion time	Days
Paclitaxel	200 mg/m^2	3 hours	1
Carboplatin	AUC=6	30-60 minutes	1

7.2.1 Concurrent and Consolidation Chemotherapy Guidelines

1. Ototoxicity: For grade ≥ 3 toxicity discontinue carboplatin permanently
2. Hypersensitivity reactions: For grade 3 reactions, in subsequent cycles use double dose steroids pretreatment and decrease infusion rate for the first 1/3 of the infusion. For last 2/3 of infusion, double the rate of the infusion. For documented grade 4 hypersensitivity reactions to paclitaxel discontinue paclitaxel
3. **Cardiotoxicity:** If patient develops chest pain, hypotension, or arrhythmia other than asymptomatic bradycardia, the paclitaxel infusion should be stopped and patients should not receive further paclitaxel. For asymptomatic sinus bradycardia, the infusion does not need to be stopped and patient should be observed carefully for development of symptoms of bradycardia.
4. Hepatic dysfunction

AST **Bilirubin**	Paclitaxel
< 2.0 ULN and < 1.5 mg/dl	100%
2.0-5.0 X ULN and < 1.5 mg/dl	50%
> 5.0 X ULN or ≥ 1.5 mg/dl	0%

Check labs weekly and if labs return to normal (AST< 2.0 x ULN and bilirubin < 1.5 mg/dl) within 3 weeks, reinstitute paclitaxel at 100% of dose. If AST > 5.0 x ULN or bilirubin > 1.5 mg/dl after 3 weeks, consider discontinuing chemotherapy.

7.2.2 Concurrent Chemotherapy Guidelines
Concurrent chemoradiotherapy: given weekly during the duration of thoracic radiation.

Treatment administration

Agent	Dose	Infusion time	Days
Paclitaxel [a]	45 mg/m^2	1 hour	Weekly
Carboplatin [b]	AUC=2	30 minutes	Weekly

AUC= area under curve

[a] Premedications for Paclitaxel
1. Dexamethasone 20 mg PO on the evening prior to and morning of paclitaxel or 20 mg IV 30 minutes prior to paclitaxel administration.
2. Diphenhydramine 50 mg IV (or equivalent) 30 minutes prior to paclitaxel administration.
3. Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) 30 minutes prior to paclitaxel.

[b] Carboplatin should be infused following the administration paclitaxel

The Calvert formula (Dose = AUC X [CrCl + 25]) will be used to calculate the carboplatin dose. Carboplatin dose calculated using the Calvert equation, and using the baseline creatinine obtained prior to day 1of CRT. The patient's glomerular filtration rate as creatinine clearance (CrCl) in mL/min will be estimated using the

Cockcraft-Gault formula, and the maximum CrCl that will be used in the calculation of carboplatin dose is a CrCl=125.

Cockcroft-Gault formula:

For males: Creatinine clearance (mL/min) = (140 – age) x weight in kilograms
72 x serum creatinine in mg/dl

For females: use same formula but multiply by 0.85 for creatinine clearance.

Dose Modifications during Concurrent Therapy

Dose levels during concurrent therapy

Agent	Starting dose	Dose level -1
Paclitaxel	45 mg/m^2	Not applicable
Carboplatin	AUC=2	Not applicable

There will be no dose modifications for paclitaxel and carboplatin during concurrent chemotherapy

Guidelines for holding Paclitaxel/Carboplatin for Hematologic Toxicity

Toxicity NCI CTCAE Grade (CTCAE v 4.0)	**Paclitaxel Dose At Start of Subsequent treatment of Therapy[a]**	**Carboplatin Dose at Start of Subsequent Therapy[a]**
Neutropenia		
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Hold therapy[b]	Hold therapy[b]
4 (<500/mm^3)	Hold therapy[b]	Hold therapy[b]
Neutropenic fever	Hold therapy[b]	Hold therapy[b]
Thrombocytopenia		
1 (<LLN-75,000/mm^3)	Maintain dose level	Maintain dose level
2 (50,000-74,999/mm^3)	Hold therapy[b]	Hold therapy[b]
3 (25,000-49,999/mm^3)	Hold therapy[b]	Hold therapy[b]
4 (<25,000/mm^3)	Hold therapy[b]	Hold therapy[b]
Other Hematologic toxicities	There will be no dose modifications for changes in leukopenia or lymphopenia.	

[a] Dose levels are listed above

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

Doses that are missed during weekly schedule concurrent with radiation will not be made up
If paclitaxel and/or carboplatin doses must be withheld for greater than two consecutive weeks, the drug(s) may be held permanently for the duration of concurrent therapy.

Parameters for holding Paclitaxel/Carboplatin therapy for Non-Hematologic Toxicity during concurrent Therapy

Worst Toxicity NCI CTCAE Grade (CTCAE v 4.0) [a,b]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy**[b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy**[c]
Neuropathy[c]		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other Non-Hematologic toxicities		
≥ Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

a. For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, follow the guidelines listed above.
b. Paclitaxel for Neuropathy :If paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of concurrent therapy

c. Carboplatin Dose Modifications for Renal Toxicity **:** A > 10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose

7.2.3 Consolidation Chemotherapy Guidelines

Consolidation chemotherapy and/or immunotherapy will be at the discretion of the treating medical oncologist based on clinical assessment. The consolidation phase will begin 4 weeks after completion of radiotherapy (Cycles 5 and 6; Cycle = 21 days). If the patient is unable to begin chemotherapy at the 4-week time point following radiotherapy, the chemotherapy may be delayed up to an additional 4-weeks. Patients will be required to have an ANC≥ 1,500/mm^3 or platelet count > 100,000 mm^3.

Treatment administration

Agent	Dose	Infusion time	Days
Paclitaxel [a]	200 mg/m^2	3 hours	1
Carboplatin [b]	AUC=6	30-60 minutes	1

Premedications for Paclitaxel

1. Dexamethasone 20 mg PO on the evening prior to and morning of paclitaxel or 20 mg IV 30 minutes prior to paclitaxel administration.
2. Diphenhydramine 50 mg IV (or equivalent) 30 minutes prior to paclitaxel administration.
3. Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) 30 minutes prior to paclitaxel.
4. Anti-emetic therapy should be given at the discretion of the treating physician.

[b] The Calvert formula (Dose = AUC X [CrCl + 25]) will be used to calculate the carboplatin dose. Carboplatin dose calculated using the Calvert equation, and using the creatinine on day 1 of each cycle in order to adjust for any potential change in renal function. Patient's glomerular filtration rate as creatinine clearance (CrCl) in mL/min will be estimated using the Cockcraft-Gault formula, and the maximum CrCl that will be used in the calculation of carboplatin dose is a CrCl=125.

Cockcroft-Gault formula:

For males: Creatinine clearance (mL/min) = $\frac{(140 - \text{age}) \times \text{weight in kilograms}}{72 \quad \text{serum creatinine in mg/dl}}$

For females: Use same formula but multiply by 0.85 for creatinine clearance

Dose Modifications During Consolidation Therapy

Dose levels for paclitaxel and carboplatin during consolidation chemotherapy

Agent	Starting dose	Dose level -1
Paclitaxel	200 mg/m2	150 mg/m2
Carboplatin	AUC=6	AUC=4.5

Paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity

Toxicity NCI CTCAE Grade (CTCAE v4.0)	**Paclitaxel Dose at Start of Subsequent Cycles of Therapy[a,c]**	**Carboplatin Dose at Start of Subsequent Cycles of Therapy[a,c]**
Neutropenia		
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recover in 1 week, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recovered in 1 weee, decrease by 1 dose level when ≥ 1,500 mm^3
3 (500-999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recovered in 1 week, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recovered in 1 week, decrease by 1 dose level when ≥ 1,500 mm^3

4 (<500/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Thrombocytopenia		
1 (≥ 75,000/mm^3)	Maintain dose level	Maintain dose level
2 (50,000-74,999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recovered in 1 week, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recovered in 1 week, decrease by 1 dose level when ≥ 75,000 mm^3
3 (25,000-49,999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recovered in week, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not recovered in 1 week, decrease by 1 dose level when ≥ 75,000 mm^3
4 (<25,000/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3
Other Hematologic toxicities	There will be no dose modifications for changes in leukopenia or lymphopenia.	

[a] Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level will not be allowed.
[b]Repeat lab work weekly and resume chemotherapy based on this table.
[c]Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation cycles.

Paclitaxel/Carboplatin Dose Modifications for Non-Hematologic Toxicity During Consolidation Therapy

Worst Toxicity NCI CTCAE Grade (CTCAE v4.0) [a]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy**[b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy**[b]
Neuropathy		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold treatment until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities		
Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

a. For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study drugs. For neuropathy, follow the guidelines above.
b. Dose level are relative to the worst toxicities in previous cycle

Paclitaxel Dose Modifications for Neuropathy: if paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of the consolidation therapy.

7.3 Interim PET-CT

Patients will undergo an interim PET-CT after 4 weeks of radiation therapy between 48Gy and 54 Gy. The interim PET-CT may be delayed up to 60 Gy. Patients can have diabetes but their blood sugar must be <200 mg/dL at the time of interim PET-CT simulation. If the PET-CT cannot be completed due to hyperglycemia or other issues, the patient will complete radiation therapy to a dose of 60 Gy with no boost. The PET-CT will be obtained based on institutional standards. In general, patients will be administered 8-15mCi (exact activity prescribed based on patient weight) of ^{18}F-FDG through IV injection and rested before PET-CT scanning. The PET imaging will be started approximately 60 minutes after FDG injection with acquisition time of 3.5 minutes per bed position. The iterative algorithm incorporating point spread function (PSF) and time of flight (TOF) will be used for PET-CT image reconstruction. In conjunction with the PET, the patient will undergo a CT-Sim treatment planning scan for re-planning.

The planning PET-CT will be exported to our treatment planning software. The treating radiation oncologist will contour all sites of residual FDG-avid disease (defined as disease with FDG uptake > background uptake in the liver assessed using visual analysis supplemented with semi-quantitative values such as SUVmax) that corresponds with areas of original involvement. These volumes will be reviewed with a nuclear medicine physician and/or radiologist to assess response and confirm residual FDG-avid disease. Patients who achieve a complete metabolic response, defined as complete resolution of FDG uptake, with FDG uptake less than the mean standardized uptake value of the liver corrected for lean body mass, and indistinguishable from that of the surrounding background, will not be eligible for a boost. A boost plan will be designed using the same expansion criteria as previously outlined. Patients will be eligible for a boost (2 Gy qd to 12 Gy, 6 fractions/week, total dose 72 Gy) if all of the following are met:

Eligibility for Boost

Dosimetric criteria (composite of initial and boost plans)

1. Lung V20 ≤ 35%
2. Spinal cord Dmax <50Gy
3. Esophageal V60 ≤ 20%
4. Heart V30 ≤ 50%
5. Brachial plexus Dmax ≤ 64 Gy

Clinical criteria

1. No evidence of local, regional, or distant progression on interim PET-CT
2. No grade 3-4 non-hematologic toxicity related to radiation therapy after completing 60 Gy

If dose-volume histogram (DVH) metrics to an organ exceeds any of these criteria based on the initial plan, but the boost plan does not contribute any further dose to that organ, then the patient is still eligible for a boost.

7.4 Treatment Assessments

Patients will be assessed on a weekly basis as part of routine clinical care by the radiation oncologist and treatment-related toxicities will be prospectively recorded. Patients will also be evaluated routinely by the medical oncologist per the standard of care. As necessary patients will be seen more often.

Blood work will be obtained weekly during treatment at the discretion of the treating medical oncologist.

8.0 Confidentiality and Protection of Research Subjects

All study-related materials will be stored electronically on password-protected computers within locked offices. Paper study-related forms will similarly be stored in locked offices. All personnel involved in the conduct and analysis of data from the study will have ethics training in the protection of research subjects. The research data security plan (RDSP) will be reviewed and approved by the appropriate IT security personnel.

9.0 Protocol Management and Data Collection

This study will be conducted in accordance with Good Clinical Practice guidelines and Duke University School of Medicine policies. Data will be entered on the study specific e-forms in a password protected REDCap database.

9.1 Adverse Events:

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of radiation therapy, whether or not related to use of the radiation therapy. Abnormal laboratory values that require therapy, adjustment in prior therapy, or are grade 2 and higher will be considered an adverse event and will be captured. All AEs at the start of concurrent chemoradiation therapy (CRT) through 30 days post CRT will be captured in the adverse events case report.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

10.0 Risk/Benefit Assessment

Patients with locally-advanced NSCLC are at high risk of relapse and death. Long-term (4-5 years) survival is ~15-20% in patients with good performance status without significant weight loss. Local failure after concurrent chemotherapy and radiation therapy occurs in ~50% of patients. Thus, increasing the intensity of RT is rational and may improve clinical outcomes for these patients.

<u>Risks of Radiation to the Lung:</u>

The expected acute side effects of RT to the lung include fatigue, skin erythema, esophagitis, low blood counts, alopecia in the radiation field that may not grow back, cough, chest discomfort, and potentially pneumonitis. The risk of grade 3-4 esophagitis with conventional therapy occurs in 15-25% of patients.

Less likely but serious side effects of RT to the lung include difficulty breathing, shortness of breath, irritation and/or damage to the heart, irregular or rapid heartbeat, heart failure, irritation and/or damage to the spinal cord,

narrowing of the esophagus, and death. It is possible that the risk of severe esophagitis (requiring treatment breaks, feeding tubes, hospitalization, etc.) will be greater with accelerated treatment, especially if a radiation boost dose is administered. We will attempt to avoid this by utilizing IMRT as appropriate, particularly if the esophageal V60 > 17%, which can better spare normal tissues from the high dose component of treatment. Further, a boost will only be pursued if strict dosimetric constraints can be met and the patient is not having high-grade toxicity at the end of standard therapy.

Also, it is possible that the use of an accelerated RT schedule and or a boost (which can potentially increase the volume of lung exposed to RT) will increase the risk of lung injury, acute pneumonitis in particular. The patients will be monitored weekly during RT and regularly after treatment to evaluate these toxicities. Finally, it is possible that a higher radiation dose could lead to excess mortality, as evidenced in RTOG 0617[16]. As local failure remains a dominant pattern of disease recurrence, which occurs in the majority of patients with stage III NSCLC, interest remains in pursuing selective boosts using much smaller RT fields that should be associated with far less toxicity that giving a full escalated dose to all sites of original involvement.

Risk of Chemotherapy

Common side effects associated with carboplatin/paclitaxel include alopecia, thrombocytopenia, neutropenia, anemia, anorexia, nausea and vomiting, fatigue, arthalgias, and myalgias. Less common but potentially serious side effects include nephrotoxicity, hypersensitivity reaction, peripheral neuropathy, sensory peripheral neuropathy, dermatitis, mucositis, dysgeusia, and hearing loss and/or ringing in the ears.

Risks of the Interim PET-CT

The interim PET-CT requires the use of diagnostic radiation. This research will give a study patient the equivalent of about twelve extra years' worth of this natural radiation, which is far less than the therapeutic radiation they will receive for their malignancy. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space (e.g., being a passenger on airline flights), some arises from naturally-occurring radioactive forms (e.g., radon) in the soil, water, and building materials. The increased risk of a radiation-induced cancer from the interim PET-CT is deemed to be very low.

All initial staging modalities requiring by this study (laboratory work, PET-CT, MRI) are standard modalities to evaluate the extent of disease. Radiation therapy and chemotherapy are standard for patients with locally-advanced NSCLC. The use of IMRT is an accepted method of planning and delivering radiation therapy. As such, all treatment-related expenses will be charged to the patient and/or their insurance carrier. The cost of the interim PET-CT will be borne by the Department of Radiation Oncology.

11.0 Statistical Considerations

The primary objective of the study is to determine the metabolic complete response rate, assessed using interim PET-CT, in an accelerated fashion (2 Gy/fraction, 6 fractions/week) with concurrent chemotherapy. Secondary objective are (1) to determine how many patients will be eligible for an RT boost using an interim PET-CT scan at 48Gy to 54 Gy of RT, delivered in an accelerated fashion (6 fractions/week) with concurrent chemotherapy; (2) to evaluate clinical outcomes including overall survival, progression-free survival, and local control with an accelerated and adaptive RT approach; and (3) to correlate clinical outcomes (survival, progression-free survival, local control) with interim PET-CT responses using PERCIST criteria.

Sample size justification

The sample size of this single arm phase II trial is determined such that we have adequate power to detect an increase of the metabolic complete response rate (MCRR) from 8% to 20% among patients who receive

accelerated and adaptive radiation therapy and concurrent chemotherapy in locally advanced NSCLC. We observed an 8% metabolic complete response rate in our prior feasibility study[19]. In other words, if the true MCR rate is 20% or greater, this approach would be worthy of further investigation. On the other hand, if the true MCR rate is 8% or less, there is an interest in concluding that the combined chemoradiotherapy is not worthy of further investigation. The hypothesis is:

$$H0: p \leq 0.08 \text{ versus } H1: p \geq 0.20$$

where p is the true MCR rate after the combined chemoradiotherapy.

We will use Simon's 2-stage design to evaluate the MCR of the experimental therapy [26] The 2-stage design allow a futility test after stage I patients have been evaluated for MCR rate. The specific design described below is also the design that yields the smallest maximum sample size under the null hypothesis (minmax) among all designs satisfying type I error of 0.10 and type II error of 0.15.

Specifically, the first stage of the trial will enroll 32 patients. If there are 2 or fewer patients who responds (complete response) among the 32 patients, the trial will be terminated; otherwise, the trial will move forward to enroll additional 15 patients. If 6 or fewer patients among the total of 47 patients who responds, the experimental therapy will be concluded as not worthy of further investigation; otherwise it will be concluded that the experimental therapy has sufficient activity worthy of further investigation. The above design has expected sample size 39.2 under the null hypothesis. The early stopping probability at stage I is 0.5226. The actual type I and type II errors are 0.0772 and 0.1480, respectively.

Given expected attrition rate of 8% due to early withdrawal before completing the treatments or ineligibility, we will enroll 51 patients to this study in order to observe 47 evaluable patients.

Accrual rate and accrual duration

The phase II trial will register a total 51 patients. We expect approximately 1 locally advanced patients who meet the eligibility criteria will be enrolled per month. It will take approximately 51 months to reach the target accrual. Follow up of at least 24 months will be required for all patients for progression free survival and overall survival.

Statistical analysis methods:

For the cohort of the patient who meet eligibility criteria and receive radiotherapy with concurrent chemotherapy, the metabolic complete response (MCR) rate, as assessed using interim PET-CT, will be estimated using the UMVUE method [27] and its exact 80% confidence interval and the p-value will be calculated [28].

The proportion of the patients who are eligible for an RT boost after completing a standard dose of RT (60 Gy), delivered in an accelerated fashion (6 fractions/week) with concurrent chemotherapy, will be estimated as well as its confidence interval.

The overall survival (OS and progression-free survival (PFS) for the treated patients will be characterized by Kalan-Meier estimator. The medial OS and median PFs will be estimated as well as their 95% confidence intervals. The local control rate for the treated patients will be estimated as well as its 95% confidence intervals. The correlation between outcomes (survival, progression-free survival, local control) with interim PET-CT responses per PERCIST criteria by univariate analysis and multivariate analysis. For survival endpoints, the univariate analysis will be log-rank test and the multivariate analysis will be Cox proportional hazard model in which baseline prognostic factors will be adjusted.

The type of adverse events, the frequency of each type and its grade will be summarized

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Appendix A: Boost Eligibility Worksheet

Phase II Study of Accelerated and Adaptive Radiation Therapy for Locally-Advanced NSCLC

Patient Name: **MRN:** **Study ID:**	**Interim PET date:**	**Investigator:**

Eligibility for Boost: Patients cannot be considered eligible for boost radiation therapy for this study unless all of the following dosimetric and clinical constraints are met.

Interim PET-CT *(Clinical criteria based on interim PET)*	Residual Disease evident?	Yes No
	Local progression?	Yes No
	Distant progression?	Yes No
	Regional progression?	Yes No
Clinical Criteria	Grade 3-4 non-hematologic toxicities	Yes No
Dosimetric Criteria	Lung V20 ≤ 35%	Yes No
	Spinal Cord Dmax < 50 Gy	Yes No
	Esophageal V60 ≤ 20%	Yes No
	Heart V30 ≤ 50%	Yes No
	Brachial plexus Dmax ≤ 64Gy	Yes No
Based on the following criteria (circle one)	**Eligible** (proceed to 72Gy)	**Ineligible** (proceed to 60 Gy)

By signing below, the investigator acknowledges that s/he participated in the treatment plan and concurs with the documentation above for radiation boost as outlined by the Pro00083154 study protocol.

_____
Printed Name of Examiner

_____ _____
Signature of Examiner Date