NRG ONCOLOGY

NRG-LU001
ClinicalTrials.gov NCT02186847

RANDOMIZED PHASE II TRIAL OF CONCURRENT CHEMORADIOTHERAPY +/- METFORMIN HCL IN LOCALLY ADVANCED NSCLC

This trial is sponsored by the National Cancer Institute (NCI) and will be led by NRG Oncology.

Study Team (1-NOV-2018)

Co-Principal Investigator/Radiation Oncology
Theodoros (Theos) Tsakiridis, MD
Juravinski Cancer Center
699 Concession Street
Hamilton, Ontario, Canada L8V 5C2
905-387-9495 /FAX 905-575-6326
tsakirid@hhsc.ca

Co-Principal Investigator/Radiation Oncology
Heath Skinner, MD, PhD
UPMC Hillman Cancer Center
Research Pavilion, Suite 2.6a
5117 Centre Avenue
Pittsburgh, Pa 15213-1863
412-623-3275/FAX 412-623-7761
skinnerh@upmc.edu

Medical Oncology Co-Chair
Rafael Santana-Davila, MD
Seattle Cancer Care Alliance
825 Eastlake Avenue E; Mailstop G4940
Seattle, WA 98109
206-288-2190/FAX 206-288-2226
rafaelsd@uw.edu

Translational Science Co-Chair
Bo Lu, MD
Thomas Jefferson University
111 S. 11th Street
Philadelphia, PA 19107
215-955-6705/FAX 215-503-0013
Bo.Lu@jeffersonhospital.org

Radiology Co-Chair
Jeremy Erasmus, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 1478
Houston, TX 77030
713-792-5878/FAX 713-794-4361
JErasmus@mdanderson.org

Medical Physicist Co-Chair
Anthony J. Doemer, MS
Henry Ford Health System
2799 W. Grand Blvd.
Detroit, MI 48202
313-916-0234/FAX 313-916-3264
ADOEMER1@hfhs.org

Senior Statistician
Chen Hu, PhD
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103
215-940-4842/FAX 215-928-0153
huc@nrgoncology.org

NRG ONCOLOGY

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RANDOMIZED PHASE II TRIAL OF CONCURRENT CHEMORADIOTHERAPY +/- METFORMIN HCL IN LOCALLY ADVANCED NSCLC

Study Team (Continued)

NRG Oncology Contact Information (1-NOV-2018)

Data Manager: For questions concerning eligibility or data submission	Jeff Serianni NRG Oncology 1818 Market Street, Suite 1720 Philadelphia, PA 19103 215-574-3248/Fax: 215-930-8840 SerianniJ@NRGOncology.org Amy Krystkiewicz, RN NRG Oncology 1818 Market Street, Suite 1720 Philadelphia, PA 19103 267-940-9415 KrystkiewiczA@NRGOncology.org
RTQA: For questions concerning RT data submission	Jennifer Presley IROC Philadelphia – RT QA Center ACR Clinical Research Center 1818 Market Street, Suite 1720 Philadelphia, PA 19103 215-574-3153 jpresley@acr.org
RTQA: For questions concerning data submission to TRIAD	Triad-Support@acr.org
Protocol Development: For questions concerning protocol and informed consent versions & amendments	Fran Bradley NRG Oncology 1818 Market Street, Suite 1720 Philadelphia, PA 19013 215-940-8893/Fax: 215-928-0153 BradleyF@NRGOncology.org
NRG Oncology Lung Committee Chair	Jeffrey D. Bradley, MD Washington University 4921 Parkview Place St. Louis, MO 63110 314-362-4633/Fax: 314-362-8521 jbradley@wustl.edu

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Protocol Agent (5/7/15)

Agent	**Supply**		**IND #**
Carboplatin	Commercial		Exempt
Paclitaxel	Commercial		Exempt
Metformin HCL	Commercial		Exempt

Participating Sites
☐ U.S. Only
☐ Canada Only
☒ U.S. and Canada
☒ Approved International Member Sites

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NRG Oncology
1-800-227-5463, ext. 4189

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NRG ONCOLOGY

NRG-LU001

Randomized Phase II Trial of Concurrent Chemoradiotherapy +/- Metformin HCL in Locally Advanced NSCLC

SCHEMA

STRATIFY

Zubrod Performance Score

1. 0
2. 1

Histology

1. Squamous
2. Non-Squamous

Clinical Stage

1. IIIA
2. IIIB

RANDOMIZE

Arm 1: Concurrent Chemoradiotherapy

RT: 60 Gy/30 fx with chemotherapy for 6 weeks

Followed by Consolidation Chemotherapy for 6 weeks

Arm 2:

MET Dose Escalation: 1000 mg to 2000 mg daily for 2 weeks

Concurrent Chemoradiotherapy + MET: RT: 60 Gy/30 fx with Chemotherapy and MET (2000 mg, p.o. daily) for 6 weeks

Consolidation Chemotherapy + MET: Consolidation chemotherapy for 6 weeks and MET (2000 mg p.o. daily) for 10 weeks.

See Section 7.0 for details/doses of study drugs. See Section 5.0 for details of pre-registration requirements.

Patient Population: (See Section 3.0 for Eligibility)
Pathologically proven diagnosis of Stage IIIA or IIIB non-small cell lung cancer; patients must have unresectable disease, are medically inoperable, or are not willing to undergo surgical management.

Required Sample Size: **168**

ELIGIBILITY CHECKLIST (8/4/14)

(page 1 of 4)

NRG Oncology Institution #
NRG-LU001
Case #

The following questions will be asked at Study Registration:
3D-CRT and/or IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION. See Section 5.0.

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (Last First Middle)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at a VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date

_____ 18. Medical Oncologist's name

_____(Y/N) 19. My samples and related information may be kept in a Biobank for use in future health research.

_____(Y/N) 20. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

NRG Oncology Institution #
NRG-LU001
Case #

_____ 21. MedDRA disease code

_____(Y/N) 22. Specify use of IMRT

_____(0/1) 23. Zubrod Performance Score

_____ 24. Histology (Squamous Cell Carcinoma or Non-Squamous Cell Carcinoma)

_____(IIIA/IIIB) 25. Clinical Stage

_____ 26. Histologic Confirmation Date

_____ 27. Lung Tumor Histology

_____(Y/N) 28. Does the patient have measurable disease?

_____(Y/N) 29. Does the patient have unresectable disease, are they medically inoperable, or are they unwilling to undergo surgical management?

_____ 30. History and Physical Exam Date

_____ 31. Date of CT scan or MRI of the chest and abdomen

_____ 32. Date of MRI (or CT) of the brain with contrast (unless medically contraindicated)

_____ 33. Date of whole body FDG-PET/CT

_____ 34. Date CBC panel was performed

_____ 35. ANC (cells/mm^3)

_____ 36. Platelets (cells/mm^3)

_____ 37. Hemoglobin (g/dL)

_____ 38. Labs assessment date

_____ 39. Serum creatinine

_____ 40. Serum creatinine ULN

_____ 41. Creatinine Clearance

NRG Oncology Institution #
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Case #

_____ 42. SGOT (AST)

_____ 43. SGOT (AST) ULN

_____ 44. SGPT (ALT)

_____ 45. SGPT (ALT) ULN

_____ 46. Alkaline Phosphatase

_____ 47. Alkaline Phosphatase ULN

_____ 48. Total Bilirubin

_____ 49. Total Bilirubin ULN

_____ 50. Fasting Glucose

_____ 51. Serum albumin (g/dL)

____(Y/N/NA) 52. If the patient is of childbearing potential, has she had a negative serum pregnancy test performed within 72 hours prior to registration?

____(Y/N/NA) 53. If the patient has post-obstructive pneumonia, do they no longer require intravenous antibiotics at the time of registration?

_____(Y/N) 54. Was a thoracotomy performed within the last 3 weeks?

____(Y/N/NA) 55. If a pleural effusion is present, were all of the criteria from Patient Eligibility met?

____(Y/N/NA) 55. If the patient is a woman of childbearing potential or a male participant did they agree to practice adequate contraception throughout the study?

_____(Y/N) 57. Does the patient have a mixed small cell and non-small cell histology?

_____(Y/N) 58. Distant metastases present?

_____(Y/N) 59. Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer) within the last 3 years?

_____(Y/N) 60. Has the patient had prior systemic chemotherapy for the study cancer?

_____(Y/N) 61. Has the patient had prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

_____(Y/N) 62. Is the patient currently using metformin, other oral hypoglycemic agents, or insulin?

NRG Oncology Institution #
NRG-LU001
Case #

_____(Y/N) 63. Prior allergic reaction to paclitaxel or other taxanes or carboplatin?

_____(Y/N) 64. Does the patient have a history of chronic kidney disease or lactic acidosis?

_____(Y/N) 65. Weight loss within the past month (%)

_____(Y/N) 66. Diagnosis of Type I or Type II Diabetes Mellitus?

_____(Y/N) 67. Uncontrolled neuropathy greater than or equal to grade 2 regardless of cause?

_____(Y/N) 68. Hospitalized for unstable angina and/or CHF in last 6 months?

_____(Y/N) 69. Transmural MI in last 6 months?

_____(Y/N) 70. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?

_____(Y/N) 71. Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration?

_____(Y/N) 72. Severe hepatic disease, defined as a diagnosis of Child-Pugh Class B or C hepatic disease?

_____(Y/N) 73. Is the patient HIV positive with a CD4 count less than 200 cells/microliter?

_____(Y/N) 74. End-stage renal disease (on dialysis or dialysis has been recommended)?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background and Rationale

There is an urgent need to improve clinical outcomes in non-squamous cell lung cancer (NSCLC) patients for whom the current standard of care of concurrent chemoradiotherapy offers poor survival. It is estimated that each year in U.S. and Canada more than 250,000 people are diagnosed with lung cancer and more than 180,000 die from the disease (Jenak 2011). More than 80% of lung cancer patients are diagnosed with NSCLC, which often presents at advanced stages in patients not eligible for surgical resection. Such patients are managed with concurrent chemoradiotherapy.

This study, will investigate whether the addition of the anti-diabetic drug Metformin can be well tolerated and improve progression free survival (PFS) in patients with locally advanced NSCLC treated with standard concurrent chemoradiotherapy.

1.1.1 Radiotherapy Treatment (RT) of Locally Advanced NSCLC

The dose of thoracic RT for locally advanced NSCLC (60-63 Gy, 2–2.1Gy per fraction) was established by an RTOG study more than 30 years ago (Perez 1980). RTOG-73-01 showed improved survival with 60 Gy RT in 30 fractions of 19% at 2 years. The radiographic response rate was approximately 60% (Perez 1980), local failure within the radiation field was approximately 25% and 45%, and distant metastasis rates were 15% and 35% at 6 and 12 months, respectively. Other studies with RT doses of 60-64 Gy reported median survival of 10-14 months for stage IIIA/B patients (Okawara 2006). Dillman (1996) reported OS of 70% and 40% at 6 and 12 months, respectively, and probability for PFS 50% and 20% at the same time point when patients were treated with 60 Gy in 30 fractions. Also, Le Chevalier (1991) showed a 2-year overall survival (OS) rate of only 14% and 1-year local control of 15% after treating locally advanced NSCLC with RT alone (65 Gy in 26 fractions). A meta-analysis of individual patient data from 52 trials by the NSCLC Collaborative Group (1995) indicated OS of about 75% at 6 months and 40% at 12 months in patients treated with RT alone (30–60 Gy). These data suggest that curative thoracic RT (60-63 Gy), when used alone without chemotherapy, offers locally advanced NSCLC patients a median survival of 10-12 months and OS of 42% at 12 months (NSCLC Group 1995).

1.1.2 Local Control with Radiotherapy

A major cause of poor outcomes in locally advanced NSCLC is the high resistance of these tumors to RT. Radiographic assessments suggest local recurrences in up to 60% of lung cancers treated with high dose RT, but bronchoscopy studies have documented even greater local and regional failure rates of up to 85% in patients treated with RT alone (Le Chevalier 1992). Such results have led to an on-going search for radio-sensitizing agents.

1.1.3 Role of Chemoradiotherapy

Over the last 3 decades, chemotherapy has been investigated as neo-adjuvant, concurrent, or adjuvant treatment to improve local control and distant metastases rates achieved with high-dose RT in locally advanced NSCLC. Meta-analyses and systematic reviews indicate an absolute survival advantage of 3-4% at 2 years and an increase in median survival by 1.7 months with the addition of chemotherapy to RT (Sandulache 2012, Pierotti 2013). Introduction of concurrent chemotherapy with high-dose chest radiation in trials performed between 1988 and 2003 produced small improvements in progression-free survival (PFS) and more significant enhancement of OS compared to sequential chemoradiotherapy regimens. A meta-analysis of 6 trials by Auperin (2010), showed average OS of 60% and 15.1% and PFS of 40.5% and 11.6%, at 1 and 5 years (vs. OS 59% and 10.6% and PFS of 37.9% and 9.4%, at 1 and 5 years, for sequential chemoradiotherapy).

1.1.4 Dose-Escalated RT

A number of efforts have been made to improve these outcomes. Early phase studies of dose escalated radiotherapy and concurrent chemoradiotherapy showed promise to improve outcomes in this disease, with 2 recent meta-analyses exhibiting a benefit to this approach (Partridge 2011, Machtay 2012). Unfortunately, a recent phase III study of dose escalation (RTOG 0617) did not produce the expected results, with the dose-escalated arm closed early after an interim futility analysis (Bradley 2011). Although toxicity did not appear to be significantly different between the

2 arms, the number of treatment-related deaths in the dose-escalated arm (7 patients) underscores the need for radio-sensitizers that improve the therapeutic ratio with a minimum of toxicity.

1.2 NSCLC Resistance to Cytotoxic Therapy: The Need for Rational Development of Sensitizing Therapies

NSCLC exhibits a high degree of resistance to chemoradiotherapy. We need to understand in depth NSCLC tumor and radiation biology in order to develop rational therapies that will reliably improve the efficacy of cytotoxic therapy and clinical outcomes in this disease. Pre-clinical laboratory work by the Co-Principal Investigators of the proposed trial suggests that RT activates the novel metabolic and genomic stress sensor AMPK-kinase (AMPK), which inhibits the survival mediator mammalian target of rapamycin (mTOR) and activates tumor suppressors and cell cycle regulators such as p53 and the cyclin-dependent kinase inhibitor $p21^{cip1}$ to inhibit cancer growth and induce cell death. This pathway represents a promising therapeutic target, which can be engaged with well tolerated agents such as the anti-diabetic drug metformin (Jalving 2010, Pollack 2012).

1.2.1 Metformin (MET) in Combination with Radiotherapy and Chemotherapy

Several epidemiologic studies have shown a reduction of NSCLC incidence with MET use in patients with type II diabetes mellitus (Hsieh 2012, Mazzone 2012, Noto 2012). Furthermore, on meta-analysis of the available literature, MET use was found to be associated with a decrease in cancer mortality in all sites (RR 0.66, p=0.005) (Noto 2012). Multiple studies have associated MET use to improved outcomes following radiotherapy or chemoradiotherapy in several disease sites (Sandulache 2013, Skinner 2012, Skinner 2012b, Skinner 2013). Additionally, several studies have linked improved survival following lung cancer diagnosis and MET use (Currie 2012, Tan 2011). Specifically, Tan and colleagues (2011) showed that LA-NSCLC patients taking MET had a median OS of 20 months. The remaining patients were then stratified by glucose control regimen (insulin vs. other); with median OS being approximately 13 months in both groups. This is in line with our own observations in a similar patient population, with MET use being independently associated with improved OS on multivariate analysis (Tsakiridis and Skinner unpublished observations; see Figure 4 below).

MET is a well-tolerated anti-hyperglycemic agent used by more than 120 million patients worldwide. Furthermore, MET also is indicated for treatment of non-diabetic patients, specifically in poly-cystic ovarian syndrome (PCOS). Randomized controlled trials demonstrated the safety and efficacy of MET in preventing diabetes and improving metabolic and hormonal parameters in non-diabetic patients with insulin resistance and polycystic ovary syndrome (PCOS) (Tang 2012). Other studies also showed the safety of MET in patients with non-alcoholic fatty liver disease (Shyangdan 2011) and in breast cancer patients (Bayley 2012).

1.3 Pre-Clinical Evidence

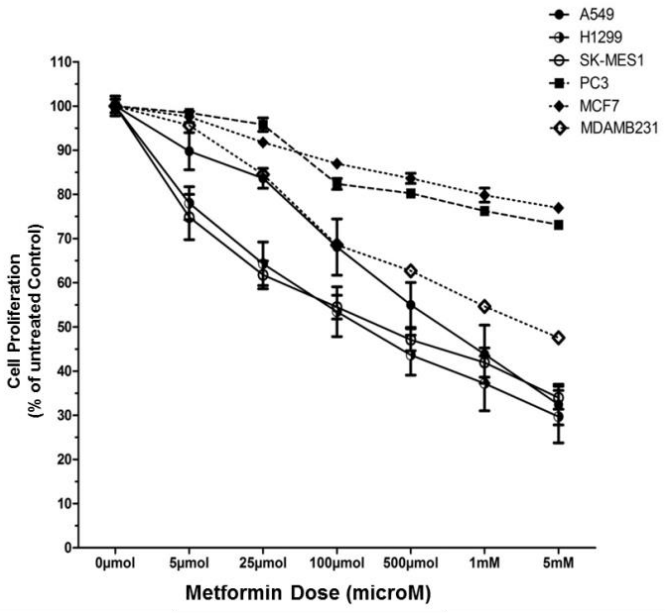
The investigators have significant experience examining the relationship between AMPK, metabolism, and radio-sensitivity (Skinner 2012, Sandulache 2012, Sanli 2010). We have observed that radiation alone regulates AMPK expression and activity and inhibits mTOR (Sanli 2010, Sanli 2012, Storozuk 2012). Studies from a number of laboratories, including those of the principal investigators, demonstrated that AMPK not only is a metabolic but also a genomic stress sensor that mediates cell cycle checkpoints and activates signaling events leading to radio-sensitization and cancer cell death (Sanli 2013). Further, we observed that MET can perturbate the metabolic function of cancer cells (Sandulache 2012). In early studies, we showed that lung cancer cells have significantly higher sensitivity to MET compared to other cancers, such as breast and prostate cancer cells, while the drug does not alter the proliferation rates of non-cancer cells at low microM doses of MET (Storozhuk 2013: supplemental data; see Figure 1A- B).

Figure 1A: Metformin (MET) Decreases Proliferation of Various Human Cancer Cell Lines
Lung carcinoma cells (A549, H1299, SK-MES1), prostate carcinoma cells (PC3) and breast cancer cells (MCF7 and MDA-MD231) were treated with increasing concentrations of MET

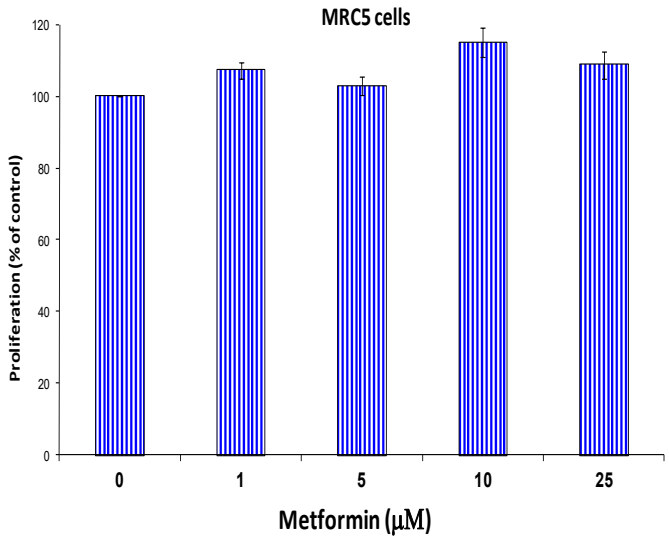
(0µmol-5mM) for a period of 48 hours. DNA content, as a marker of cell proliferation, was determined by crystal violet staining. Mean+/-SE of 3 independent experiments are shown.

Figure 1B: Metformin (MET) Does Not Influence Proliferation of Normal Human Lung Embryonic Fibroblast Cells (MRC5)
Cells were treated with increasing concentrations of MET (0µmol-25µmol) for 48 hours. DNA content, as a marker of cell proliferation, was determined by crystal violet staining. Mean+/-SE of three independent experiments are shown.

A.



B.



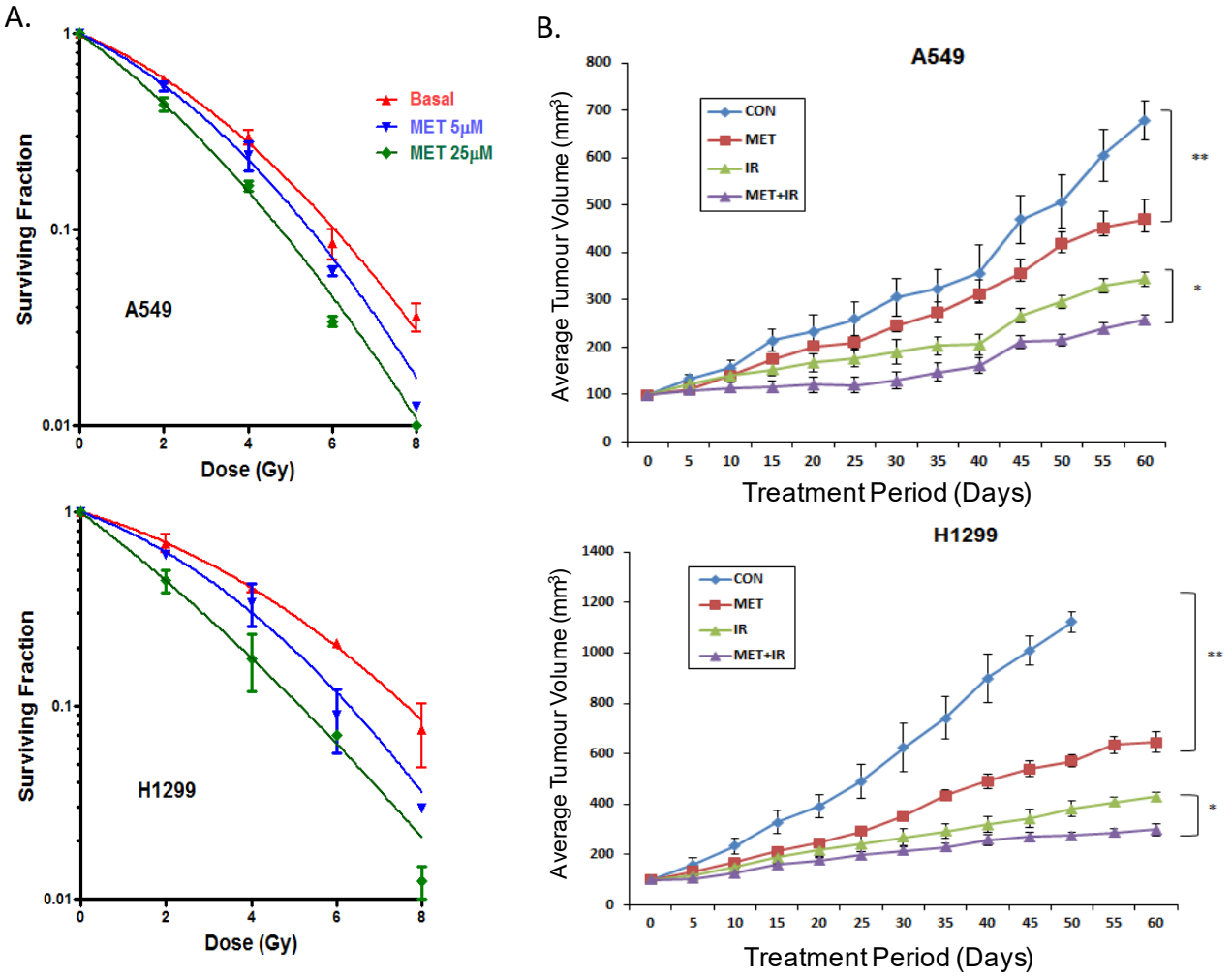
Most importantly, we observed that in a variety of pre-clinical models MET is a potent radiosensitizer (Skinner 2012, Sandulache 2012, Sanli 2010, Storozhuk 2013). Specifically in lung cancer, the addition of low μM doses (2.5 – 25 μM) of MET to clinical doses of RT (2 - 8 Gy) radio-sensitizes human NSCLC cells (Figure 2A) and increases the cytotoxicity of radiotherapy in NSCLC tumors (Figure 2B) (Storozhuk 2013). Further, we observed that MET enhances the anti-angiogenic and pro-apoptotic actions of RT in tumors (Storozhuk 2013). Figure 2C shows results of quantification of at least 3 separate immunoblotting experiments and Figure 2D shows representative immunohistochemistry images demonstrating increased expression of the apoptosis marker cleaved caspace 3 when MET was combined with RT treatments. Importantly, MET inhibits NSCLC cell proliferation at doses (μM) that can be safely achieved in the serum of patients treated with standard oral doses of MET (Graham 2011). Further, work by other groups suggested that MET enhances the cytotoxicity of chemotherapy in pre-clinical NSCLC models (Iliopoulos 2011, Rocha 2011).

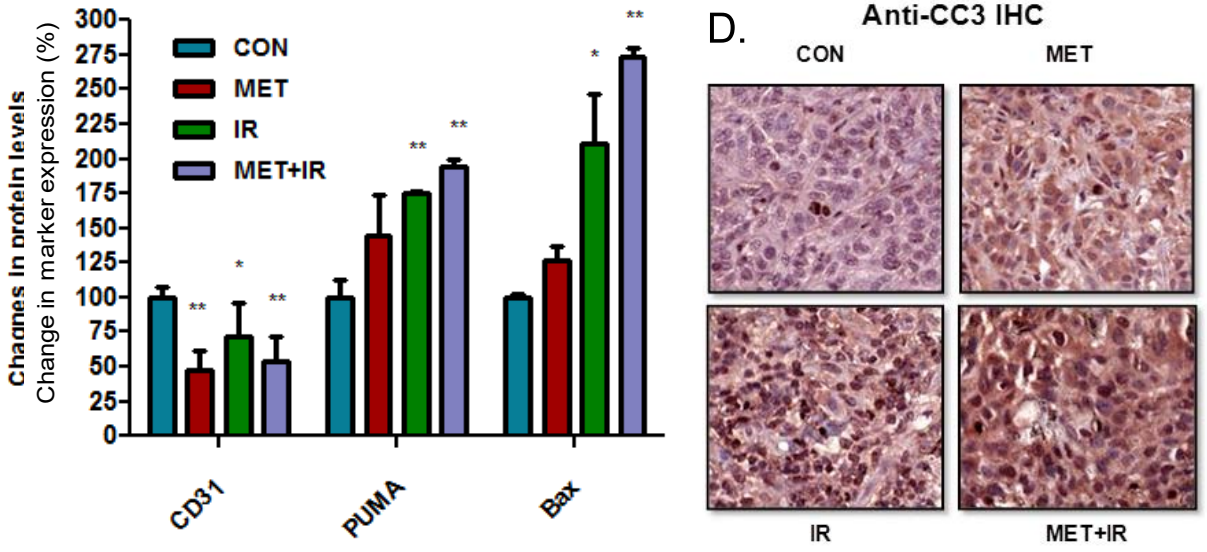
Figure 2: MET Increases Cytotoxicity of Chemotherapy and Radiation
A. Two widely used in-vitro models of human NSCLC, A549 and H1299 cells were subjected to clonogenic assays after treatment with 0 (Basal) 5 or 25 μM metformin (MET) and increasing doses of radiation (RT) (0-8 Gy). Colony formation was evaluated after 7 days, and the results were fitted into the linear quadratic model. Mean+/-SE of 3-4 independent experiments are shown.

B. A549 and H1299 cells were grafted into immunodeficient nude mice and treated with or without oral MET 300 mg/kg/day for 8 weeks and/or a single fraction of conformal radiotherapy of 8 Gy when tumors reached 100mm^3. Tumors were then left to grow for 60 days. * : P<0.05 ** : P < 0.01

C. Protein extracted from A549 xenograft tumors treated as indicated in B was analyzed by immunoblotting for the expression of the angiogenesis marker CD31 and the apoptosis markers PUMA and Bax. * : P<0.05 ** : P < 0.01

D. Fixed A549 xenografts from control and MET, RT, and MET+RT treated animals (as indicated in B) were processed for immunohistochemical analysis using an antibody specific for the apoptosis marker Cleaved Caspace-3 (CC3). Representative images from 3 independent experiments are shown.





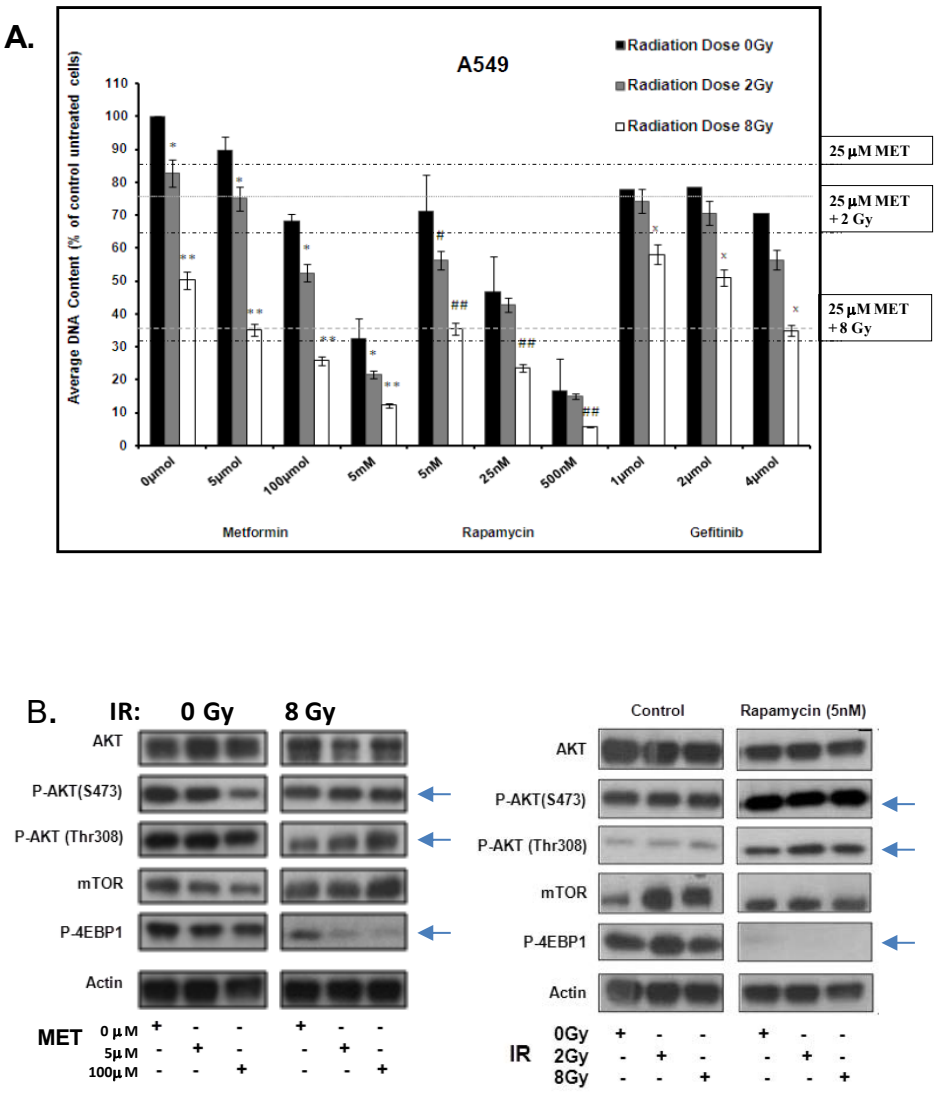
The ability of MET to inhibit lung tumor cell growth and sensitize the cells to radiation at doses of the drug that can be achieved clinically with minimal toxicity suggested that MET may indeed have meaningful activity in human lung cancer. For that, we took steps to compare MET to common targeted therapy agents and to examine retrospectively the potential effects of MET in clinical outcomes in lung cancer patients treated with curative chemoradiotherapy.

First, we compared MET to Epidermal Growth Factor Receptor (EGFR) inhibitor gefitinib and the widely used mTOR inhibitor rapamycin. MET (5 – 25 μM) in combination with 2 or 8 Gy RT achieved equal or better inhibition of lung cancer cell proliferation than clinically achievable doses of rapamycin (5nM) and gefitinib (1μM) (see Figure 3A). Furthermore, we examined the effect of MET on the Akt-mTOR pathway that is involved in cancer cell survival and resistance to cytotoxic therapies. Figure 3B shows that unlike rapamycin, which is known to inhibit mTOR but to cause activation of Akt, an event believed to contribute to the failure of drugs of this class to offer lasting anti-tumor effects, MET caused a consistent blockage of both Akt and mTOR signals in lung cancer cells. These results offer an additional line of evidence indicating the promise of MET for clinical activity in lung cancer.

Figure 3: MET is a More Potent Radiosensitizer Compared to EGFR and mTOR inhibitors
A. Comparison of the Anti-Proliferative Effects of MET with Rapamycin or Gefitinib in Untreated and Irradiated A549 Lung Cancer Cells
A549 lung cancer cells were treated with MET (5μM-5mM), rapamycin (5nM-500nM), or gefitinib (1μM-4μM) for 24 hours before treatment with 0, 2, or 8 Gy RT. Cells were fixed 48 hours later. DNA content, as a marker of proliferation, was determined with crystal violet staining. Mean+/-SE of 3-4 independent experiments are shown. Statistically significant differences compared to corresponding control cells (not treated with either agent) within the 0 Gy, 2 Gy, and 8 Gy radiation treatment groups are shown (*:P<0.05, **:P<0.01 for MET treated cells, #:P<0.05, ##:P<0.01 for rapamycin treatment, and ×:P< 0.05,××: P<0.01 for gefitinib treatment respectively). Grey horizontal lines facilitate a visual comparison of the effects of 5μM MET + 2 Gy RT and 5μM MET + 8 Gy RT with the rest of the treatment conditions. Dashed black horizontal lines indicate the effects of 25μM MET alone or in combination with 2 or 8 Gy RT.

B. Effects of MET and Rapamycin Without or With 2 and 8 Gy Radiation Treatment on Expression and Phosphorylation of Akt, mTOR and the mTOR Target Translation Initiation Inhibitor 4-EBP1

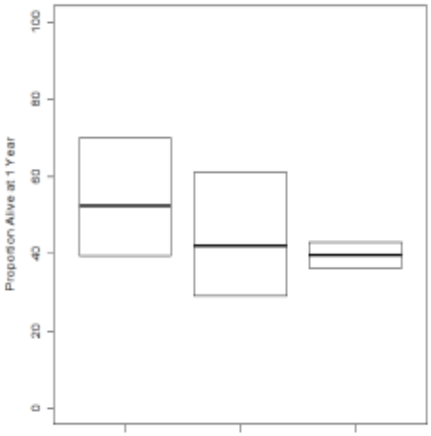
A549 cells were treated with MET 5 or 100 µM or rapamycin (0nM or 5nM) for 24 hours followed by an additional incubation of 24 hours after treatment with RT (0, 2, or 8 Gy). The cells were washed and lysed. Lysates were analyzed with immunoblotting using indicated antibodies. Representative images of 3 independent experiments are shown for total and phosphorylated Akt (S473 and T308), mTOR and phosphorylated 4EBP1. See arrows pointing at the differential effects of MET versus rapamycin on Akt phosphorylation.



In addition, early clinical evidence suggests that MET may be well capable of enhancing treatment response in LA-NSCLC patients treated with curative doses of chemo-radiotherapy. Independent retrospective analyses from the Juravinski Cancer Center, ON, Canada and the M.D. Anderson Center, TX, USA (Tsakiridis et al., unpublished observations, Welsh et al., in review; see Figure 4 below), show that diabetic patients with LA-NSCLC have improved survival if their diabetes is treated with MET vs. insulin or insulin secretagogeus. Interestingly, it appears that such patients that are typically treated with 1000 – 2500mg of MET daily may reach OS rates that are higher than average rates of non-diabetic patients, while patients treated with insulin tend to have similar to or worse survival rates than control non-diabetics. These findings are supported by observations of benefits to MET treatment in outcomes in other tumors of the upper aero-digestive tract (Sandulache 2013, Skinner 2013). To date, we have not detected any evidence of

increased chemoradiotherapy toxicity in diabetic patients treated with MET who have received standard curative concurrent chemoradiotherapy for lung cancer (see Figure 4C below).

Figure 4: Retrospective Clinical Evidence of Lung Cancer Treatment with Combined Metformin and Chemoradiotherapy
A & B: Retrospective analysis of 1-year survival of stage III NSCLC patients treated at the Juravinski Cancer Center (A) and the University of Texas MD Anderson Cancer Center with chemo-radiotherapy (B). Diabetic patients were separated in those treated with MET versus those treated with other hypoglycemic agents.
C: Toxicity due to therapy in the patients described in B. No significant difference in toxicity between groups was observed.



1.4 Rationale for This Study: Selected Approach and Trial Design

We propose an open-label randomized phase II study of standard therapy with concurrent chemoradiotherapy +/- metformin (MET). 1:1 randomization and stratification variables of performance status, clinical stage, and histology of NSCLC tumor will be utilized.

MET has a favorable safety record, with no significant long-term toxicity and has been used for the treatment of diabetes mellitus in North America for over 15 years. Although diabetic patients on MET are being treated frequently with high dose chest chemoradiotherapy, there are no reports of increased chemoradiotherapy toxicity with the drug.

Phase I and II studies showed the safety of MET use in non-diabetic patients (Wu 2012, Bittner 2011, Boulton 2011, Kjøtrød 2011, Kim 2099, Schwimmer 2005). Metformin does not cause hypoglycemia and has favorable metabolic effects on insulin resistance and obesity (McCarthy 2004, Bosi 2009). Unlike its parent drug phenformin, MET does not cause significant lactic acidosis in standard therapeutic doses (Salpeter 2010).

In the last decade, several epidemiologic studies have shown that the use of MET is associated with a decreased incidence of cancer. Furthermore, MET use has been associated with improved outcomes when used with RT or chemotherapy. Currently, there are more than 80 clinical trials registered at clinicaltrials.gov investigating MET in different cancer sites, including more than 40 trials actively recruiting patients. Only 3 of these studies investigate MET in lung cancer, including 1 study in the setting of chemoprevention and 2 studies in stage IV NSCLC in combination with chemotherapy or targeted therapy.

Based on the information discussed above, currently, there is no substantial basis or need for a phase I study with MET in patients with LA-NSCLC.

A randomized phase II approach will be a properly controlled study to demonstrate early evidence of efficacy of the intervention, substantiate further the safety of MET when combined with curative chemoradiotherapy.

The presence of the control arm will provide appropriate comparison because:

- Significant improvements in lung cancer staging and radiotherapy delivery over the last decade diminish the value of historical control data;
- It allows the expansion of eligible chemotherapy regimens in this study;
- Patients on the control arm will provide valuable samples for biomarker studies .

An open label is utilized since the early low grade gastrointestinal toxicity of MET use (gas and mild diarrhea) make the intervention obvious while a double blind placebo control study would be significantly more costly with little additive benefit.

1.5 Translational Science (8/10/16)

Development of predictive biomarkers of MET action is a valuable secondary objective of this study. These studies will provide useful information for the rational design of future clinical trials with this drug in NSCLC and other disease sites. To achieve this goal, it is vital to collect blood and tumor tissue bio-specimens during the trial to be used for future analysis depending on the outcomes of this trial. Submission of tissue/blood is optional for patients enrolled on this trial. All specimens will be sent to the NRG Oncology Biospecimen Bank – San Francisco for banking for this future translational science study.

Tissue banking is predicated by 2 separate hypotheses. These hypotheses will be tested after the study is complete, and additional funding will be obtained from other sources to test these hypotheses.

1. Mutation in TP53, STK11 (LKB1) and/or KRAS predicts improved PFS in patients treated with metformin.

   Multiple pre-clinical studies have linked mutation in TP53 to sensitivity to the antineoplastic and therapeutic sensitizing effects of metformin (Skinner 2012, Buzzai 2007, Sandulache 2012 (Pierotti 2013). However, this may not be a universal effect, particularly in combination with radiotherapy (Storozhuk 2013, Ben Sahra 2010). Additional work has linked inactivation of LKB1 (STK11) with increased sensitivity to biguanides *in vivo* in a KRAS mutated NSCLC model (Shackleford 2013). As NSCLC has a preponderance of mutations in all of the above sites (TCGA Lung: TP53~50-80%, STK11 ~2-15%, KRAS~2-27%), an increased sensitivity to metformin conferred by these mutations would be advantageous, and result in an even greater improvement in PFS following metformin administration.

Biopsy tissue of consenting patients will be collected at baseline. Tumor tissue will be evaluated by an experienced pathologist for tumor content. DNA extraction from tissue blocks will be performed. This will be followed by PCR analysis of mutation status and immunohistochemistry of

selected fixed tumor tissue to detect expression levels. Analysis of the mutation status and expression levels of p53, LKB1 and K-RAS, will help demonstrate whether these genes can serve as potential biomarkers predictive of MET response in the future.

Blood samples of consenting patients will be collected at baseline, weeks 1 and 6 of chemo/RT (corresponding to weeks 3 and 8 of the metformin treatment period for patients randomized to Arm 2), and at 6 month follow-up visit (see Section 10.2). Serum and EDTA plasma will be isolated from blood samples and stored for future analysis. Whole blood samples also will be collected and stored for future analysis. The time points of collection are designed to help extract the effect of MET on serum/plasma markers at the time when the drug has reached its full treatment dose and before chemoradiotherapy is initiated (week 3 of metformin treatment period for patients randomized to Arm 2), at the time when steady state maximum drug levels will be combined with chemoradiotherapy (week 8 of metformin treatment period for patients randomized to Arm 2) and at the time at which both concurrent chemoradiotherapy and MET treatments would be complete (week 32).

In blood based studies, we will examine whether:

i. plasma MET levels and modulation of plasma fasting insulin level and lipid profile by the drug correlate with the clinical response to MET;

   Studies in non-diabetic breast cancer patients showed that MET treatment reduces significantly fasting insulin levels by 22.4% and LDL-cholesterol by 9.1% (insulin: from 70.7$\pm$30.4 to 54.9$\pm$30.0 pmol/L (Mean$\pm$SD) and fasting LDL-cholesterol: 2.86$\pm$0.86 to 2.6$\pm$0.63 mmol/L) (Goodwin 2008). We will investigate whether plasma MET levels and metabolic response of patients in terms of reduction of fasting insulin and LDL-cholesterol levels in response to MET correlate with tumour response to the drug in terms of PFS.

ii. levels of phosphorylated AMPK, $p70^{S6k}$ and 4EBP1 (P-AMPK, P-$p70^{S6k}$, P-4EBP1) in blood cell lysates can correlate with plasma MET levels and predict response to the drug.

   The work of the Co-Principal Investigators (Storozhuk 2013) and others (Rocha 2011) shows that MET mediates its action through activation of AMPK leading inhibition of the mTOR-p70S6k / 4EBP1 pathway. This is detected as inhibition of the phosphorylation and activity of p70S6k, which leads to inhibition of this ribosomal kinase and inhibition of 4EBP1 phosphorylation, which permits 4EBP1 to inhibit gene translation (see Figure 3 above). Collection of buffy coats will allow us to test the novel hypothesis that phospho-proteomic analysis of this bio-specimen could provide useful biomarkers of MET action.

   To achieve these objectives we will use the following:

   i. standard biochemical analysis platforms;
   ii. lysates of blood cells and immunoblotting using phosphorylation specific antibodies.

2.0 OBJECTIVES

2.1 Primary Objective

To determine whether MET added to chemoradiotherapy can improve progression-free survival (PFS) in patients with locally advanced NSCLC

2.2 Secondary Objectives

- Determine the effects of MET on overall survival (OS), time to local-regional progression (LRP), and time to distant metastasis (DM);
- Evaluate the effect of MET on chemoradiotherapy toxicity (CTCAE, v. 4) within 1 year of completion of all treatment;
- Collect biospecimens to develop biomarkers of MET activity:
  - Investigate potential serum biomarkers of MET response: serum MET levels, insulin and lipid levels;

- Evaluate MET activity on peripheral blood cells (in a subset of patients);
- Investigate potential tumor biomarkers of MET response: tumor NSCLC histology and tumor mutational status (*TP53, STK11 [LKB], K-RAS*).

3.0 PATIENT SELECTION (8/10/16)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

For questions concerning eligibility, please contact the study data manager.

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of Stage IIIA or IIIB non-small cell lung cancer within 84 days of registration; eligible histologies include adenocarcinoma, adenosquamous, large cell carcinoma, squamous carcinoma, non-lobar and non-diffuse bronchoalveolar cell carcinoma or non-small cell lung cancer NOS).

3.1.2 Patients must have measurable disease;

3.1.3 Patients must have unresectable disease, be medically inoperable, or unwilling to undergo surgical management;

3.1.4 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination, including documentation of height, weight, BSA, and vital signs, within 30 days prior to registration;
- CT scan with IV contrast or MRI imaging (if CT scan with contrast is medically contraindicated) of the lung and upper abdomen through the adrenal glands, required within 45 days prior to registration (recommended within 30 days prior to registration);
- MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated) within 45 days prior to registration; **note**: The use of intravenous contrast is required for the MRI or CT. An MRI without contrast is only permitted if the patient has a contrast allergy.
- Whole-body FDG-PET/CT required within 45 days prior to registration (recommended within 30 days prior to registration; **note**: patients do not need to have a separate CT of the chest and upper abdomen with contrast if PET/CT imaging includes a high quality CT with contrast.

3.1.5 Zubrod Performance Status 0-1;

3.1.6 Age ≥ 18;

3.1.7 CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);

3.1.8 Adequate renal function within 14 days prior to registration, defined as serum creatinine within normal institutional limits or creatinine clearance must be at least 60 ml/min;

3.1.9 Adequate hepatic function within 14 days prior to registration, defined as total bilirubin ≤ 1.5 x upper limit of normal (ULN) for the institution and ALT, AST, and alkaline phosphatase ≤ 2.5 x ULN for the institution;

3.1.10 Fasting blood glucose ≤ 125 mg/dL within 14 days prior to registration;

3.1.11 Serum albumin > 3.0 g/dl within 14 days prior to registration;

3.1.12 For women of childbearing potential, a serum pregnancy test within 72 hours prior to registration;

3.1.13 Patients with post-obstructive pneumonia are eligible provided they no longer require intravenous antibiotics at registration;

3.1.14 Patients must be at least 3 weeks from prior thoracotomy (if performed);

3.1.15 If a pleural effusion is present, the following criteria must be met at registration to exclude malignant involvement (incurable M1a disease):

- When pleural fluid is visible on both the CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative;
- Effusions that are minimal (i.e. not visible under ultrasound guidance) and that are too small to safely tap are eligible.

3.1.16 Women of childbearing potential and male participants must practice adequate contraception throughout the study;

3.1.17 Patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with mixed small cell and non-small cell histologies;

3.2.2 Patients with distant metastasis;

3.2.3 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.2.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

3.2.5 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.6 Patients currently using metformin, other oral hypoglycemic agents or insulin;

3.2.7 Patients with any history of allergic reaction to paclitaxel or other taxanes or carboplatin;

3.2.8 Patients with a history of chronic kidney disease or lactic acidosis;

3.2.9 Patients with ≥ 10% weight loss within the past month;

3.2.10 Severe, active co-morbidity, defined as follows:

- Diagnosis of Type I or Type II Diabetes Mellitus;
- Uncontrolled neuropathy ≥ grade 2 regardless of cause;
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration**;**
- Severe hepatic disease, defined as a diagnosis of Child-Pugh Class B or C hepatic disease.
- HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol.
- End-stage renal disease (ie, on dialysis or dialysis has been recommended).

3.2.11 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (8/10/16)

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

Note: Failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1.1 The patient must be evaluated by a Radiation Oncologist and Medical Oncologist within 42 days prior to the start of treatment and must be approved to proceed prior to initiation of study treatment.

4.1.2 Before starting metformin, obtain the patient's eGFR. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended.

5.0 REGISTRATION PROCEDURES (1-NOV-2018)

Access requirements for OPEN, Medidata Rave, and TRIAD:

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR)

(https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR Help Desk by email at < RCRHelpDesk@nih.gov >.

5.1 Radiation-Specific Pre-Registration Requirements (1-NOV-2018)

5.1.1 Phantom Irradiation for IMRT

Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select “Credentialing” and “NRG”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and NRG Oncology Headquarters that the institution has completed this requirement. Subsequently, NRG Oncology Headquarters will update RSS at CTSU. Credentialing for IMRT allows the institution to also use 3D-CRT and no additional phantom irradiation is needed for this treatment modality.

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. IROC Houston will be the entity to notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org

	Treatment Modality	Key Information
	Photons	
Facility Questionnaire	X	Complete or update your online electronic Facility Questionnaire. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	To determine whether your institution needs to complete any further credentialing requirements, complete this form under Credentialing on the IROC Houston web site (address above).
Phantom Irradiation	X	See Section 5.0 above describing phantom irradiation requirements for specific motion management techniques. Questions may be directed to IROC Houston.

5.2 Digital RT Data Submission to NRG Oncology Using TRIAD (1-NOV-2018)

TRIAD is the image exchange application used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the IROC website https://www.irocqa.org/Resources/TRIAD.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.3 Regulatory Pre-Registration Requirements (1-NOV-2018)

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

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the

CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Requirements for NRG-LU001 site registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.

5.3.2 Submitting Regulatory Documents:

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Non-English Speaking Canadian and Non-North American Institutions:
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved, NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.3.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must also complete the following documents and submit to the CTSU Regulatory Office via the Regulatory Submission portal:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.3.4 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

*For institutions that **do not have an approved LOI** for this protocol:*

International sites must submit an LOI to NRG Oncology to receive approval to participate in this trial. For more details see link below:
http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx .

*For institutions that **have an approved LOI** for this protocol:*

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.4 Registration (1-NOV-2018)

5.4.1 OPEN Registration Instructions

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

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. See Section 5.0 for obtaining a CTEP-IAM account.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the web site https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

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

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

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

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number.

6.0 RADIATION THERAPY (5/7/15)

See Section 5.2 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

Patients randomized to Arm 1 (concurrent chemotherapy and radiation therapy) must begin treatment within 14 days after randomization.

Patients randomized to metformin (Arm 2) must begin metformin within 14 days after randomization and every effort must be made to begin concurrent chemotherapy and radiation therapy 14 days after beginning metformin. Concurrent chemoradiotherapy and metformin ideally should start on a Monday.

Protocol treatment will be scored according to the Compliance Criteria table in Section 6.7.

It is recommended that radiation therapy be delivered after chemotherapy per Section 7.0.

6.1 Treatment Technology

This protocol requires photons and 3D-CRT or IMRT techniques are permitted. *Tomotherapy and VMAT are allowed. Use of CyberKnife is not permitted for this trial.

***Note**: Institutions that previously have been credentialed for one IMRT delivery technique (e.g. standard gantry mounted linear accelerator using fixed gantry angles) must repeat the credentialing process if the institution elects to use tomotherapy. Contact IROC Houston with any questions concerning further credentialing requirements.

Daily IGRT is required for all patients enrolled on this trial.

6.2 Immobilization and Simulation

6.2.1 Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

6.2.2 Simulation Imaging

Efforts should be made so that simulation CTs take place before initiation of metformin therapy. Contiguous CT slices of 3 mm slice thickness should be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. Contrast-enhanced CT-simulation is recommended but not required in this study. If simulation is performed prior to the initiation of metformin therapy, I.V. contrast may be administered during CT-simulation to assist in treatment volume delineation. If simulation is performed after initiation of metformin therapy, contrast enhancement during CT-simulation should be avoided and contrast-enhanced diagnostic CTs and PET/CTs should be used to guide tumor and normal organ volume definition. In the event that contrast-enhanced datasets are used for treatment planning, the density of the contrast should be overridden to a representative background electron density.

6.2.3 Motion Management Technique

Motion management is highly recommended for this protocol. In instances in which motion management is not possible, larger expansion volumes will be used to adequately cover the motion-related uncertainties. The types of motion management allowed on this study are 4DCT, active breath-hold, gated breathing, and abdominal compression.

6.3 Imaging for Structure Definition, Image Registration/Fusion and Follow Up (5/7/15)

A whole-body FDG-PET/CT and a CT scan with IV contrast or MRI imaging (if CT scan with contrast is medically contraindicated) of the lung and upper abdomen through the adrenal glands are required within 45 days prior to registration (recommended within 30 days prior to registration) as part of staging and to assist in volume delineation in all eligible patients (see Section 3.1.4 for details).

The Imaging and Radiation Oncology Core (IROC) group will be involved in the collection of the pre-treatment PET/CT and CT with contrast. IROC also will be involved in the collection of the follow-up CT scans (or MRIs) of the chest and upper abdomen with contrast at 3 months post-treatment and at the time of progression as well as the time point immediately prior to progression. (See Section 12.3 for digital imaging data submission.) If there is no progression per institutional assessment, the patient should continue to have a CT scan or MRI imaging of the chest and upper abdomen as indicated in Section 11.2.3 (see also Appendix I, Table of Follow Up Assessments) but those scans do not need to be submitted.

IROC Imaging also will be involved in the future analysis of CT imaging data as part of a central review of radiographic response/recurrence.

6.4 Accounting for Tumor Motion Approaches and Internal and Setup Margins (5/7/15)

Internal margin (IM): The IM used will be dictated by the motion management decision made at time of simulation. It is required for all cases, with the exception of instances in which simulation is done with 4DCT to develop a MIP of tumor volume.

1. If the simulation is done with a free-breathing CT only, the IM will be 1 cm in the superior-inferior direction and 0.5 cm in the axial direction.
2. If simulation is done with abdominal compression, the IM will be 0.8 cm in the superior-inferior direction and 0.5 cm in the axial direction.
3. If simulation is done using an active breath-hold or gated breathing technique, the IM will be 0.5 cm in all directions.
4. If simulation is done using a 4DCT to develop a maximum intensity projection or a summation of all phase contours of the tumor volume, no IM is needed.

Setup margin (SM): Daily IGRT is a requirement for this trial; therefore, the SM will be 0.5 cm in all directions.

6.4.1 Definition of Target Volumes and Margins (8/10/16)

All structures must be labeled for digital RT data submission as listed in the table below. Capital letters, spacing and use of underscores must be applied exactly as indicated. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

The structures marked as “Required” in the table must be contoured and submitted with the treatment plan.

Standard DICOM Name	Description	Detailed Specification
GTV_6000	GTV to receive 60 Gy **Required for free breathing, active breath hold or gating motion management techniques**	The primary tumor and clinically positive lymph nodes seen on the planning CT (> 1cm short axis diameter) and pre-treatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged. An ITV is defined at this point as the enveloping GTV motion over the course of a respiratory cycle.
iGTV_6000	Defined as the enveloping GTV motion over the course of the entire respiratory cycle **Required when a 4DCT is used to encapsulate entire breathing cycle volume**	The primary tumor and clinically positive lymph nodes seen on the planning CT (> 1cm short axis diameter) and pre-treatment PET scan (SUV > 3) over the course of a respiratory cycle.
CTV_6000	CTV to receive 60 Gy **Required when GTV is drawn**	The CTV is defined to be the GTV plus a 0.5cm to 1cm margin as appropriate to account for microscopic tumor extension.
ITV_6000	ITV to receive 60 Gy **Required when iGTV is drawn**	The ITV will be equal to the iGTV plus a 0.5cm to 1cm clinical margin as appropriate to account for microscopic tumor extension.
PTV_6000	PTV to receive 60 Gy **Required**	The PTV will be equal to the CTV+IM+SM **OR** ITV+SM. IM and SM are defined in Section 6.4 above. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited up to 0.5cm towards this particular dimension (skin or spinal cord).

6.5 Definition of Critical Structures and Margins (5/7/15)

Note: All required structures must be labeled for digital RT data submission exactly as listed in the first column of the table below. Capital letters and spacing must be used exactly as indicated. Resubmission of data may be required if labeling of structures does not conform to the DICOM Standard Name listed.

Standard DICOM Name	Description	Detailed Specification	
SpinalCord		Boundaries: The bony limits of the spinal canal	
		Cranial	Top of C1 (or first CT slice)

	Required	Caudal	Bottom of L2 (or last slice of CT)
Lungs	**Both Lungs minus GTV 6000 (or iGTV 6000)** **Required**	Boundaries: Use Lung OAR Atlas*	
		Other notes: Both lungs merged into 1 structure and excluding the overlap with GTV_6000 or iGTV	
Esophagus	**Required**	Boundaries: The esophagus contour should include the mucosa, submucosa, and all muscular layers out to the fatty adventitia.	
		Cranial	Bottom of cricoid
		Caudal	GE junction
BrachialPlexus	**Required for upper lobe tumors**	The ipsilateral brachial plexus should be contoured for upper lobe tumors	
Heart	**Required**	Cranial	Ascending aorta
		Caudal	apex
External	**Required**	External contour of patient encompassing all internal organs on each slice	
NonPTV	**Required**	External (as described above) minus PTV	

*Investigators can access the Lung OAR Atlas at
http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx

6.6 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priorities in Section 6.8 should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Dose specification technique**
PTV_6000	60	2.0	30	Covering exactly 95% of PTV

6.7 Compliance Criteria (8/10/16)

The compliance criteria listed below will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Target Volume Constraints and Compliance Criteria

Name of Structure	**Dosimetric* parameter**	**Per Protocol**	**Variation Acceptable****	
PTV_6000	$D_{95\%}$(Gy)	60 Gy	58.8 to 61.2Gy (excluding 60 Gy)	
	D_{min}(Gy)	≥ 57 Gy	≥54 Gy	
	D_{max}(Gy)	≤ 72 Gy	≤75 Gy	

***All values are for a small volume of 0.03 cc.**

****The Variation Acceptable category extends the Per Protocol category numbers to allow for more challenging treatment planning problems. The Variation Acceptable range does not include the Per Protocol values. Plans will be scored as Deviation Unacceptable when Per Protocol and Variation Acceptable constraints are not met.**

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable*	
SpinalCord	$D_{0.03cc}$(Gy) (max)	≤ 50 Gy	na	
Lungs	V_{5Gy}(%)	≤ 65%	≤70%	
	V_{20Gy}(%)	≤ 35%	≤37%	
	D_{mean}(Gy)	≤ 20 Gy	≤22 Gy	
Esophagus	V_{35Gy}(%)	≤ 50 %	≤55 %	
	V_{70Gy}(%)	≤ 20 %	≤25 %	
	D_{mean}(Gy)	≤ 34 Gy	≤37 Gy	
BrachialPlexus	$D_{0.03cc}$(Gy) (max)	≤63 Gy	≤66 Gy	
Heart	V_{30Gy}(%)	≤ 50%	≤55%	
	V_{45Gy}(%)	≤ 35%	≤ 40%	
	$D_{0.03cc}$(Gy) (max)	≤ 70 Gy	≤ 75 Gy **	

***The Variation Acceptable category extends the Per Protocol category numbers to allow for more challenging treatment planning problems. The Variation Acceptable range does not include the Per Protocol values. Plans will be scored as Deviation Unacceptable when Per Protocol and Variation Acceptable constraints are not met.**
**** When this value cannot be achieved, treatment plans must be modified to move dose distribution hotspots away from the heart to avoid having the case scored as a Deviation Unacceptable.**

Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	
Overall Treatment time	≤ 45 days	46-51 days	
Interruptions (other than holidays or weekends)	0-2 days	3-7 days	

Note: Cases will be scored as Deviation Unacceptable when the time limits given above are not met.

6.8 Treatment Planning Priorities and Instructions (8/10/16)

6.8.1 Planning priorities are listed in order of decreasing importance:

1. SpinalCord
2. Lungs
3. PTV
4. Esophagus
5. Heart
6. BrachialPlexus

If lung dose constraints are exceeded, several solutions can be entertained:

- For 3D-CRT: Increase the weighting of AP/PA treatments by 1, and reduce the obliques. This can be done as long as the cord dose, which takes precedence, is not exceeded.
- For 3D-CRT or IMRT: 'Make sure that the GTV (or ITV) to CTV margin is reduced to no less than the minimum allowable amount of 0.5 cm as suggested in the table of section 6.4.1 above' and/or reduce the PTV by choosing another motion management option with smaller internal margins.

It is recommended that the esophagus not to be circumferentially irradiated with > 60 Gy (i.e. the 60 Gy isodose line should not encompass the entire axial cross-section of the esophagus at any level).

6.8.2 Re-planning due to Atelectasis or Pleural Effusion

Due to various physiological reasons, it may be in the interest of best clinical practice to re-simulate the patient and re-plan to account for drastic anatomical changes (adaptive therapy regimens excluded).

Re-simulation

- Repeat CTs will be of the same type (4D, breath-hold, etc.) as the initial planning CT depending upon the motion management strategy being used.

Re-contouring

- The GTV or iGTV, spinal canal, lungs and other OARs will be reviewed by a physician. Any modifications to an OAR must be denoted by the structure name (see Table in Section 6.5) followed by the number of the scan (1 for 1st re-simulation, 2 for the 2nd re-simulation). GTV or iGTV do not require modifications, unless they lie > 3mm outside the originally contoured GTV or iGTV. GTV or iGTV should be re-contoured if tumor regression develops within the previously contoured region, but the CTV (or ITV) and PTV should remain the same. Re-contouring may also be necessary if the GTV shifts relative to other anatomy or deforms. In this case the CTV should be adjusted to the new iGTV/GTV + margin, and a new PTV should be created.
  Important note: Even though the GTV may change substantially during the course of radiotherapy, the CTV is assumed to retain its volume. Therefore, the CTV (or ITV) should not be reduced even if the GTV or iGTV has regressed in the repeat CT scans. The assumption is that there is likely to be microscopic disease present where GTV or iGTV was initially positioned. The CTV (or ITV) shape may change depending on changes in the surrounding anatomy.

Re-planning

- Re-planning should be performed assuming this new CT will receive 30 fractions of treatment at 2Gy/fx. Planning goals should be to meet the protocol's dosimetric criteria before adjusting the number of fractions to the number intended to treat with the re-plan.
- For patients requiring re-planning, the following procedure is to be used to estimate the summed dose distributions. Beam configurations for the original and the re-plans used for treatments will be applied to the re-simulation CT. The dose distributions computed for each of the configurations will be summed weighted according to the number of fractions each distribution used.
- All plans developed and used for treatments and the corresponding CT images will be submitted to IROC Philadelphia-RT Core Lab.

6.9 Dose Calculations

6.9.1 Required algorithms

Acceptable choices of algorithm are listed at http://irochouston.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. Any algorithm used for this study must be credentialed by IROC Houston.

6.9.2 Primary dataset for dose calculation

The primary dataset for dose calculation must be a free-breathing CT that was acquired along with 4DCT, an average intensity pixel CT (AveIP) generated from the 4DCT, the breath-hold/gated CT, or the free-breathing CT acquired with no other motion management. Maximum Intensity Pixel (MIP) generated images from 4DCTs may not be used as the primary dose calculation dataset.

6.9.3 Dose matrix resolution

Dose grid size should be ≤ 3 mm in all directions.

6.10 Patient-specific Quality Assurance (QA)

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

6.11 Treatment Delivery (8/10/16)

Daily Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

6.12 R.T. Quality Assurance Reviews (5/7/15)

The Co-Principal Investigators, Theos Tsakiridis, MD, and/or Heath Skinner, MD will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at IROC Philadelphia-RT. Drs. Tsakiridis and Skinner will perform the next review after complete data for the next 20 cases enrolled has been received at IROC Philadelphia-RT. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at IROC Philadelphia-RT, whichever occurs first.

6.13 Radiation Therapy Adverse Events

6.13.1 Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥ 20 Gy, usually within the first 6 months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

6.13.2 Esophagitis

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If Grade 4 (CTCAE, v. 4) esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to ≤ 3 treatment days. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, investigators must notify the Co-Principal Investigators, Drs. Skinner and Tsakiridis.

7.0 DRUG THERAPY

Patients randomized to Arm 1 (concurrent chemotherapy and radiation therapy) must begin treatment within 14 days after randomization.

Patients randomized to metformin (Arm 2) must begin metformin within 14 days after randomization and every effort must be made to begin concurrent chemotherapy and radiation therapy 14 days after beginning metformin. Concurrent chemoradiotherapy and metformin ideally should start on a Monday.

7.1 Treatment

Chemotherapy and radiation therapy (RT) must begin on the same day. It is recommended that RT be delivered after chemotherapy. All chemotherapy doses must be calculated by the

investigator based on actual body weight. All standard of care chemotherapy is administered as per respective institutional guidelines.

7.1.1 Chemotherapy Concurrent with Radiation

Patients will receive paclitaxel (50 mg/m^2 IV) and carboplatin (AUC-2 IV) weekly on days 1, 8, 15, 22, 29, and 36 from start of chemoradiotherapy, intravenously weekly concurrent with thoracic radiation.

7.1.2 Consolidation Chemotherapy

Patients will receive two 21-day cycles of consolidation treatment beginning 28-42 days after completion of radiation therapy with paclitaxel (200 mg/m^2) and carboplatin (AUC 6) on days 1 and 22 administered intravenously.

7.1.3 Chemotherapy Administration (8/10/16)

Carboplatin dose should be calculated using the Calvert formula [(Total carboplatin dose mg) = (target AUC) x (CrCl + 25)].

CrCl (ml/min) = (140-age) (Actual weight in kg) x 0.85 (females only)/72 x serum Creatinine (mg/dl).

The GFR should not exceed 125 ml/min. If the calculated GFR based on the Calvert formula is greater than 125 ml/min, a GFR of 125 ml/min should be used. **The maximum carboplatin dose for an AUC = 2 should not exceed 300 mg, and for an AUC = 6 should not exceed 900 mg.** A measured CrCl from a 24 hour urine collection may also be used. Note: For subsequent weekly doses, a > 10% change in the serum creatinine, based on weekly calculated creatinine clearance or a > 10% change in weight, will warrant a recalculation of the carboplatin and paclitaxel dose

Chemotherapy drugs will be administered intravenously by intravenous drip. The paclitaxel during the concurrent phase 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. During the consolidation phase, the administration of carboplatin and paclitaxel should follow institutional standards in regards to duration of infusion, premedications and standard antiemetics.

7.1.4 Timing of Treatment

If the day of chemotherapy falls on a holiday, chemotherapy should be administered on the next full working day following the holiday (e.g., if the day 8 dose falls on Thanksgiving, the next chemotherapy dose would be given the following Monday). Doses that are missed during the weekly schedule concurrent with RT will not be made up but will be documented. If breaks from chemotherapy are required for longer than 15 days, protocol chemotherapy will be discontinued. RT will continue, and the patient will remain on study and will be followed as specified in the protocol.

7.1.5 Metformin Treatment (5/7/15)

All patients randomized to metformin (Arm 2) will go through metformin dose escalation. Patients will start metformin within 14 days after randomization, ideally on a Monday 2 weeks prior to initiation of concurrent chemotherapy and radiation. The starting dose is 500 mg p.o. BID (before breakfast and dinner) 7 days/week. On day 8, this dose will be escalated to 500 mg TID before meals for a total daily dose of 1500 mg. On day 15, ideally a Monday that should coincide with the initiation of concurrent chemotherapy and radiation, the midday dose will increase by an additional 500 mg for a total daily dose of 2000 mg (500 mg in the morning, 1000 mg midday, and 500 mg in the evening). If day 15 falls on a holiday or there are unforeseen circumstances that delay the initiation of chemotherapy and radiation, the patient should continue on the 1500 mg daily dose until the start of chemoradiation when the patient will begin a total daily dose of 2000 mg daily.

When concurrent chemotherapy and radiation is completed, Arm 2 patients will continue daily metformin for a total of 10 more weeks. Consolidation chemotherapy begins 4-6 weeks after the end of concurrent chemoradiotherapy.

Metformin should be taken 1-2 hours before meals and before chemotherapy on days on which this occurs. For compliance assessment, patients will be required to track daily doses of metformin by maintaining a daily medication diary that is located here: http://www.rtog.org/LinkClick.aspx?fileticket=Hztq94-tFCw%3d&tabid=290.

Supply
In this study the investigational agent (metformin) will not be supplied to centers. Metformin HCL is commercially available and very economical. Therefore, sites are strongly encouraged to provide the required amount of metformin to patients from the site pharmacy free of charge by using a small portion of the site's case reimbursement to cover the cost. Because Metformin HCL is investigational in this trial, in most cases the patient's health plan/insurance company will not pay for the drug.

7.1.6 Temporary Interruption, Reduction, and Re-Initiation of Metformin Treatment (8/10/16)

The risk of hypoglycemia in euglycemic patients is exceedingly low, as hypoglycemia does not occur in patients receiving metformin alone under usual circumstance. Because patients in this trial might have a low caloric intake due to complications of treatment, patients randomized to metformin (Arm 2) will undergo weekly blood glucose monitoring. If based on these lab values or associated symptoms, the treating physician diagnoses hypoglycemia, study drug treatment will be halted, while concurrent chemoradiation or chemotherapy continues. Once blood glucose normalizes, metformin will be restarted and the dose should be decreased by 500 mg with daily monitoring of blood glucose. Acceptable doses of metformin are 2000, 1500, 1000, or 500 mg every day. If there are no symptoms or signs of hypoglycemia in 1 week, daily monitoring is no longer needed. The site will record any dose de-escalation and re-escalation in source documentation.

In the event of grade 2 or 3 gastrointestinal toxicity (typically involving flatulence or diarrhea), patients will be supported with loperamide, at dosing schedules recommended in the package insert. Gastrointestinal side effects typically subside within 4-6 weeks of initiating metformin treatment. In the event that grade 2 gastrointestinal toxicity persists during or following the completion of concurrent chemotherapy and radiation, metformin dose de-escalation will be permitted when symptoms are deemed to be due to metformin alone and not due to systemic therapy or other reasons. Efforts should be made to maintain the dose as close to the suggested total daily treatment dose (2000 mg) as much as possible. Alterations to the daily intake schedule of metformin should be the first steps to be taken to reduce gastrointestinal symptoms, including taking metformin with food rather than before meals or modifying drug intake from the TID schedule to a BID dosing of 1000 mg (2 tablets of 500 mg with morning and evening meals), keeping the doses 12 hours apart. If alterations in schedule are insufficient in reducing gastrointestinal toxicity to ≤ grade 1, the metformin dose should be decreased by 500 mg for 1 week with loperamide support until symptoms subside. If GI toxicity has not resolved in 1 week, then decrease the dose by another 500 mg; do this weekly until GI toxicity resolves. Efforts should be made to re-escalate the dose of metformin back to 2000 mg total daily dose 2 weeks after patients remain free of grade 2 toxicity. At least 2 attempts should be made to re-escalate the dose to 2000 mg/day after each dose de-escalation takes place.

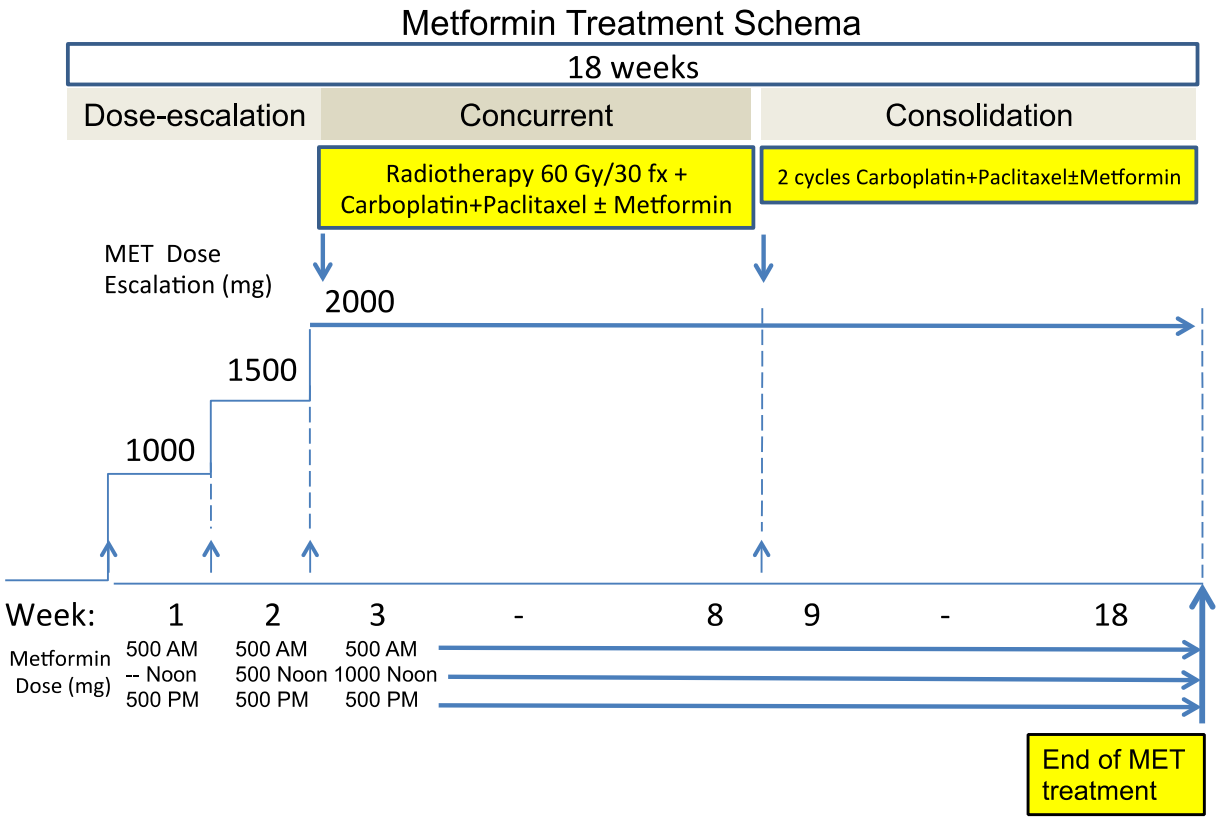
In the event that re-escalation to a higher dose cannot be achieved without grade 2 toxicity, patients will be maintained at the highest tolerable dose for the remainder of the metformin treatment period. Acceptable doses of maintenance metformin are 2000, 1500, 1000 or 500 mg every day. The site will record any dose de-escalation and re-escalation in source documentation.

Metformin treatment interruption will be permitted according to local guidelines at the time of routine CT scans with contrast infusion. Obtain an eGFR annually in all patients taking metformin. Discontinue metformin if eGFR ≤ 30 mL/minute/1.73 m2. If eGFR is between 30-45 mL/minute/1.73 m2, perform eGFR every 1-2 weeks until recovery to ≥45, then resume normal metformin doses.

Patients whose treatment is interrupted for any reason except intolerable toxicity will be encouraged to resume and continue with their assigned therapy. Sites will record compliance (and reasons for

non-compliance) in source documentation. The visit schedule for those patients who discontinue therapy should not be modified as endpoints will be assessed for all patients regardless of study drug discontinuation as an intent-to-treat analysis will be performed.

Metformin Timeframe and Dose			
Dose Escalation		*Concurrent Treatment*	*Consolidation Treatment*
Days 1-7	Days 8-14	Days 15-56	Days 57-126
1000 mg	1500 mg	2000 mg	2000 mg
500 mg AM 500 mg PM	500 mg AM 500 mg Noon 500 mg PM	500 mg AM 1000 mg Noon 500 mg PM	500 mg AM 1000 mg Noon 500 mg PM



7.2 Study Agents

Please see Section 7.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

Non-Canadian International Institutions:
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol.

7.3 Dose Modifications (5/7/15)

7.3.1 Dose Modifications during Concurrent Chemoradiation

The following dose levels are used for dose modifications during the concurrent chemoradiation phase. There will be no dose reduction below level -1.

Dose Level	Carboplatin	Paclitaxel
0	AUC 2	50 mg/m^2
-1	AUC1	40 mg/m^2

Hematologic Toxicity during Concurrent Chemoradiation

Dose Modification on Day of Administration of Concurrent Chemotherapy And Radiation

		Platelet count	
		< 80K	>80K
ANC x1000 ANC	≥ 1	Hold*	Continue same dose level
	<1	Hold*	Hold*

*Check weekly and resume therapy at previous dose (no dose reduction) when counts recover to ANC ≥ 1,000 and platelets ≥ 80,000/mcl. There will be no dose reduction for hematologic toxicities during the concurrent phase.

If dose reduction is required during chemoradiation, no re-escalation is allowed in subsequent chemoradiation cycles. However, paclitaxel and carboplatin will be started at dose level 0 for the consolidation cycles.

If paclitaxel and/or carboplatin are held for greater than 2 consecutive weeks, the drugs will be held permanently for the duration of concurrent therapy but should be restarted for the consolidation phase. If during the consolidation phase chemotherapy is held for more than 3 weeks, then it should be discontinued.

7.3.2 Febrile Neutropenia during Concurrent Chemoradiation

Febrile neutropenia occurring during chemoradiation will result in a decrease of the carboplatin and paclitaxel dose level by –1. Febrile neutropenia occurring despite dose reduction during chemoradiation will result in discontinuation of carboplatin, but continuation of paclitaxel at the previous dose (-1 dose level). Radiation therapy is held for neutropenia (ANC < 500/mcl); radiation therapy may be restarted when the ANC ≥ 1000/mcl. Filgrastim, sargramostim or pegfilgrastim are not allowed during radiation treatment.

7.3.3 Dose Modifications during Consolidation Chemotherapy

The following dose levels are used for dose modifications during the consolidation phase. There will be no dose reduction below level -1.

Dose Level	Carboplatin	Paclitaxel
0	AUC 6	200 mg/m^2
-1	AUC 4.5	150 mg/m^2

Hematologic Toxicity during Consolidation Chemotherapy

Dose Modification on Day of Administration of Consolidation Cycle

		Platelet count	
		< 100K	>100K
ANC	≥ 1.5	Hold*	Continue same dose level

	<1.5	Hold*	Hold*

*Check weekly and resume therapy at previous dose (no dose reduction) if counts recover within 1 week to ANC ≥ 1,500 and platelets ≥ 100,000/mcl. If not, decrease by 1 dose level when ANC 1,500 mm^3 platelets ≥ 100,000/mcl. Use of growth factors for neutropenia during consolidation are allowed at the discretion of the treating oncologist. Dose delays greater than 3 weeks will warrant discontinuation of chemotherapy for the consolidation cycles.

7.3.4 Febrile Neutropenia during Consolidation Chemotherapy

Febrile neutropenia occurring during consolidation will result in a decrease of both the carboplatin and paclitaxel doses by 1 dose level. Filgrastim, sargramostim or pegfilgrastim are allowed during the consolidation phase at the discretion of the treating medical oncologist.

7.3.5 Renal Toxicity during Concurrent or Consolidation Chemotherapy

Renal Toxicity: There are no dose modifications for renal toxicity. It is not necessary to change the dose of carboplatin unless the calculated dose changes by ≥ 10%.

7.3.6 Neurotoxicity during Concurrent or Consolidation Chemotherapy

- Paclitaxel doses should be modified for neurologic toxicity (see below). Serum magnesium and calcium levels should be checked; folate and vitamin B12 levels may need to be evaluated especially in older patients.
- Grade 1: Give paclitaxel at full dose.
- Grade ≥ 2: Hold paclitaxel until neurotoxicity resolves to ≤ grade 1, then resume with one dose level reduction. Continue treatment with carboplatin. If paclitaxel is held for ≥ 21 days, discontinue paclitaxel, but continue treatment with carboplatin.

7.3.7 Hepatic Toxicity during Consolidation Chemotherapy (8/10/16)

Give the following doses for paclitaxel only:

		AST		
		<2.5x ULN	2.5-5 x ULN	>5 x ULN
Bilirubin	≥ 1.5 ULN	Hold* and recheck weekly	Hold* and evaluate as medically necessary, recheck weekly.	Hold* and evaluate as medically necessary, recheck weekly.
	< 1.5 ULN	Same dose level	Reduce 1 dose level	Hold* and evaluate as medically necessary, recheck weekly.

*Hold paclitaxel until AST ≤ 5 x ULN and bilirubin < 1.5 ULN, then resume treatment at one dose level lower. (Continue treatment with carboplatin. If paclitaxel is held for ≥ 21 days, discontinue paclitaxel therapy (continue treatment with carboplatin).

7.3.8 Hypersensitivity Reactions to Carboplatin

- Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate.
- Grade 2: Stop the infusion. Administer H1 and/or H2 blockers +/- dexamethasone, according to physician discretion/institutional guidelines. Restart carboplatin when symptoms resolve and pretreat before all subsequent doses of carboplatin.
- Grade 3 or 4: Patient should be removed from all protocol therapy.

7.3.9 Hypersensitivity Reactions to Paclitaxel

- Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate.
- Grade 2: Stop the infusion. Administer H1 and/or H2 blockers +/- dexamethasone according to physician discretion/institutional guidelines. Restart when symptoms resolve and pretreat before all subsequent doses.
- Grade 3 or 4: Discontinue therapy with paclitaxel.

7.3.10 All Other Non-Hematological Treatment-Related Toxicities that Exceed Grade 2 during Concurrent or Consolidation Chemotherapy (5/7/15)

For all other treatment-related toxicities that exceed grade 2: (except alopecia, nausea, vomiting, fatigue and anorexia), hold paclitaxel and carboplatin until the toxicities have resolved to grade 2 or less and resume carboplatin and paclitaxel with one dose level reduction.

7.4 Modality Review

The Medical Oncology Co-Chair, Rafael Santana-Davila, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Santana-Davila will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Dr. Santana-Davila will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

7.5 Adverse Events (1-NOV-2018)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613) In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology Operations Center by phone (215-574-3191). Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.5.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.5.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.6 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.6. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;

- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.5.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

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

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

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

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

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

7.6 CTEP-AERS Expedited Reporting Requirements (1-NOV-2018)
All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site,
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613 .

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology Operations Center by phone (215-574-3191). Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious

adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.

- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology Operations Center (215-574-3191) for source document submission assistance**.**
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action not recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 1 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies Utilizing Commercial Agents within 30 Days of the Last Administration of the Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

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

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

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent

The following are protocol-specific exceptions to expedited reporting via CTEP-AERS. Report the following adverse events (AEs) in an expedited manner only if the AEs exceed grade 3 (CTCAE, v. 5): Nausea, vomiting, diarrhea, and dehydration. Report the following AEs in an expedited manner only if the AEs exceed grade 2 (CTCAE, v. 5): Esophagitis, dysphagia. Routine adverse event reporting on the case report form fulfills safety reporting requirements for these events at the aforementioned grades.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Filgrastim, sargramostim or pegfilgrastim are allowed during consolidation chemotherapy at the discretion of the treating medical oncologist.

9.2 Non-permitted Supportive Therapy

9.2.1 Filgrastim, sargramostim or pegfilgrastim are not allowed during radiation treatment.

10.0 TISSUE/SPECIMEN SUBMISSION (5/7/15)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as

specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission (5/7/15)

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank – San Francisco provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Oncology Biospecimen Bank – San Francisco - also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue, plasma and whole blood will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking for future translational research. Specific hypotheses include:

1. TP53, LKB1 and K-RAS mutation status can predict the ability of MET to offer overall radio- and chemo-sensitization action in patients with LA-NSCLC. The clinical value of developing a reliable selection biomarker for future MET studies can be very significant, as that could spare unnecessary treatment of non-responsive patients. For that, we will collect tumor tissue and investigate those markers at the gene and protein level.
2. Fasting MET plasma levels predict response to therapy.
3. Reduction of fasting plasma insulin and LDL-cholesterol correlate with plasma MET levels and response to the drug.

Testing these markers in the samples obtained in this trial will help us determine whether future studies can utilize serum MET levels, response of insulin levels and lipid profile or phosphorylation of AMPK, $p70^{S6k}$ or 4EBP1 as predictive markers of MET response in a specific patient. These markers may be able to help monitor on-going patient response to MET therapy.

10.2 Specimen Collection for Tissue Banking and Translational Research (Recommended) (8/10/16)

For patients who have consented to participate in the tissue/blood component of the study (See sample informed consent).

The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

10.2.1 One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block); it does not have to be the diagnostic slide itself.)

10.2.2 A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. If sites are unable to provide block or punch, 10-15 unstained slides are an acceptable alternative. **Note:** A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number and block number that corresponds to the Pathology Report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank – San Francisco - if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

10.2.5 Three tubes of blood (2 tubes x 10 ml each for plasma collection and 1 tube x 5-10 ml for whole blood) will be collected from participating patients at baseline, 2 tubes of blood x 10 ml each for plasma at weeks 1 and 6 of concurrent chemoradiotherapy (corresponding to weeks 3 and 8 of the metformin treatment period for patients randomized to Arm 2) and at the 6 month follow up visit as described below in Table 10.2.7.

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The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG Oncology protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.2.6 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the ST Form the storage conditions used and time stored.

10.2.7 Specimen Collection Summary (8/10/16)

Specimens for Tissue Banking/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsy (must match the H&E slide being submitted)	Block or punch shipped ambient
PLASMA: 2 X 10 mL of anticoagulated whole blood in EDTA tubes #1 (purple/ lavender top) and centrifuge	At baseline, weeks 1 and 6 of chemo/RT (corresponding to weeks 3 and 8 of metformin treatment period for patients randomized to Arm 2), and at 6 month follow-up visit (as indicated in Appendix I).	Frozen plasma samples containing **0.5 mL** per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
Whole blood for DNA: 1x 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment Note: If site missed this collection time point they may collect whole blood for DNA at a later time point instead but must note this on the ST Form.	Frozen whole blood samples containing **1 mL** per aliquot in 1ml cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier

10.2.8 Submit materials for Tissue Banking and Translational Research as follows:

U. S. Postal Service Mailing Address: <u>For Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For Trackable FFPE and ALL Frozen Specimens</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.3 Reimbursement

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.4 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.4.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See Appendix I

11.2 Details of Evaluations

11.2.1 <u>Pre-Treatment Evaluations</u>

- Tumor measurements: Measure in at least 1 dimension and record the longest dimension as ≥ 10 mm with CT scan (or MRI) of the chest and upper abdomen. The CT scan or MRI must be performed from the lung apices through the adrenal glands. **Note**: A baseline CT of the chest and upper abdomen is required and must be submitted for central evaluation (see Section 6.3)
- Institutions are highly encouraged to utilize the same imaging modality (CT or MRI) for each follow-up scan, if possible.
- A baseline whole body FDG-PET/CT scan must be performed from skull base through perineum and is required to complete staging and assist in treatment volume delineation. Serum glucose must be measured (ideally within 1 hour of FDG administration). If the serum

glucose concentration is found to be > 200 mg/dL, the study should be rescheduled. The referring physician or primary physician will be contacted to optimize blood glucose control. Use of iodine or gadolinium contrast is required unless medically contraindicated. The PET/CT scan must be submitted for central evaluation (see Section 6.3).

- All imaging with IV contrast must be performed prior to initiating treatment with metformin.

11.2.2 Evaluations During Treatment

- History and physical examination must include recording of pulse, BP, weight and body surface area.
- BSA should be recalculated if there is a change of more than 10% of body weight, compared to the registration weight.
- Patients should have a CBC with differential, serum creatinine, and for Arm 2 patients, blood glucose weekly during concurrent chemotherapy and radiation.
- Patients should have a CBC with differential bilirubin, AST/ALT, alkaline phosphatase, and for Arm 2 patients, blood glucose within 48 hours prior to every cycle of consolidation chemotherapy. **Note**: If hypoglycemia was detected in an Arm 2 patient during concurrent chemotherapy, then the patient should have weekly monitoring during consolidation treatment.

11.2.3 Evaluations in Follow Up (8/10/16)

- History and physical examination must include recording of pulse, BP, weight and body surface area.
- All patients must have a follow-up CT scan of the chest and upper abdomen with contrast or MRI at 3 months from end of radiotherapy and the CT or MRI must be submitted for central evaluation (see Section 6.3).
- All patients must have a follow-up CT scan of the chest and upper abdomen or MRI at 6, 9, and 12 months from the end of radiotherapy or until progression, whichever comes first.
- Follow-up CT scans of the chest and upper abdomen with contrast or MRIs are recommended every 3 months for year 2, every 6 months for years 3-5, then annually, until patients show evidence of progression. Central submission of these chest CTs/MRIs is **not** required unless progression occurs at any of these time points. If progression occurs the imaging for the time point at which progression occurred and the imaging for the time point immediately preceding the progression must be submitted centrally.
- Other imaging sites (e.g. extremities, head) should be imaged per institutional routine if there is a suspicion of new metastatic disease. If new metastatic disease at any such anatomic site is confirmed and contributes to the declaration of progressive disease, this imaging must be submitted centrally.
- Current ACR guidelines do not require cessation of metformin following iodinated contrast administration in patients with normal renal function and no comorbidities that would increase the risk of iodinated contrast induced nephropathy (ACR Manual on contrast media, v.9, 2013). Nevertheless, local institutional policy can be used regarding temporary cessation of metformin following administration of iodinated contrast for CT scan or MRI.

11.3 Measurement of Response

Response will be evaluated in this study using the revised RECIST guideline. Version 1.1 will be sued as a guideline to determine study eligibility. (https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf).

- **Complete Response (CR)**: Disappearance of all target lesions;
- **Partial Response (PR)**: At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD;
- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for Progressive Disease (PD), taking as reference the smallest sum LD since the treatment started.

11.4 Measurement/Definition of Progression/Recurrence

Progression is defined as change in a known lesion(s) not related to post-treatment effects as defined below:

- At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Additionally the absolute increase must be greater than 5 mm.
- Appearance of ≥1 new lesions not related to post-treatment effect.

Progression is further divided into local, regional or distant progression:

- Local: Progression within the PTV.
- Regional: Progression outside the PTV but within the same lobe of the lung as the primary tumor or in regional lymph nodes (AJCC 7th edition)
- Distant: Progression at any other site (including pleural or pericardial effusion)

11.5 Criteria for Discontinuation of Metformin Treatment (5/7/15)

- Unacceptable toxicity; see Section 6.0 and Section 7.0 for further information.
- Progression of disease;
- Development of a 2nd primary upper aerodigestive tract malignancy (lung, esophagus, head and neck);
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (8/10/16)

This study will utilize Medidata Rave® for remote data capture (RDC) of all data. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave see Section 5.0 of the protocol.

Each person responsible for data entry must be on the NRG Oncology roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS (Regulatory Support System), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org or by or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1 Summary of Data Submission (8/10/16)

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

sections provide information about expedited reporting. For this trial the *{form name}* is used for routine AE reporting in Rave.

For reporting of secondary cancers or other report forms available in Rave:
Indicate form for reporting in Rave, timeframes, and if loading of the pathology report is required.

Folder	Form/Item
Registration via the OPEN System	• ***Subject Enrollment***
Enrollment Forms When pushed into RAVE there will be 4 forms representing registration	• ***Eligibility Checklist*** • ***Step Information*** • ***Treatment Assignment*** • ***Demography***
Baseline	• ***Diagnostic Staging*** • ***Work Up*** • ***SOC Imaging*** • ***Lymph Node Assessment*** • ***Patient History*** *(formerly known as the A5)* • ***Pathology Report***
RT Plan Upload	• ***Digital Data****-(Upload of e-mail confirmation from TRIAD submission required)*
Concomitant Medications	• ***Concomitant Medication*** *(only required if patient is taking concomitant medications)*
Dose Escalation (Week 1) (Only if randomized to Arm 2)	• ***Metformin*** • ***Any Adverse Events?*** • ***Adverse Events*** *(if any adverse events? = 'yes'* • ***On Treatment Labs MET***
Dose Escalation (Week 2) (Only if randomized to Arm 2)	• ***Metformin*** • ***Any Adverse Events?*** • ***Adverse Events*** *(if any adverse events? = 'yes'* • ***On Treatment Labs MET***
Concurrent Treatment	• ***RT Administration*** • ***RT Treatment-****if was radiation therapy given = 'yes'* • ***Protocol Specific RT Questions*** *If was radiation therapy given = 'yes'* • ***Any Adverse Events?*** • ***Adverse Events –*** *if any adverse events? = 'yes'* • ***Carboplatin (concurrent)*** • ***Paclitaxel (concurrent)*** • ***Metformin*** *(if randomized to Arm 2)* • ***On Treatment Labs 01*** *(up to 11 additional weeks may be added by user if needed)*

End of All RT	• ***End of All RT*** *(this form should be completed for all patients after their final day of any protocol RT)*
Consolidation Treatment	• ***Any Adverse Events?*** • ***Adverse Events –*** *if any adverse events? = 'yes'* • ***Carboplatin (consolidation)*** • ***Paclitaxel (consolidation)*** • ***Metformin*** *(if randomized to Arm 2)* • ***On Treatment Labs 01*** *(up to 11 additional weeks may be added by user if needed)*
<u>Years 1-2</u> **4-6 Week Follow-Up** **3 Month Follow-Up** **6 Month Follow-Up** **9 Month Follow-Up** **1 Year Follow-Up** **15 Month Follow-Up** **18 Month Follow-Up** **21 Month Follow-Up** **2 Year Follow-Up** **<u>Years 3-5</u>** **30 Month Follow-Up** **3 Year Follow-Up** **42 Month Follow-Up** **4 Year Follow-Up** **54 Month Follow-Up** **5 Year Follow-Up** **<u>Years 6-10+</u>** **6 Year Follow-Up** **7 Year Follow-Up** **8 Year Follow-Up** **9 Year Follow-Up** **10 Year Follow-Up**	• ***Any Adverse Events?*** • ***Adverse Events –*** *if any adverse events? = 'yes'* • ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted = 'yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Pulmonary Function Tests*** *– if PFTs performed = 'yes'* • ***Primary Cause of Death*** *– If Vital Status = 'dead'*
CTEP-AERS	• **CTEP-AERS *Upload Form*** *– used by HQ to upload* CTEP-AERS *reports, sites have read only access to this folder/form*
Source Documentation Upload	• ***Source Documentation Upload*** *– used by sites in the event that source documentation needs to be uploaded to HQ*
IROC Imaging Progression and **IROC Imaging – Prior to Progression**	• ***SOC Imaging*** *(these will only be used if the patient progresses after 12 months off treatment)*

12.2 Summary of Dosimetry Digital Data Submission (8/10/16)
(Submit to TRIAD; see Section 5.0 for account access and installation instructions.)
(Note: Choose **RT Plan Upload** for the TimePoint ID in TRIAD for items below in Sec. 12.2)

<u>Item</u>	**<u>Due</u>**
Preliminary Dosimetry Information	
Digital Data Submission – Treatment	Within 1 week of start of RT
Digital data submission includes the following, all in DICOM format:	

• Planning CT and PET	
• RT Structure File: must include all required target volumes and critical structures, labeled exactly as defined per Sec. 6.4.1 (Target Volumes) and 6.5 (Critical Structures)	
• RT Plan File: Digital beam geometry beam sets	
• RT Dose File: Doses for concurrently treated beams	
• The "LU-0001 Datasheet" is available in the Forms section of the of the NRG Oncology/RTOG web site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1327&mode=html&ptid=383. Submit via TRIAD with the digital data listed above.	
• Upon submission of digital RT data via TRIAD, complete an online Digital Data Submission Form (DDSI Form), found on the NRG Oncology/RTOG web site under the 'Core Lab' section http://www.rtog.org/CoreLab/TRIAD.aspx	

12.3 Summary of Required Diagnostic Imaging Digital Data Submission (8/10/16)
(Submit to TRIAD; see Section 5.0 for account access and installation instructions.)
(Note: Choose appropriate **Imaging** TimePoint ID in TRIAD for items below in Sec. 12.3)

Item	Timepont
Digital data submission includes the following, all in DICOM format:	
• Pre-treatment Whole body PET/CT	Baseline
• Pre-treatment Chest CT/MRI	Baseline
• Follow-up Chest CT/MRI	At 3 months post-radiotherapy
• Follow-up Chest CT/MRI	At progression (first scan demonstrating evidence of progression)
• Follow-up Chest CT/MRI	Immediately prior to progression
• Other post therapy imaging (e.g. brain CT/MR, CT A/P, extremity imaging), if used to document distant progression.	At progression

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

Progression-free survival (PFS), defined as the interval from randomization to progression or death due to any cause, whichever occurs first.

13.2 Secondary Endpoints

- Overall survival (OS), defined as the interval from randomization to death due to any cause
- Time to local-regional progression (LRP), defined as the interval from randomization to local or regional progression;
- Time to distant metastasis (DM), defined as the interval from randomization to distant metastasis;
- Adverse events definitely, probably, or possibly related to treatment (CTCAE, v. 4) within 1 year of completion of all treatment.

13.3 Stratification

Patients will be stratified by Zubrod Performance Score (0 vs. 1); histology (squamous vs. non-squamous); and clinical stage (IIIA vs. IIIB).

13.4 Sample Size and Power Justification

In LA-NSCLC, the expected 1-year progression-free survival (PFS) with the concurrent chemoradiotherapy is assumed to be 50% based on RTOG 0617 (Bradley 2011). The target improvement for the added MET is to increase the 1-year PFS to 65%. Assuming the PFS are exponentially distributed (at least approximately) with constant hazards in the both treatment arms, the primary hypothesis is equivalent to reduce the monthly hazard λ from 0.0578 to 0.0359, i.e., a hazard ratio of 0.622 or 37.8% relative hazard reduction. This study will be a randomized phase II screening trial as proposed by Rubinstein et al (2005). The randomization of experimental and standard arms is set to be 1:1. With 152 analyzable patients (76 analyzable patients per arm) and 102 PFS events, there will be 85% power to detect a 37.8% relative reduction in hazard at a significance level of 0.1 (one-sided). Adjusting for a 10% rate of ineligibility, **a maximum of 168 patients is required for this trial**.

For the most recently completed RTOG trial in the same patient population, the randomized phase III study RTOG 0617, the average monthly accrual rate was more than 10 cases/month. Therefore, a monthly accrual rate of 7 patients is assumed in this study, and the total accrual is expected to be completed in 2 years. The study is expected to reach the required number of PFS events 1 year after accrual completion. During the first 6 months following activation, little accrual is anticipated while the trial is being approved by institutional review boards (IRBs). A total of 3.5 years is projected to observe the required number of PFS events and conduct the final analysis (if applicable).

13.5 Statistical Analysis Plan

13.5.1 Statistical Methods

PFS is defined as the time from randomization to disease progression or death from any cause, whichever occurs first. A rigorous definition of disease progression is provided in Section 11.4 (a second primary cancer is not treated as a PFS event). PFS rates will be estimated using the Kaplan-Meier method (1958), and the differences between arms will be tested using a log-rank test (Mantel 1966). A multivariate analysis with the Cox proportional hazard model (1972) for PFS will be performed with the stratification variables as fixed variables to assess the treatment effect adjusting for patient-specific risk factors.

Overall survival (OS) is similarly analyzed as time-to-event data, where the OS rates will be estimated using the Kaplan-Meier method, and the differences between treatment arms will be tested using the log-rank test. A competing risks analysis approach also will be used when analyzing time to local-regional progression (TTLRP) and time to distant metastasis (TTDM). For TTLRP, only local-regional progression will be counted as events (failures), and patients who die or have a distant metastasis without a local-regional progression will be treated as competing risk. Analogously, for TTDM, only distant metastasis will be counted as events, and deaths or local-regional progression without distant metastasis will be treated as competing risks. A cumulative incidence approach will be used to estimate the respective rates, and the corresponding differences in LRP and DM will be evaluated using Gray's test (Gray 1988).

Due to the concerns of potential subjective bias introduced in investigator-determined progression (Dodd 2008), all PET/CT scans will be collected and archived for a planned retrospective central radiologic review. These PET/CT scans will be blindly reviewed by the Radiologic Co-Chair. The centrally-reviewed progression results will be properly incorporated in the sensitivity analyses (FDA 2007) to assure the robustness of analysis results.

The rate of treatment-related adverse events using NCI Common Terminology Criteria for Adverse Events (CTCAE, v. 4) will be reported with the frequency and severity (e.g., type, grade, and attribution) by arm, and analyzed using Chi-square test or Fisher's exact test wherever applicable. The analysis will be performed at the time of primary endpoint analysis. Logistic regression (Agresti 1990) will be used to model the distribution of adverse events with and without adjustment for covariates. Both unadjusted and adjusted odds ratios and the respective 95% confidence intervals will be computed and tested at a significance level of 0.05 (2-sided).

13.5.2 Significance Testing for Early Termination and Reporting

A group sequential test with one planned interim analysis and a final analysis will be performed. The interim analysis will be based on the primary endpoint as defined in Section 13.1.1, and will be carried out when half of the number of expected PFS events (51 events) is reached. At the planned interim analysis, the p-value from the log-rank test will be compared to 0.01 for rejecting the null hypothesis, and the observed hazard ratio (experimental/standard) will be compared with 1.0 (Wieand 1994) for futility. If the p-value associated with the resulting test statistics is less than or equal to 0.01, then we will stop accrual to the trial (if applicable) and conclude MET improves PFS of these patients; if the observed hazard ratio is greater than or equal to 1.0, a decision about whether to terminate accrual and release the results will be made after consultation with the NRG Oncology Data Monitoring Committee (DMC) and NCI/CTEP. If the efficacy boundary is not crossed and the observed hazard ratio is less than 1.0, the final analysis will occur when there are at least 102 PFS events observed. A significance level of 0.09 for the final analysis was derived in order to preserve a 0.1 significance level (1-sided) for the entire study.

At the protocol-planned interim analysis, the results from the test assessing the treatment efficacy and futility will be reported to the NRG Oncology Data Monitoring Committee (DMC). The protocol statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if either efficacy or futility boundary is crossed. The accrual rate, treatment compliance, safety of the treatments, and the importance of the study also are considered in making such a recommendation. The results will be reported to the NRG Oncology DMC. The DMC will then make a recommendation about the trial to the NRG Oncology Group Chairs.

13.5.3 Significance Testing for Final Analysis

The final analysis will be performed on an intent-to-treat basis, such that all eligible cases will be included in the arm to which the patient was randomized regardless of what treatment the patient actually received. The major analysis will occur after at least 102 PFS events have been observed, unless an early stopping rule is satisfied. It will include:

- Tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given;
- Distributions of important prognostic baseline variables;
- The frequencies and severity of AEs by treatment arms;
- Compliance rate of treatment delivery;
- Observed results with respect to the primary and secondary endpoints.

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using the stratified log-rank statistic with a significance level of 0.1 (1-sided), given that the interim analysis will have been carried out. Additional analyses of treatment effect will be performed using the Cox proportional hazards model with the stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms and any other factor known to be associated with outcome.

13.5.4 Interim Analysis to Monitor Study Progress

The NRG Oncology Data Monitoring Committee (DMC) will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community. In general, the interim reports will contain information about the patient accrual rate, a projected completion date for the accrual phase, patient exclusion rates and reasons following registration, compliance rate of treatment delivery, distributions of pretreatment characteristics and important prognostic baseline variables, and the frequencies and severity of treatment-related adverse events. The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints.

Interim reports with statistical analyses are prepared every 6 months until the initial publication reporting the treatment results has been submitted. The reports contain:

- Patient accrual rate with a projected completion date (while the study is still accruing)
- Total patients accrued

- Distributions of important pretreatment and prognostic baseline variables
- The frequencies and severity of adverse events by treatment arm
- Compliance rates of treatment delivery

13.5.5 CDUS Reporting

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

13.6 Statistical Considerations for Translation Research

The translational research objectives are considered in exploratory nature. The predictive and prognostic potential for the proposed biomarkers may become scientifically obsolete or the assay technology may evolve over time, making the technology outlined in the current protocol obsolete when the study is finished. As such, no marker assays will be conducted on the collected specimens. When sufficient information is available from the parent study, a full correlative study protocol for the marker studies detailing the scientific hypothesis, research plan, clinical outcome, assay methods for each biomarker, and a more complete statistical section (with adequate power justification and analysis plan) will be submitted and subjected to CTEP review in accordance with National Clinical Trials Network (NCTN) policies.

To determine if the study may offer exploratory yet still meaningful findings whether a mutation of interest may predict PFS changes in patients treated with metformin, we summarize the following table as a preliminary evaluation for the interaction effects between marker status (such as TP53, STK11 (LKB1) or KRAS) and treatment assignments. Based on the design parameters and the method proposed by Peterson and George [Peterson 1993], we summarize the statistical power to detect interaction effects (ratio of hazard ratios) of 0.33, at 2-sided significance level of 0.05. We denote monthly hazard rates as λ, expected number of events of respective subgroups as E[N], and the hazard ratio between marker + and - as Δ. The subscripts indicate the corresponding treatment arms. The assumed monthly hazard rates and associated expected number of events are listed in the following Table accordingly.

Prevalence of Marker +/-		Arm 1			Arm 2			Interaction	
		Marker -	Marker +	Δ_1	Marker -	Marker +	Δ_2	$\Delta_{21}= \Delta_2/ \Delta_1$	Power
0.33	λ	0.0578	0.0578	1.0	0.0487	0.0161	0.33	0.33	63.2%
	E[N]	38	19		35	8			
	λ	0.0505	0.0758	1.5	0.0442	0.0219	0.5	0.33	70.4%
	E[N]	35	21		33	11			
	λ	0.0459	0.0918	2.0	0.0408	0.0269	0.67	0.33	72.1%
	E[N]	34	22		32	12			
0.5	λ	0.0578	0.0578	1.0	0.0586	0.0193	0.33	0.33	74.7%
	E[N]	28	28		28	14			
	λ	0.0471	0.0707	1.5	0.0497	0.0246	0.5	0.33	77.2%
	E[N]	26	31		26	17			
	λ	0.0407	0.0813	2.0	0.0438	0.0289	0.67	0.33	77.8%

	E[N]	24	32		25	19			

Based on the table above, the proposed study will have a reasonably good power to detect a strong predictive (interaction) effect (HR=0.33).

13.7 Gender and Minorities

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	4	6	10
Not Hispanic or Latino	66	92	158
Ethnic Category: Total of all subjects	70	98	168
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	1	1
Asian	2	2	4
Black or African American	7	10	17
Native Hawaiian or other Pacific Islander	0	1	1
White	61	84	145
Racial Category: Total of all subjects	70	98	168

REFERENCES

Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin. Oncol*. 28(13):2181–90, 2010. PMID: 20351327

Bayley J-P, Devilee P. The Warburg effect in 2012. *Curr Opin Oncol*. 24(1):62–7, 2012. PMID: 22123234

Ben Sahra I, Tanti J-F, Bost F. The combination of metformin and 2 deoxyglucose inhibits autophagy and induces AMPK-dependent apoptosis in prostate cancer cells. *Autophagy.* 6(5): 670–1, 2010.

Bittner B, McIntyre C, Jordan P, Schmidt J. Drug-drug interaction study between a novel oral ibandronate formulation and metformin. *Arzneimittelforschung*. 61(12):707–13, 2011. PMID: 22282958

Bonanni B, Puntoni M, Cazzaniga M, Pruneri G, Serrano D, Guerrieri-Gonzaga A, et al. Dual effect of metformin on breast cancer proliferation in a randomized presurgical trial. *J Clin. Oncol*. 30(21):2593–600, 2012. PMID: 22564993

Bosi E. Metformin-the gold standard in type 2 diabetes: what does the evidence tell us? *Diabetes Obes Metab*. 11 Suppl 2:3–8, 2009. PMID: 19385978

Boulton DW, Smith CH, Li L, Huang J, Tang A, LaCreta FP. Bioequivalence of saxagliptin/metformin extended-release (XR) fixed-dose combination tablets and single-component saxagliptin and metformin XR tablets in healthy adult subjects. *Clin Drug Investig*. 31(9):619–30,2011. PMID: 21819160

Bradley JD, Paulus R, Komaki R, Masters G, Forster K, Schild SE, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/− cetuximab for stage IIIa/IIIb non-small cell lung cancer: Preliminary findings on radiation dose in RTOG 0617. *IJROBP*. 81(5 (Supplement), 2011.

Buzzai M, Jones RG, Amaravadi RK, Lum JJ, DeBerardinis RJ, Zhao F, et al. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. *Cancer Res*. 15;67(14):6745–52, 2007.

Cox DR. Regression models and life tables. *J Royal Stat Soc* (series B). 34:187-229, 1972.

Currie CJ, Poole CD, Jenkins-Jones S, Gale EAM, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. *Diabetes Care*. 35(2):299–304 2012. PMID: 22266734

Dillman RO, Herndon J, Seagren SL, Eaton WL Jr., Green MR. Improved survival in stage III non-small-cell lung cancer: Seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst*. 88: 1210-1215, 1996.

Faubert B, Boily G, Izreig S, Griss T, Samborska B, Dong Z, et al. AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo. *Cell Metab*. 17(1):113–24, 2013. PMID: 23274086

Goodwin PJ, Pritchard KL, Ennis M, et al. Insulin-lowering effects of metformin in women with early breast cancer. *Clin Breast Cancer*. 8(6): 501-5, 2008.

Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong JK, et al. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet*. 50(2):81–98, 2011. PMID: 21241070

Hsieh M-C, Lee T-C, Cheng S-M, Tu S-T, Yen M-H, Tseng C-H. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. *Exp Diabetes Res*. 2012; 2012:413782. Epub 2012 Jun 5. PMID: 22719752

Iliopoulos D, Hirsch HA, Struhl K. Metformin decreases the dose of chemotherapy for prolonging tumor remission in mouse xenografts involving multiple cancer cell types. *Cancer Res*. 71(9):3196–201, 2011. PMID: 21415163

Jalving M, Gietema JA, Lefrandt JD, De Jong S, Reyners AKL, Gans ROB, et al. Metformin: taking away the candy for cancer? *Eur. J. Cancer*. 46(13):2369–80, 2010. PMID: 20656475

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 61(2):69–90, 2011. PMID: 21296855

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Stat Assoc*. 53: 457-481, 1958.

Kim B-H, Shin K-H, Kim J, Lim KS, Kim K-P, Kim J-R, et al. Pharmacokinetic comparison of a new glimepiride 1-mg + metformin 500-mg combination tablet formulation and a glimepiride 2-mg + metformin 500-mg combination tablet formulation: a single-dose, randomized, open-label, two-period, two-way crossover study in healthy, fasting Korean male volunteers. *Clin Ther*. 31(11):2755–64, 2009. PMID: 20110017

Kjøtrød SB, Carlsen SM, Rasmussen PE, Holst-Larsen T, Mellembakken J, Thurin-Kjellberg A, et al. Use of metformin before and during assisted reproductive technology in non-obese young infertile women with polycystic ovary syndrome: a prospective, randomized, double-blind, multi-centre study. *Hum. Reprod*. 26(8):2045–53, 2011. PMID: 21606131

Le Chevalier T, Arriagada R, Quoix E, et al. A Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: First analysis of a randomized trial in 353 patients. *J Natl Cancer Inst*. 83: 417-423, 1991.

Le Chevalier T, Arriagada R, Tarayre M, et al. Significant effect of adjuvant chemotherapy on survival in locally advanced non-small-cell lung carcinoma. *J Natl Cancer Inst*. 84: 58, 1992.

Machtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. *IJROBP*. 82(1):425–34, 2012. PMID: 20980108

Makowski L, Hayes DN. Role of LKB1 in lung cancer development. *Br. J. Cancer*. 99(5):683–8, 2008. PMID: 18728656

Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Reports. 5(3): 163-170, 1966. PMID: 5910392

Mazzone PJ, Rai H, Beukemann M, Xu M, Jain AK, Sasidhar M. The effect of metformin and thiazolidinedione use on lung cancer in diabetics. *BMC Cancer*. 12(1):410, 2012. PMID: 22978440

McCarthy EA, Walker SP, McLachlan K, Boyle J, Permezel M. Metformin in obstetric and gynecologic practice: a review. *Obstet Gynecol Surv*. 59(2):118–27, 2004. PMID: 14752300

Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. *British Med J.* 311: 899-909, 1995.

Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PLoS ONE*. 7(3):e33411, 2012. PMID: 22448244

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 35:549–556, 1979. PMID: 497341

Okawara G, Mackay JA, Evans WK, Ung YC. Management of unresected stage III non-small cell lung cancer: a systematic review. *J Thorac Oncol*. 1: 377-393, 2006.

Partridge M, Ramos M, Sardaro A, Brada M. Dose escalation for non-small cell lung cancer: analysis and modelling of published literature. *Radiother Oncol*. 99(1):6–11, 2011. PMID: 21458088

Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer*. 45: 2744-2753, 1980.

Pierotti MA, Berrino F, Gariboldi M, Melani C, Mogavero A, Negri T, et al. Targeting metabolism for cancer treatment and prevention: metformin, an old drug with multi-faceted effects. *Oncogene*. 32(12):1475–87, 2013.

Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. *Cancer Discov*. 2(9):778–90, 2012. PMID: 22926251

Rocha GZ, Dias MM, Ropelle ER, et al. Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. *Clin Cancer Res*. 17:3993-4005, 2011. PMID: 21543517

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. (4):CD002967, 2010. PMID: 20393934

Sandulache VC, Skinner HD, Ow TJ, Zhang A, Xia X, Luchak JM, et al. Individualizing antimetabolic treatment strategies for head and neck squamous cell carcinoma based on TP53 mutational status. *Cancer*. 118(3):711–21, 2012. PMID: 21720999

Sandulache VC, Hamblin JS, Skinner HD, Kubik MW, Myers JN, Zevallos JP. Metformin use is associated with improved survival in patients with laryngeal squamous cell carcinoma. *Head Neck*. 2013 Jun 19. PMID: 23784886

Sanli T, Rashid A, Liu C, Harding S, Bristow RG, Cutz J-C, et al. Ionizing Radiation Activates AMP-Activated Kinase (AMPK): A Target for Radiosensitization of Human Cancer Cells. *IJROBP*. 78(1):221–9, 2010. PMID: 20615625

Sanli T, Steinberg GR, Singh G, Tsakiridis T. AMP-activated protein kinase (AMPK) beyond metabolism: A novel genomic stress sensor participating in the DNA damage response pathway. *Cancer Biol Ther*. Review.15(2): 2013. Epub ahead of print. PMID: 24100703

Sanli T, Storozhuk Y, Linher-Melville K, et al. Ionizing radiation regulates the expression of AMP-activated protein kinase (AMPK) in epithelial cancer cells: modulation of cellular signals regulating cell cycle and survival. *Radiother Oncol.* 102(3):459-65, 2012.Epub 2012 Jan 5. PMID: 22225791

Schwimmer JB, Middleton MS, Deutsch R, Lavine JE. A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. *Aliment. Pharmacol. Ther*. 21(7):871–9, 2005. PMID: 15801922

Shackleford DB, Abt E, Gerken L, Vasquez DS, Seki A, Leblanc M, et al. LKB1 Inactivation Dictates Therapeutic Response of Non-Small Cell Lung Cancer to the Metabolism Drug Phenformin. *Cancer Cell*. 23(2):143–58, 2013. PMID: 23352126

Shyangdan D, Clar C, Ghouri N, Henderson R, Gurung T, Preiss D, et al. Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review. *Health Technol Assess*. 15(38):1–110, 2011. PMID: 22059955

Skinner HD, McCurdy MR, Echeverria AE, Lin SH, Welsh JW, O'Reilly MS, et al. Metformin use and improved response to therapy in esophageal adenocarcinoma. *Acta Oncol.* 52(5):1002-9, 2013. PMID: 22950385

Skinner HD, Sandulache VC, Ow TJ, Meyn RE, Yordy JS, Beadle BM, et al. TP53 disruptive mutations lead to head and neck cancer treatment failure through inhibition of radiation-induced senescence. *Clin. Cancer Res*. 18(1):290–300, 2012b. PMID: 22090360

Skinner HD, Crane CH, Garrett CR, Eng C, Chang GJ, Skibber JM, et al. Metformin use and improved response to therapy in rectal cancer. *Cancer Med.* 2(1):99–107, 2013. onlinelibrary.wiley.com/doi/10.1002/cam4.54/abstract

Storozhuk Y, Sanli T, Hopmans SN, Schultz C, Farrell T, Cutz J-C, et al. Chronic modulation of AMP-Kinase, Akt and mTOR pathways by ionizing radiation in human lung cancer xenografts. *Radiat Oncol*. 7:71, 2012. PMID: 22607554

Storozhuk Y., Hopmans S., Sanli T., et al. Metformin inhibits growth and enhances radiation response of non-small cell lung cancer (NSCLC) through ATM and AMPK. *Brit J Canc*. 108(10):2021-32, 2013. PMID: 23632475

Tan B-X, Yao W-X, Ge J, Peng X-C, Du X-B, Zhang R, et al. Prognostic influence of metformin as first-line chemotherapy for advanced nonsmall cell lung cancer in patients with type 2 diabetes. *Cancer*. 117(22):5103–11, 2011. PMID: 21523768

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev*. 5:CD003053, 2012. PMID: 22592687

U.S. Food and Drug Administration. Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics. Washington, D.C. U.S. Food and Drug Administration. 2007: 1-19.

Wieand S, Schroeder G, O'Fallon JR. Stopping when the experimental regimen does not appear to help. *Stat Med*. 13(13-14):1453-8, 1994.

Wu R-R, Jin H, Gao K, Twamley EW, Ou J-J, Shao P, et al. Metformin for treatment of antipsychotic-induced amenorrhea and weight gain in women with first-episode schizophrenia: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry*. 169(8):813–21, 2012. PMID: 22711171

APPENDIX I STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (8/10/16)
*See Section 11.2 for details and exceptions

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)
History/physical exam, including height, weight, BSA, and vital signs	30	
Performance status	X	
CT scan with contrast or MRI of lung and upper ab through adrenals (see. 3.1.4)	45	
MRI or CT of brain with contrast	45	
Whole-body FDG-PET/CT	45	
CBC/differential; ANC, platelets; hemoglobin	14	
Serum creatinine or creatinine clearance and eGFR	14	
Total bilirubin, ALT, AST, Alk Phos, Blood glucose	14	
Serum albumin	14	
Serum pregnancy (if applicable)	72 hrs. prior to registration	
Examination by Rad Onc & Med Onc		42
†Tissue submission for banking	X	
†Whole blood and plasma submission for banking	X	

†For patients who consent to participate in this component of the study

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (8/10/16)

*See Section 11.2 for details and exceptions

Assessments	During Treatment		
	Weekly during MET Dose Escalation (Arm 2 Only)	Weekly during Concurrent Treatment	Within 48 hours Prior to Each Cycle of Consolidation Treatment
History & Physical exam		X	X
BSA Recalculation		If there is a change of more than 10% of body weight, compared to the registration weight	
CBC/differential and serum creatinine		X	X
Bilirubin, AST/ALT, alk phos			X
Blood glucose for Arm 2 patients	X	X	X See Section 11.2 for details.
Adverse events evaluation	X	X	X
†Plasma submission for banking		At week 1 and 6 of chemo/RT (corresponding to weeks 3 and 8 of metformin treatment period for patients randomized to Arm 2) (see Section 10.2.5)	

†For patients who consent to participate in this component of the study

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (8/10/16)

*See Section 11.2 for details and exceptions

Assessments	Follow Up			
	At 4-6 weeks from end of RT	At 3 months from end of RT	At 6, 9, and 12 mos. from end of RT or until progression, whichever is first	q3 mos. x 2 years; q6 mos. x 3 years; then annually
History & Physical exam	X	X		X
Performance status	X	X		X
Follow-up CT scan of chest and upper abdomen with contrast or MRI		X	X	See recommended timeframes in Section 11.2
Imaging of other sites (e.g. extremities, head)	These sites should be imaged per institutional routine if there is suspicion of new metastatic disease; see Section 11.2.			
Biopsy			Recommended for any recurrence, whether based on CT scan or PET/CT	
Adverse event evaluation	X	X		X
†Plasma submission for banking			At 6 month follow up visit (see Section 10.2.5)	

†For patients who consent to participate in this component of the study

APPENDIX II: ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX III: AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

LUNG

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor.
Tis	Carcinoma *in situ*
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodules in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*
M1b	Distant metastasis

* Most pleural (and pericardial effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element, and the patient should be classified as M0.

STAGE GROUPING	
Occult Carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1a-b, N0, M0
Stage IB	T2a, N0, M0
Stage IIA	T2b, N0, M0
	T1a-b, N1, M0
	T2a, N1, M0
Stage IIB	T2b, N1, M0
	T3, N0, M0
Stage IIIA	T1a-b, N2, M0
	T2a-b, N2, M0
	T3, N1-2, M0
	T4, N0-1, M0
Stage IIIB	T1a-b, N3, M0
	T2a-b, N3, M0
	T3, N3, M0
	T4, N2-3, M0
Stage IV	Any T, Any N, M1a-b

APPENDIX IV: BIOSPECIMEN COLLECTION (5/7/15)

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For ALL Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal (ST) Form has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

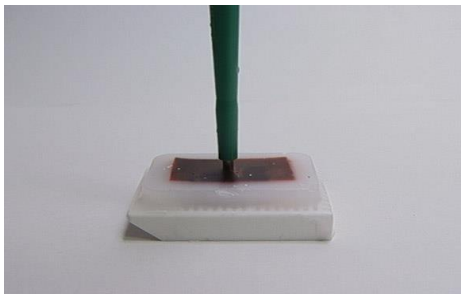
- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking it might break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible keep Serum, Plasma, and Whole Bloods in separate bags.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank – San Francisco by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

APPENDIX IV: BIOSPECIMEN COLLECTION)
NRG Oncology FFPE SPECIMEN PLUG KIT INSTRUCTIONS

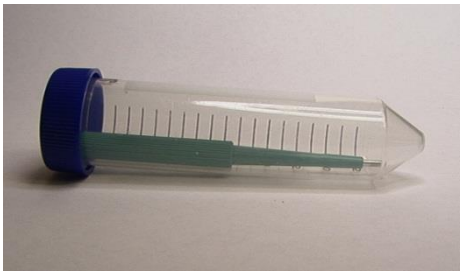
This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank – San Francisco. The plug kit contains a shipping tube and a punch tool.



Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen ID and block ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank – San Francisco and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.
Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or call 415-476-RTOG(7864)/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

APPENDIX IV: BIOSPECIMEN COLLECTION

Courier Address (FedEx, UPS, etc.): <u>For ALL Frozen Specimens or Trackable shipments</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

APPENDIX IV: BIOSPECIMEN COLLECTION

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of Plasma, or whole blood *(as specified by the protocol)*:

Kit contents:

- Two Purple Top EDTA tube for plasma (A)
- One Purple Top EDTA tube for Whole Blood (B)
- Thirty-five (15) 1 ml cryovials for pre-tx; 45 1 ml cryovials for other plasma time point
- Biohazard bags (2) and Absorbent shipping material (2)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

PREPARATION AND PROCESSING OF PLASMA AND WHOLE BLOOD:

APPENDIX IV: BIOSPECIMEN COLLECTION

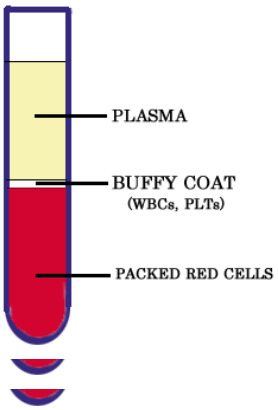
(A) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 8) as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot **0.5 ml plasma** into as many cryovials as are necessary for the plasma collected (5 to 8) labeled with the NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.



(B) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot **1.0 ml blood** into as many cryovials as are necessary for the blood collected (3 to 5) labeled with the NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

APPENDIX IV: BIOSPECIMEN COLLECTION

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For ALL Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu