

CLINICAL TRIAL PROTOCOL

A Phase II Study to Investigate a Combination of Metformin with Chemo-Radiotherapy in Patients with Locally Advanced Non-Small Cell Lung Cancer

Advanced Lung Cancer Treatment with **ME**tformin and Chemo-**RA**diotherapy

ALMERA Study

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Qualified Investigator Acknowledgement

This acknowledgement serves to document the agreement of the Qualified Investigator at each participating clinical centre to conduct this clinical trial in accordance with the dated version of the protocol as specified. The dated version of the protocol is agreed to by the Sponsor, the Ontario Clinical Oncology Group (OCOG) and the clinical trial Principal Investigator(s), and has been approved by Health Canada, if applicable.

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I have read this clinical trial protocol and by signing this form, agree to the following:

- (i) To maintain confidentiality. Understanding that this protocol and any supplemental information that may be added is confidential information and is the property of OCOG.
- (ii) To conduct this clinical trial in accordance with this protocol, applicable national and local regulations related to the conduct of research involving human subjects; ICH Good Clinical Practice guidelines.
- (iii) To ensure that personnel designated to perform study related procedures are under my supervision and that medical care and decisions made in respect of this study are my responsibility. To maintain and provide to OCOG documentation of the delegation of study related procedures.

QUALIFIED INVESTIGATOR (one per Clinical Centre)

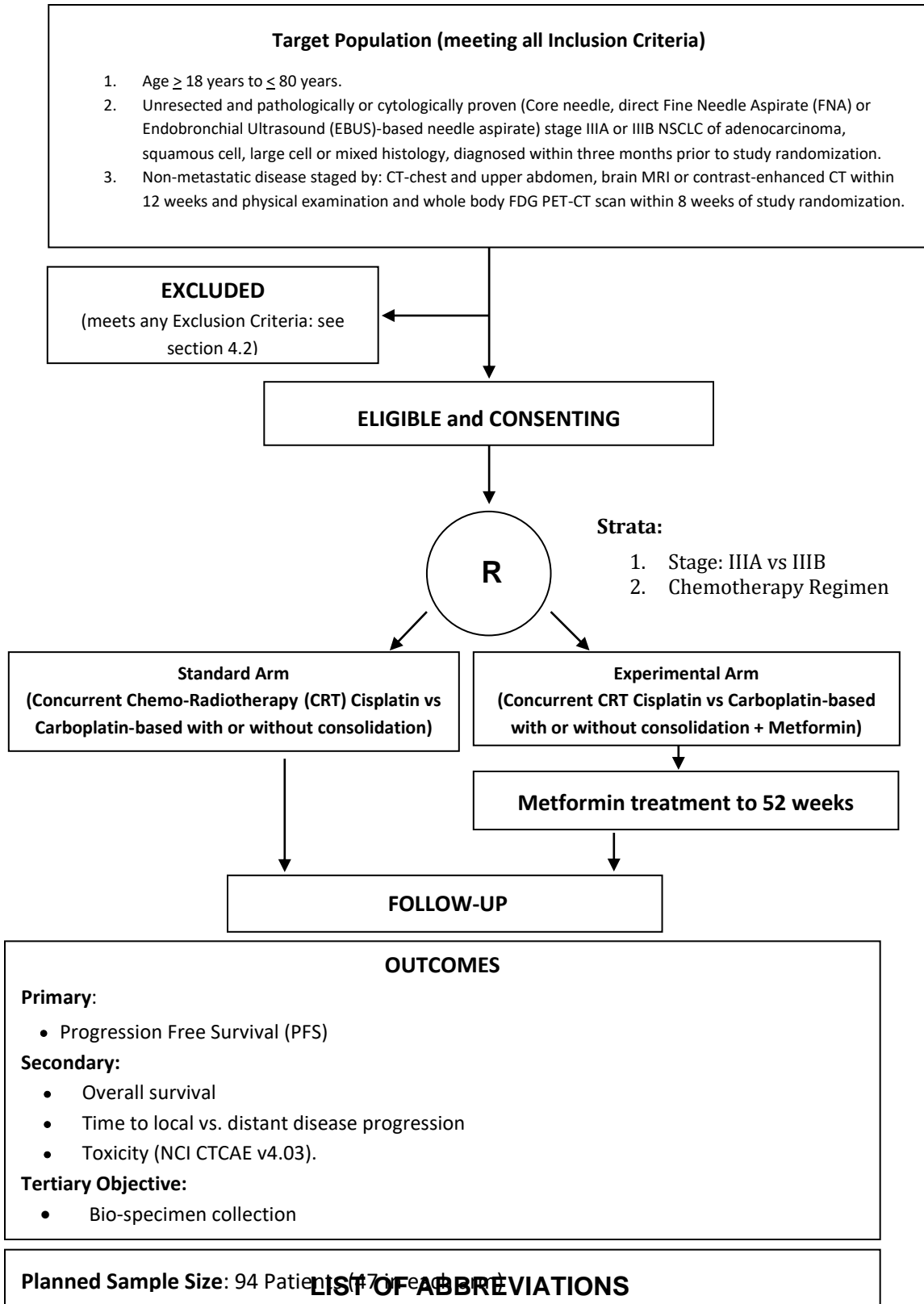
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STUDY SCHEMA



4D CT	Four Dimensional Computed Tomography
AE	Adverse Event
AIDS	Auto Immune Deficiency Syndrome
ATM	Ataxia Telangiectasia Mutate
BARL	Bay Area Research Logistics
CBCT	Cone Beam CT
CDK	Cyclin Dependent Kinase
CMC	Coordinating and Methods Centre
CRF	Case Report Form
CRT	Chemo-Radiotherapy
CT	Chemotherapy
DDR	DNA Damage Response
DSMC	Data Safety Monitoring Committee
DVH	Dose Volume Histogram
EBUS	Endobronchial Ultrasound
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
FDG	Fluoro-deoxy-glucose
GCP	Good Clinical Practice
GTV	Gross Tumour Volume
ICF	Informed Consent Form
IGF-IR	Insulin Like Growth Factor I Receptor
IMRT	Intensity Modulated Radiotherapy
IRIS	Interactive Registration/Randomization System
IROC	Imaging and Radiation Oncology Core
ITT	Intention to Treat
ITV	Internal Target Volume
LRC	Loco-Regional Disease Control
MS	Median Survival
NCIC-CTG	National Cancer Institute Canada - Clinical Trials Group
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
OAR	Organs at Risk
COG	Ontario Clinical Oncology Group
ORCCID	Online Remote Collection of Clinical Information and Data
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFTs	Pulmonary Function Tests
PTV	Planned Target Volume

QI	Qualified Investigator
RCT	Randomized Clinical Trial
REB	Research Ethics Board
RPC	Radiological Physics Center
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
TKR	Tyrosine Kinase Receptor
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VMAT	Volume Modulated Arc Therapy

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1. BACKGROUND and RATIONALE

Lung cancer is the leading cause of cancer mortality in North America. It is estimated that in Canada, during 2012, more than 25,600 people were diagnosed with lung cancer and approximately 20,000 died from the disease (Canadian Cancer Society 2012). About 80% of lung cancer patients present with non-small cell lung cancer (NSCLC). NSCLC is composed of three main histologies; adenocarcinomas, squamous cell and large cell carcinomas. Up to 40% of patients present with locally advanced NSCLC (stage IIIA/B, see Appendix I for TNM Classification) that is frequently inoperable. For these patients standard therapy involves combined modality therapy consisting of high dose thoracic radiotherapy (RT) (60-63Gy over 6 weeks), delivered with concurrent platinum-based chemotherapy in patients with good performance status (1). However, such patients who receive combination chemo-radiotherapy (CRT) still have poor outcomes with a median survival (MS) of 16-17 months and an overall survival (OS) at 5 years of about 15% (1).

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 CRT.

1.1 Radiotherapy Treatment of Locally Advanced NSCLC

The dose of thoracic RT for locally advanced NSCLC (60-63Gy, 2–2.1Gy per fraction) was established by a Radiation Therapy Oncology Group (RTOG) study more than 30 years ago (2). RTOG-73-01 showed improved survival with 60Gy RT in 30 fractions of 19% at 2 years, compared to lower RT doses. The radiographic response rate was approximately 60% (2), local failure within the radiation field was approximately 25% and 45% at 6 and 12 months, respectively. The corresponding data for distant metastasis rates were 15% and 35%. Other studies with RT doses of 60-64Gy reported median survivals of 10-14 months for stage IIIA/B patients (3). In 1990, Dillman 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 60Gy in 30 fractions (4). Also, Le Chevalier reported a 2 year OS rate of only 14% and 1 year local control of 15% after treating locally advanced NSCLC with RT alone (65Gy in 26 fractions) (5). A meta-analysis of individual patient data from 52 trials by the NSCLC Collaborative Group(6), indicated OS of about 75% at 6 months and 40% at 12 months in patients treated with RT alone (30–60Gy). These data suggest that curative thoracic RT (60-63Gy), when used alone, without chemotherapy (CT), offers locally advanced NSCLC patients a median survival of 10-12 months and OS of 42% at 12 months (6).

1.2 Issue of Poor Local Control

A major cause of poor outcomes in locally advanced NSCLC is the high resistance of these tumours 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, e.g. up to 85% in patients treated with RT alone (7). Such results have led to a search for radio-sensitizing agents to improve the results of RT, unfortunately with little success to date.

1.3 Role of Chemo-Radiotherapy (CRT)

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 two years and an increase in median survival by 1.7 months with the addition of chemotherapy to RT (3, 6). In the 1990s, studies showed the superiority of concurrent cisplatin-based chemotherapy with RT compared to sequential treatment (8, 9). Auperin et al. conducted a meta-analysis of studies of sequential CRT vs concurrent CRT. Their results supported concurrent CRT as the treatment of choice. Compared to sequential chemotherapy and RT, concurrent CRT increased OS by 5.7% (from 18.1 to 23.8 %) at 3 years and by 4.5% (from 10.6 to 15.1%) at 5 years, while 1 year OS was similar, about 60% with the two treatments. PFS in the concurrent CRT arm was 40.5%, and 16% at 1 and 3 years. Collectively, these studies suggest that the current gold-standard therapy of platinum-based concurrent CRT is associated with a median survival of 16-17 months and 1 year OS and PFS of 60% and 40%, respectively (10).

1.4 The Impact of Positron Emission Tomography (PET) on Staging and Treatment of NSCLC

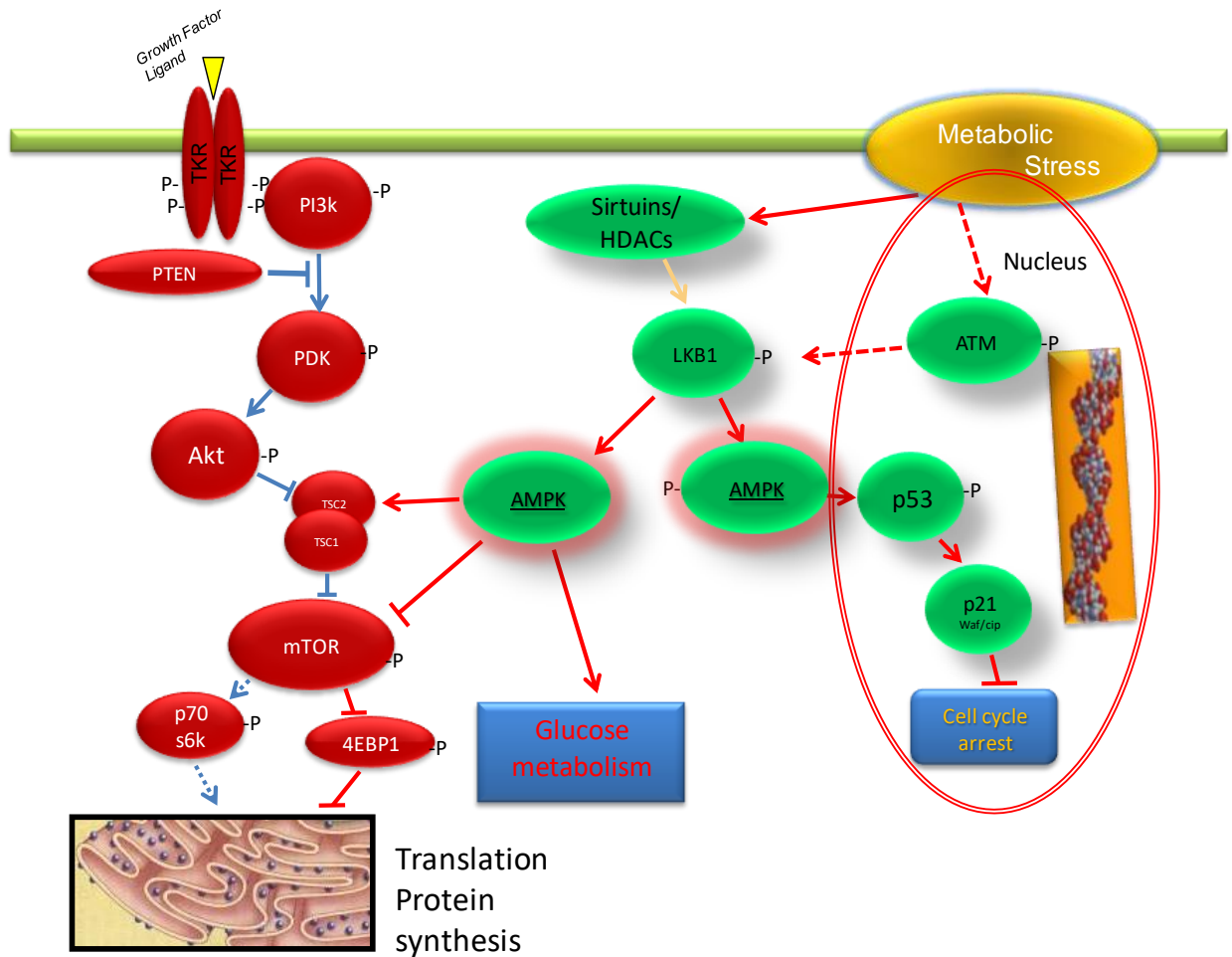
The introduction of ¹⁸Fluoro-deoxy-glucose (FDG) PET, an imaging investigation that detects tumour metabolic activity based on glucose uptake, has had a significant impact on our current approaches on staging and RT volume delineation for NSCLC (11, 12). Studies showed the prognostic value of PET and the utility of pre-treatment PET in selecting patients for combined modality CRT (13-15). PET staged patients are shown to have improved outcome due to stage migration induced by the ability of PET to detect up to 30% distant metastasis in locally advanced NSCLC patients not found to have metastasis by other modalities (16). The impact of PET on outcomes began to be detected in recent clinical trials with stage III NSCLC patients treated with Cisplatin-based CRT. A recent Hoosier Group (17, 18) trial, which included about 60% PET-staged patients, showed OS of 70% and PFS of 45% at 1 year (compared to 60% and 40%, respectively, observed in older trials and meta-analysis (10)). Currently, due to the influence of PET staging, there is no reliable historical control for PFS or OS in locally advanced NSCLC. Therefore, there is need for randomized rather than single arm phase II studies in this disease.

1.5 Molecular Pathways Involved in Tumour Growth and Radio-resistance (Targeted Therapeutics)

1.5.1 Growth Factor Receptor Pathways

Tyrosine kinase receptors (TKR) such as the Epidermal Growth Factor Receptor (EGFR) and Insulin-like Growth Factor I Receptor (IGF-IR) stimulate growth and survival of cancer cells through activation of complex intracellular signaling pathways(19) (Figure. 1).

Figure 1. Tyrosine Kinase Receptor- (TKR) and Stress-activated signaling pathways. AMPK modulates growth and cell cycle regulation pathways.



EGFR

EGFR is mutated in about 15% of NSCLC adenocarcinomas and wild type EGFR is over-expressed in up to 50% of lung cancers. EGFR inhibitors have been investigated intensively in the last 10 years (20) and in pre-clinical studies were shown to sensitize NSCLC cells to radiation (21). Initial phase II studies showed promising results (IDEAL 1-2) but subsequent phase III trials (INTACT 1 and 2) did not show improved survival with the addition of the EGFR inhibitors to chemotherapy (20). Furthermore, anti-EGFR therapy did not improve progression free survival (PFS) or OS in stage III NSCLC patients when combined with either standard dose (60Gy) or dose escalated (74Gy) CRT in the recent RTOG radiotherapy dose escalation trial (RTOG0617) (22).

IGF-I Receptor (IGF-IR)

In-vitro studies suggested that the IGF-IR pathway is associated with tumour resistance to cisplatin chemotherapy and RT in lung cancer cells (23). However, studies with IGF-IR

inhibitors produced safety concerns as fatal toxicities was reported in NSCLC patients randomized to receive anti-IGF-IR antibody therapy in combination with chemotherapy (24).

1.5.2 Downstream Mediators of Growth and Survival Signals

Mediators of TKR action are involved in the development of radiation resistance. These include the proto-oncogene Ras and cascades of lipid and protein kinases, such as phosphatidylinositol 3-kinase (PI3k) and protein kinase B (PKB/Akt) (25). PI3k activates Akt, which mediates survival in cancer cells through activation of the mammalian Target of Rapamycin (mTOR)(26), a PI3k family molecule that mediates growth of cancer cell biomass, proliferation and resistance to cytotoxic agents (27). mTOR stimulates Cap-dependent gene expression and translation through phosphorylation-mediated activation of the ribosomal p70-S6-kinase (p70^{S6k}) and phosphorylation-mediated inhibition of translation initiation inhibitor eIF4E-binding protein 1 (4-EBP1). Rapamycin analogues (Everolimus) received FDA approval for clinical use in renal carcinoma (28). In lung cancer, preclinical studies with PI3k and mTOR inhibitors showed sensitization of NSCLC xenografts to radiation (29, 30). Currently, there is no evidence of clinical benefit of such inhibitors in combination with RT or standard CRT in lung cancer. mTOR inhibitors are reported to have a relative risk of 31 for mild- and 8.8 for grade 3-4 pneumonitis, which questions their use in lung cancer (31). Further, these drugs failed to show benefit in a number of cancers. There is a need for more effective and better tolerated inhibitors of the Akt – mTOR pathways.

1.5.3 DNA Damage-activated Signaling Pathways, p53 and Cell Cycle Control

RT mediates cell killing through lethal DNA double strand breaks (DSB)s (32-34). These are detected by the kinase ataxia telangiectasia mutated (ATM) a key participant of the DNA damage response (DDR) pathway, which phosphorylates histone H2Ax (γ H2Ax), leading to recruitment of molecular DNA repair complexes at the sites of DSBs. DSB repair functions in concert with induction of cell cycle arrest activated by the p53 tumour suppressor, a key transcription factor and signal mediator. Cell stressors such as RT induce expression of p53, which acts as a transcription factor to induce genes involved in apoptosis and cell cycle arrest (35). One such gene is the Cyclin-dependent kinase (CDK) inhibitor p21^{cip1} that inhibits CDKs and leads to G1-S arrest through inhibition of the Cdk2-Cyclin E complex or G2-M arrest through inhibition of the Cdk1-CyclinB complex (36).

1.5.4 LKB1-AMPK Pathway in Cancer

LKB1 is a tumour suppressor that is mutated in Peutz-Jeghers syndrome and is associated with hamartomas, primary gut polyps, breast, colon, and lung cancer (37). Studies show up to 30% rate of LKB1 point mutations and deletions in NSCLC, ubiquitous expression of LKB1 in adult lung bronchial epithelium and a progressive loss of LKB1 as pre-malignant adenomatous hyperplasia progresses to frank invasive disease (37). The highest rate of LKB1 defects are detected in lung adenocarcinomas (34%). LKB1 defects alone are early events in LC carcinogenesis, but within K-Ras mutant tumours, they help develop an aggressive metastatic phenotype (38).

1.5.5 AMP-activated Protein Kinase (AMPK)

LKB1 mediates many of its metabolic and anti-proliferative functions through activation of AMPK (Fig. 1), a master regulator of cellular metabolic processes that is activated by an increase in the AMP/ATP ratio induced by natural metabolic stressors such as exercise, starvation and

hypoxia (39). AMPK is an ancient, evolutionally preserved, sensor of metabolic stress that at times of low energy levels, i) inhibits overall anabolic processes including energy storage, cellular growth and proliferation and ii) increases nutrient uptake and catabolism and enhance energy availability (37). AMPK is a heterotrimer of α (catalytic), and β and γ regulatory subunits. In humans two α ($\alpha 1$ and $\alpha 2$), two β ($\beta 1$ and $\beta 2$) and three γ ($\gamma 1$, $\gamma 2$ and $\gamma 3$) isoforms exist (40). LKB1 activates AMPK through phosphorylation on Thr172 of the α subunit. Activated AMPK inhibits mTOR, and its downstream action on protein synthesis and gene expression, through activation of the tumour suppressor TSC2. AMPK blocks cell cycle by increasing total and phosphorylated levels of p53 and its downstream effector p21^{cip1}. Jones et al. showed in cancer cells that glucose deprivation stimulates AMPK that in-turn phosphorylates p53 on Ser15, leading to increase in p53 activity, mediation of a metabolic checkpoint that arrest cell cycle and induces apoptosis and autophagy (41).

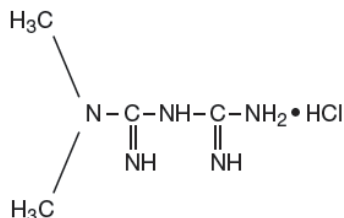
1.5.6 Role of AMPK in the Molecular Response to Ionizing Radiation

It was demonstrated that therapeutic doses of RT (2-8 Gy) induce potent time- and dose-dependent activation of AMPK in cancer cells (42). AMPK was shown to, i) transduces signals through a DDR-activated ATM-AMPK-p53-p21^{cip1} axis, ii) facilitate the DDR-induced G2-M checkpoint and iii) mediate the RT-induced cytotoxicity in clonogenic assays in NSCLC cells (42). This work suggested that AMPK is not only a sensor of metabolic but also of genomic stress.

1.6 Metformin

Metformin: (1-(diaminomethylidene)-3,3-dimethylguanidine) is a biguanide derived from the French lilac (*galega officinalis*). It is an off-white crystalline compound that is freely soluble in water.

Molecular mass = 165.63



Metformin is a well tolerated anti-diabetic agent used by more than 120 million patients worldwide (43) and it is also indicated for the treatment of polycystic ovary syndrome and non-alcoholic liver disease. Studies suggested that Metformin can lower the risk for diabetes and complications of insulin resistance in non-diabetic individuals dealing with this condition (44, 45). Doses of Metformin up to 2000 mg/day were well tolerated by non-diabetic patients in diabetic prevention studies (46). Further, retrospective studies suggested that Metformin may decrease the risk of cancer in patients with type 2 diabetes (47, 48).

In pre-clinical studies, Dowling et al. showed that Metformin activates AMPK and inhibits mTOR, leading to inhibition of breast cancer cell proliferation (49). Huang et al. showed activation of the LKB1-AMPK pathway by Metformin and delay in tumour development in PTEN-deficient mice treated with Metformin (50). Oral Metformin reduced mouse lung carcinogenesis induced by exposure to tobacco carcinogens (51).

1.6.1 Mechanism of Action

Metformin is thought to function through activation of AMPK. It inhibits complex I enzymes of the mitochondrial oxidative phosphorylation chain leading to increased AMP levels and activation of AMPK through AMP binding to the γ -subunit (39). Zakikhani et al (2006) showed that Metformin inhibits breast cancer growth in an AMPK-dependent fashion (52) and Ben-Sahra et al. observed inhibition of prostate cancer cell proliferation and cell cycle arrest through modulation of cyclin D1 with Metformin (53).

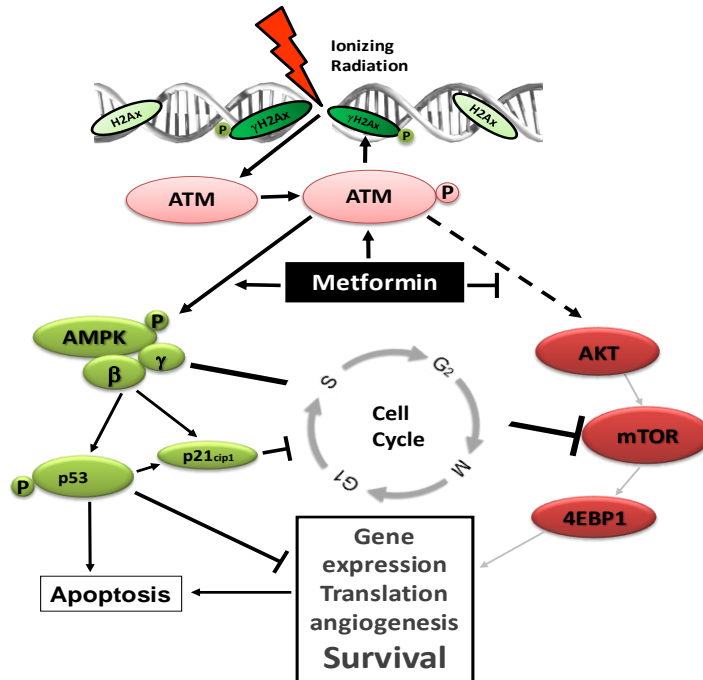
1.6.2 Interaction with Cytotoxic Therapy

Recent work suggests that Metformin can amplify paclitaxel-induced AMPK activation and enhance the cytotoxicity of chemotherapy in breast and lung cancer models (54, 55). Rocha et al (2011) showed that Metformin potentiates paclitaxel-induced activation of AMPK and inhibition of mTOR, which causes G2-M cell cycle arrest in lung cancer cells and enhances the anti-tumour activity of this chemotherapeutic agent (55).

1.6.3 Pre-clinical Evidence on the Combination of Metformin with Radiotherapy

Metformin was shown to sensitize breast cancer and sarcoma cells to RT (56). Recently, it was demonstrated that low microM levels of Metformin, which can be achieved safely in humans, can work in combination with RT to enhance NSCLC response to RT. Metformin concentrations (5 - 25 microM), that can be achieved safely in humans, were shown to inhibit proliferation and induce radio-sensitization in a variety of NSCLC culture models with diverse mutation genotypes (activating K-Ras mutation, LKB1-null vs p53-null) and histology (adeno- vs squamous cell carcinomas) (57, 58). Metformin or RT alone activated the ATM-AMPK-p53/p21^{cip1} pathway but inhibited the Akt and mTOR in both cells and xenograft tumours. Figure 2, illustrates a model of the effects of Metformin on those pathways. The available pre-clinical data suggest that the combined treatment of Metformin plus RT produces significantly higher inhibition of tumour growth and modulation of signaling events than either agent alone. Further, Metformin potentiates the anti-angiogenic effects of radiation and stimulated apoptosis. These results indicate that Metformin could be able to enhance the therapeutic ratio of RT in NSCLC. Interestingly, observation of Metformin action in diverse NSCLC models indicates that the drug has activity in the majority of NSCLCs which is independent of LKB1 or p53 mutation status.

Figure 2. Model of the molecular mechanism of action of Metformin.



1.6.4 Clinical Experience with Metformin in Cancer

In breast cancer patients treated with neo-adjuvant chemotherapy, Metformin was associated with enhanced pathologic response rates (59). A number of other retrospective studies also reported decreased cancer incidence or increased survival in diabetic patients on Metformin and worse outcomes in diabetic patients treated with sulfonylureas or insulin (60-64). A retrospective study from the Cleveland Clinic observed that diabetic patients with lung cancer, who were previously exposed to Metformin and/or another class of anti-diabetic drugs (thiazolidenediones: also known to activate AMPK), are less likely to present with metastatic disease, are more likely to present with an adenocarcinoma, and they may survive longer (65).

Currently, there are almost eighty different clinical trials investigating Metformin in breast, prostate, pancreatic, colorectal and lung cancer (ClinicalTrials.Gov, 2013) with at least forty of them actively recruiting patients. In a phase III trial, the NCIC-CTG has completed recruitment to a study designed to investigate the ability of Metformin to prevent breast cancer recurrence in patients with invasive disease that have been treated with definitive surgery with or without standard adjuvant treatments (MA.32). Currently, three studies are investigating Metformin in lung cancer. A randomized phase II study from Kimmel Comprehensive Cancer Center, Sydney, Australia, is investigating whether Metformin in combination with paclitaxel, carboplatin and Bevacizumab in stage IV NSCLC patients. A second randomized phase II study is examining Metformin in combination with anti-EGFR therapy also in the metastatic setting; while a pilot study from the Mayo Clinic MN is examining the role of Metformin in chemoprevention (ClinicalTrials.Gov, 2013).

1.7 Study Rationale

The poor response of NSCLC to standard treatments leads to high costs for hospitalization and need for palliative and end of life care. In the USA, an estimated \$12 billion dollars was spent in

2010 for the diagnosis and treatment of lung cancer and this may increase to \$18.84 billion by 2020 (National Cancer Institutes 2010 estimates).

Concurrent CRT remains the gold standard for inoperable patients with locally advanced NSCLC but clinical trials continue to show poor local control and OS (10, 66).

Recent efforts to demonstrate improved local control with RT dose escalation and/or anti-EGFR targeted therapy were not successful (RTOG0617 (67)).

The introduction of modern imaging modalities, such as PET scans, have improved the initial staging of NSCLC patients and has contributed to better reported outcomes through stage migration. However, changes with respect to staging tests, limits the value of historical controls and suggests the need for randomized controlled trial design in new studies for locally advanced NSCLC.

Metformin is a well tolerated and inexpensive drug that has the potential to improve cancer patient outcomes. The drug has metabolic benefits and is well tolerated in non-diabetic patients.

Pre-clinical work, as indicated above, provides evidence that Metformin, at levels that can be achieved safely in human circulation with standard therapeutic oral dosing, is a promising anti-cancer agent with activity in NSCLC models as a single agent and in combination with chemotherapy and RT.

Therefore, a randomized phase II clinical trial to investigate Metformin in combination with standard CRT in locally advanced NSCLC is timely. This design strategy will provide contemporary outcomes of patients receiving standard treatment, and with relatively fewer patients, it will hopefully find early evidence of efficacy.

2. STUDY OBJECTIVES

2.1 General Objective

The general objective of this study is to determine if the combination of Metformin with standard curative concurrent CRT with or without consolidation will improve outcomes of patients with locally advanced NSCLC.

2.2 Specific Objectives

2.2.1 Primary Objective

The primary objective of this study is to determine the effect of Metformin on the proportion of patients free of disease progression at 12 months after initiation of drug treatment.

2.2.2 Secondary Objectives

To evaluate the effects of Metformin on:

- i) Overall survival,
- ii) Time to disease progression (local, distant, any),
- iii) CRT toxicity (NCI CTCAE v4.03).

2.2.3 Tertiary Objectives

Participating patients will be asked to provide additional consent to allow the collection of their bio-specimens to help develop serum and tumour biomarkers of Metformin activity and clinical response.

a. **Biomarkers Predicting clinical response to Metformin:** Determine the association of Metformin response (PFS difference from mean expected of 10 months (17)) with, i) Plasma Metformin and levels of fasting glucose, insulin and lipid profile, ii) tumour histology (adenocarcinoma, squamous or large cell carcinoma) and iii) Tumour LKB1, p53 and K-Ras mutation and expression status.

b. **Biomarkers predicting Metformin activity in-vivo:** Determine whether Metformin plasma levels correlate with peripheral blood cell levels of phosphorylated AMPK, p70^{S6k} and 4EBP1. This will determine whether these markers could become pharmaco-dynamic markers for Metformin.

3. STUDY DESIGN

This is a randomized, phase II, open label study in patients with locally advanced NSCLC which will compare standard RT (60-63 Gy for 6 weeks) plus concurrent chemotherapy with or without consolidation (CRT) (standard arm) vs the same CRT plus treatment with Metformin concurrent with CRT, and continuing for a total of 12 months (experimental arm). Ninety-four eligible and consenting patients will be randomized to one of the two treatment arms. Patients randomized to the experimental arm will receive Metformin (2000 mg/day) for a period of 12 months. Patients will be continuously evaluated for toxicity, will be assessed every two weeks at clinic visits during concurrent CRT treatment and at follow up clinic visits at 3, 6, 9 and 12 months (from the date of randomization). Disease progression will be evaluated every 3 months for up to 12 months. All patients will be followed for up to 24 months (2 years) for survival.

4. PATIENT POPULATION

Eligibility status must be confirmed by the local investigator or designate prior to enrollment. It is important that no exceptions be made to the eligibility criteria. Questions related to eligibility requirements and/or specific criteria must be discussed with OCOG prior to enrollment.

4.1 Inclusion Criteria

For inclusion in this study, patients must fulfill all of the following criteria:

1. Age ≥ 18 to ≤ 80 years of age.
2. Unresected and pathologically or cytologically proven (Core needle, direct Fine Needle Aspirate (FNA) or Endobronchial ultrasound (EBUS)- based needle aspirate) stage IIIA or IIIB NSCLC of adenocarcinoma, squamous cell, large cell or mixed histology (*refer to Appendix I*), diagnosed within three months prior to study randomization.
3. Non-metastatic disease staged by: CT-chest and upper abdomen, brain MRI or contrast-enhanced CT within 12 weeks and physical examination and whole body FDG-PET/CT scan within 8 weeks prior to study randomization.

4.2 Exclusion Criteria

Patients who satisfy any of the following exclusion criteria are NOT eligible for this study.

1. ECOG performance status >2 (*refer to Appendix II*).
2. More than 10% weight loss in the past 3 months.
3. Diabetic patient or anyone currently taking Metformin, insulin or other anti-hyperglycemic therapy.
4. Pulmonary Function Test (PFTs) (within the last 12 weeks) with FEV1 < 1.2 lit/sec or less than 50% of predicted.
5. CBC and biochemical renal and liver function profiles that do not permit chemotherapy treatment (as per institutional standard of care).
6. Fasting blood sugar levels of ≥ 7.0 mmol/l (within the last 12 weeks).
7. Prior systemic chemotherapy for lung cancer.
8. Prior radiotherapy that would overlap with the planned treatment area.
9. Prior invasive malignancy within the past 3 years (except non-melanomatous skin cancer, non-invasive carcinoma in-situ of the breast, oral cavity or cervix).
10. Known Acquired Immune Deficiency Syndrome (AIDS).
11. Patients with increased risk for lactic acidosis:
 - severe congestive heart failure (NYHA: class III or IV),
 - history of metabolic acidosis,
 - alcoholic intake of > 3 drinks daily,
 - severe liver disease,
 - renal failure
12. Known hypersensitivity or allergy to Metformin.
13. Known pregnancy or lactating female patient.
14. Geographic inaccessibility for follow-up.
15. Inability to provide informed consent.

Screening assessments, blood work, including fasting blood sugar levels, and tests that are not routine, will be completed prior to randomization to confirm eligibility.

5. SUBJECT ENROLLMENT

Patients will be allocated to one of two treatment arms:

Standard Arm	standard RT (60-63 Gy for 6 weeks) plus chemotherapy (CRT) consisting of either i) 2 cycles of concurrent Cisplatin-based chemotherapy or ii) 2 cycles of concurrent carboplatin-based chemotherapy with or without
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	2 cycles of consolidation chemotherapy.
Experimental Arm	<p>standard RT (60-63 Gy for 6 weeks) plus chemotherapy (CRT) consisting of either i) 2 cycles of concurrent Cisplatin-based chemotherapy or ii) 2 cycles of concurrent carboplatin-based chemotherapy with or without 2 cycles of consolidation chemotherapy with concurrent Metformin 2000mg/day and continuing for a total of 12 months.</p> <p>Specifically: Metformin dose will be escalated over 1-2 weeks to 2000mg/day, and will remain at this dose for a total of 12 months. This involves 6-12 weeks of concurrent treatment of Metformin with CRT or consolidation chemotherapy and 38-44 additional weeks of Metformin treatment alone (<i>see Metformin and CRT Treatment Schema, Figure 3</i>)</p>

5.1 Randomization Procedure

Written informed consent will be obtained from all eligible patients prior to commencing any study related procedures. Randomization will be coordinated centrally by the OCOG Coordinating and Methods Centre (CMC) located at the Juravinski Hospital, Hamilton, Ontario. A computer-generated randomization schedule will allocate patients in an approximate 1:1 ratio using variable block sizes within the stratum to receive either the standard treatment arm or the experimental arm. After confirmation of patient eligibility and documentation of written informed consent, clinical centres will complete patient randomization by accessing the CMC's web-based Interactive Registration/Randomization System (IRIS). The system will allocate the patient to one of the two treatment arms. Patients must be randomized before any study related intervention is started.

5.2 Stratification

Eligible, consenting patients will be stratified prior to randomization by:

- (1) Tumour stage (stage IIIA vs. IIIB) NSCLC.
- (2) Chemotherapy Regimen (2 cycles of concurrent Cisplatin-based vs. Carboplatin-based chemotherapy with or without consolidation).

6. PRE-TREATMENT (BASELINE) ASSESSMENT

Refer to Appendix III: Schedule of Study Assessments and Evaluations

The pre-treatment assessment is to include the collection of patient demographics and documentation of investigations to support complete cancer staging (CT of the chest and upper abdomen, MRI or CT of the brain, whole body FDG PET-CT). PET-CT imaging must be performed within eight weeks of study enrollment. Staging MRI or contrast-enhanced CT imaging performed within 12 weeks of randomization is acceptable if there is a PET-CT (non-contrast) available within 8 weeks of randomization. PFTs performed within the last 12 weeks will be accepted, the most recent will be documented. Spirometry alone instead of full PFTs is acceptable if a complete PFT is performed before the initiation of cytotoxic therapy. All patients

will undergo a standard physical examination (within 8 weeks) that includes the measurement of height, weight and vital signs. ECOG performance status will be recorded.

A fasting blood sample will be drawn from patients who have provided consent to the correlative studies (*see Appendix IV. Correlative Studies*).

7. STUDY TREATMENT

7.1 Metformin Administration

Following randomization, patients randomized to the experimental arm will receive an escalating dose of Metformin with the aim to reach the dose of 2000 mg per day on the day of initiation of concurrent CRT treatment (this ideally will be Day 15, starting the day of Metformin treatment initiation). A two-week period of Metformin dose escalation is recommended in this study that should involve the following approach: Metformin orally 500 mg twice daily (AM and PM) for the first week (dose level 1: DL1). This will be increased to 1500 mg/day (500 mg TID) in week 2 (dose level 2: DL2) and 2000 mg/day at the beginning of week 3 (1000 mg at AM, 500 mg at noon and 500 mg at PM) (dose level 3: DL3) and be maintained at this dose thereafter. When patient treatment logistics do not allow a length of two weeks for Metformin dose escalation, a minimum of one week will be permitted. In those situations the period of DL1 would be reduced or eliminated as needed to fit the above described schema. For example, patients that have only 10 days of dose escalation period will receive DL1 for only 3 days and move to DL2 on Day 8, while patients who have only 7 days of dose escalation period will be starting Metformin treatment at DL2. Figure 3 describes the overall Metformin and CRT treatment of the entire 12 month study period (Weeks 1 to 52). Table 1 summarizes the Metformin dose escalation, maintenance dose and timing of intake for the 12 month study period.

Figure 3. Metformin and CRT Treatment Schema

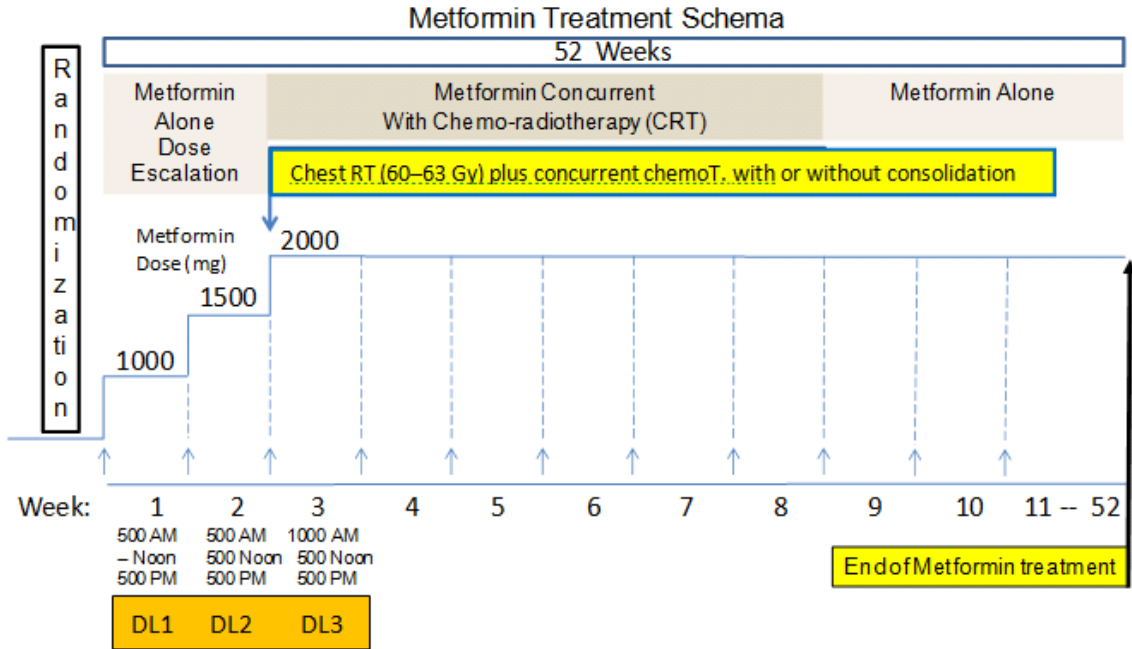


Table 1. Daily Oral Metformin Intake

TOTAL DOSE	Route of ADMINISTRATION	Weeks of Treatment	SCHEDULE
1000 mg	Oral	1	DL1: 2 tablets per day 1 tab (500 mg) before breakfast; 1 tab (500 mg) before dinner
1500 mg	Oral	2	DL2: 3 tablets per day 1 tab (500 mg) before breakfast; 1 tab (500 mg) before lunch; 1 tab (500 mg) before dinner
2000 mg	Oral	3 - 52	DL3: 4 tablets per day 2 tabs (1000mg) before breakfast; 1 tab (500 mg) before lunch; 1 tab (500 mg) before dinner

Patients will be instructed to take Metformin doses at least 4 and if possible 6 hours apart, 30-60 minutes before meals. Patients will continue on Metformin 2000 mg/day for 52 weeks following the date of randomization. Metformin is administered orally as per the scheduled intervals.

If a patient misses a dose, he/she should take the next scheduled dose at the usual time.

Loperamide will be used for gastrointestinal support for the first 8 weeks of treatment, as needed. Appropriate dose modifications for Metformin are described in Section 7.6.

7.2 Packaging and Labeling

Metformin is formulated as a 500mg tablet, white, round-shaped, film-coated. Study drug will be supplied in bottles containing 500 tablets.

Bay Area Research Logistics (BARL), located in Hamilton, ON, will be responsible for procuring the drug and labeling. Study labels will comply with the legal requirements of the province of each participating centre and are printed in both English and French.

7.3 Storage Conditions at Participating Sites

All investigational products must be kept in a secure place under appropriate storage conditions.

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated personnel have access. Upon receipt, Metformin should be stored according to the instructions specified on the drug labels (room temperature (15° to 30°C)).

7.4 Handling and Dispensing

BARL will be responsible for the storage and distribution of the study drug to the participating clinical sites as per the protocol and the sponsor's direction.

This study will utilize OCOG's web based subject registration/randomization system that will centrally control study drug allocation and management. BARL will integrate their operations with this automated system to ensure that all study drug shipments, transportation and handling requirements are strictly adhered to.

7.5 Accountability Procedures

BARL will be responsible for procuring and storing the study supply of Metformin. BARL will then be responsible for accountability when they ship the study drug to the clinical sites, providing a copy of the necessary shipment/delivery certificate for this purpose and for the disposition of the material.

At the clinical sites, the local investigator or delegate will dispense study drug to the randomized study subjects as per schedule. Under no circumstances will the local Investigator allow the investigational drug to be used in a way other than directed by the protocol.

The investigator or designee will maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. This ledger will include the identification of the study subject to whom the drug was dispensed, the quantity and the date of dispensing, and any unused drug returned to the clinical site. Study subjects must return all unused drug to the local

investigator. To assess compliance, unused pills will be counted and recorded. Drug accountability will also be reviewed centrally by OCOG during the study and at the completion of the study. Study subjects will be asked to return all unused study drug and packaging at study visits, at the end of the study or at the time of study drug discontinuation.

At study close-out, and, as appropriate during the course of the study, returned study drug, unused or expired drug should be destroyed by high temperature incineration or by the standard institutional practice, after written authorization by OCOG. Documentation of destruction is required to be completed by the clinical site. If drug destruction on site is not feasible, OCOG will provide instruction for the return of the drug. It is essential that the local investigator account for all study drug, but the task of maintaining accurate records may be delegated to a pharmacy.

7.6 Modifications to Metformin Dose or Treatment Schedule

Patients randomized to the experimental arm (CRT plus Metformin concurrent with CRT with or without consolidation and for 52 weeks) will be maintained at the total dose of 2000mg/day. Adverse events (AEs) should be treated with the appropriate maximum supportive care and dose reductions will be documented. All AEs should be graded according to NCI CTCAE (v 4.03).

The most common adverse events related to Metformin which may limit dose, particularly during initiation of therapy, are gastrointestinal (nausea, abdominal bloating, flatulence and diarrhea). A number of studies compared Metformin to placebo. DeFronzo et al. treated patients with up to 2250mg Metformin per day and observed rates of 8% for severe diarrhea and 4% for severe nausea (68). Other studies which used 1500 - 1750 mg/day reported diarrhea rates of 5-14.5%, similar rates for flatulence and constipation rates of 6% (69-71). In most cases gastrointestinal symptoms improved with time.

Loperamide may be used for gastrointestinal support for the first 8 weeks of treatment, as required.

7.6.1 Temporary Interruption, Reduction and Re-initiation of Metformin Treatment

In the event of grade 2 or 3 gastrointestinal toxicity (typically involving flatulence or diarrhea), patients will be supported with loperamide. Typically, gastrointestinal side effects subside within 4-6 weeks of initiating Metformin treatment. Following the period of concurrent CRT with or without consolidation and in the event that grade 2 toxicity persists, Metformin dose de-escalation will be permitted when symptoms are deemed to be due to Metformin 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 (2000mg) as much as possible. Alterations to the daily schedule of drug intake should be the first steps to be taken to reduce gastrointestinal symptoms. Such examples include taking the medication with food rather than before and modifying drug intake from the suggested schedule (TID) to 1000mg (two tabs of 500mg, BID), keeping the

doses 12 hours apart. If required, the dose should be decreased by 500 mg per day for 1 week (dropping 500 mg each week) with loperamide support until symptoms subside. Efforts should be made to re-escalate the dose of Metformin to 2000mg (total daily) 2 weeks after patients remain free of grade 2 toxicity for 2 weeks. At least two attempts should be made to re-escalate the dose to 2000mg/day after each time a 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 tolerable dose for the remainder of the Metformin treatment period. Acceptable doses of maintenance Metformin are 2000, 1500, 1000 or 500 mg OD. Dose de-escalation and re-escalation will be documented.

Metformin treatment interruption will be permitted according to local guidelines at the time of routine CT scans of the chest that will involve contrast infusion.

Subjects whose treatment is interrupted for any reason except intolerable toxicity will be encouraged to resume and continue with their assigned therapy. Compliance (and reasons for non-compliance) will be documented. The visit schedule for those subjects 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.

7.7 Permanent Discontinuation of Metformin Treatment

Subjects may stop Metformin treatment in the following instances:

- Unacceptable toxicity as defined in Section 7.6.
- Intercurrent illness which would, in the judgement of the investigator, affect assessment of clinical status to a significant degree, and requires discontinuation of protocol therapy.
- Intercurrent illness (e.g. including diabetes, congestive heart failure, renal failure) precluding continuation of study medication.
- Development of a new invasive primary cancer (other than basal cell carcinoma or squamous cell carcinoma of the skin that has been adequately treated)
- Detection of distant disease progression
- Decision by the study sponsor to stop the study (e.g. based on DSMC recommendation related to safety)
- Request by the patient.
- Completion of therapy as per protocol.

Metformin treatment should not be discontinued solely due to detection of local disease progression.

7.7.1 Therapy After Metformin Treatment is Discontinued

Patient management following permanent discontinuation of Metformin is at the discretion of the Investigator.

7.7.2 Follow-up After Metformin Treatment is Discontinued

Efforts should be made to maintain the schedule of assessments as per protocol and continue follow-up, even if the subject discontinues protocol treatment prematurely.

8. RADIOTHERAPY – CHEMOTHERAPY – ADDITIONAL THERAPIES

RT as part of CRT will ideally start during the third week of Metformin treatment (see Figure 3 Metformin and CRT Treatment Schema). Delays of up to one further week for RT planning or radiotherapy or chemotherapy scheduling issues are allowable. During this period patients will be maintained on the standard daily dose of Metformin of 2000mg.

8.1 Radiotherapy

The primary tumour and involved lymph nodes will be treated with 60-63 Gy in 30 fractions, over 6 weeks.

8.1.1 Standard Chest Radiotherapy

Utilization of Intensity Modulated RT (IMRT) planning and delivery will be encouraged but three-dimensional conformal RT (3D-conformal RT) will also be acceptable in this study. Volume Modulated Arc Therapy (VMAT) and tomotherapy will generally be discouraged. VMAT-based planning and treatment will be permitted in centres that use it routinely for RT treatment of locally advanced NSCLC, or in the event that IMRT and 3D-conformal RT approaches fail to achieve desired normal tissue dose constraints. It is recommended that tumour motion during the respiratory cycle be assessed at the time of simulation by 4-dimensional CT (4D-CT) when available. Positron Emission Tomography (PET)-CT imaging for staging will be required and PET information should be incorporated into RT planning. Efforts should be made that simulation CTs take place before initiation of Metformin therapy. In this situation utilization of intravenous contrast delivery during CT simulation will be encouraged but not required. In the event that this will not be possible, contrast infusion will be discouraged and contrast enhanced diagnostic CTs should be used to guide tumour and normal organ volume delineation. RT delivery shall take place under image guidance by matching bony anatomy on planning with that visible in either orthogonal kilovoltage x-rays or kilovoltage Cone Beam CT (CBCT).

Technical Factors:

Position, Immobilization and Simulation

Patients will be immobilized in the supine position on a flat table. In-house immobilization devices such as Wing-Boards or commercial devices are acceptable. Contiguous CT scan image slices will be obtained starting from the level of the cricoid cartilage extending inferiorly through the entire liver volume. Gross Tumour volume (GTV) Internal Target Volume (ITV), Planned Target Volume (PTV) and normal organs will be outlined on all appropriate CT slices.

Motion Compensation

Acceptable ways to account for respiratory tumour motion include: i) 4D CT to describe the ITV, ii) automatic breath hold control (Elekta ABC device) or iii) respiratory gating (Varian RPM system).

Radiotherapy Target Volumes

Target volume definition should be in accordance with the 1993 ICRU report #62. 4D-CT simulation and planning is encouraged.

Gross Tumour Volume (GTV)

Primary tumour and clinically positive lymph nodes detected by either the planning CT (> 1 cm in short axis diameter), by mediastinal biopsy with mediastinoscopy or Endobrochial Ultrasound (EBUS) or with pre-treatment PET scan (SUV > 3) will constitute the GTV. Volume may be disjointed. Elective nodal RT will not be utilized in this study since it is shown to offer limited clinical benefit (72-74). In the event of lobar collapse or pleura effusion, PET imaging or radiology review of CT scans will be used to help distinguish tumour from fluid or atelectasis.

Internal Target Volume (ITV)

If 4D CT is not used, ITV will be defined as the GTV plus a 1 - 1.5 cm margin to account for microscopic tumour extension and respiratory motion. In this case, fluoroscopy is recommended to assess tumour motion to refine the inferior-superior ITV margins. If 4D-CT is used, a contour that encompasses the shape and position of the GTV throughout respiration should first be created (e.g. using the Maximum Intensity Projection (MIP) image). This contour should then be expanded by 0.5 to 1.0 cm for microscopic tumour extension to define the ITV. Institutions may use alternative approaches for constructing the ITV on 4D CT. In the event that 4D-CT is not available but breath hold or respiratory gating is used GTV expansion to ITV can be limited to 0.5 cm in the axial plane and 1 cm in the superior-inferior direction.

Planning Target Volume (PTV)

The PTV is defined as the ITV plus a margin of 0.5 cm to 1 cm to account for setup errors and interfraction motion. The margin can be non-isotropic as long as it is in the above range in each axis.

Organs at Risk

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=SPINALCANAL, 2=BLUNGS, 3=ESOPHAGUS, 4=R/LBPLEXUS, and 5=HEART. The names of the OARs must be as indicated.

- **SPINALCANAL**

The dose to the spinal canal would be the highest priority dose constraint and should be met irrespective of other constraints. Maximum total (direct and scatter) point dose to the spinal canal will not exceed 50.5 Gy.

- **BLUNGS** (total normal bilateral lung volume minus the ITV)

The dose-volume constraint to the lungs is the second highest priority and should be met, except if it conflicts with the cord dose constraint. Graham et al(75) reported that the risk of grade 2+ radiation pneumonitis was 0% in V20 was <22%, 7% if V20 was 22-31%, 13% when V20 was 32-40% and 36% when V20 was > 40% in patients treated with radiation alone. Therefore, 37% has been adopted as the cut-off point for identifying high risk for pneumonitis. A maximum of 37% of the volume is allowed to receive 20 Gy or higher (V20 Gy \leq 37%). The mean lung dose (MLD) should be ideally below 18 Gy and never exceed 20 Gy. It is desirable that the volume of normal lung tissue receiving 5Gy (V5) will be kept below 50% (of the total volume). In all cases V5 should not exceed 65%. If either of these constraints is exceeded the following solutions will be considered, i) increase the weighting of Anterior=Posterior fields as long as the cord dose (above) is not exceeded, ii) reduce the ITV to the minimum range suggested above, iii) use respiratory gating techniques to define ITV and reduce finally PTV volume.

- **ESOPHAGUS**

Efforts should be made, when possible, to reduce the mean dose to the esophagus to 34 Gy or less. This is not an absolute requirement but it is recommended. The V60 (% volume of esophagus receiving 60 Gy or higher) will be calculated for each patient.

- **R/LBPLEXUS (ipsilateral plexus)**

Brachial plexus dose will be kept below 66 Gy.

- **HEART**

Efforts should be made to keep V60 Gy \leq 33%, V45 Gy \leq 66%, and V40 Gy \leq 100% of the heart.

Beam Energies

Beam energies of 6–18 MV must be utilized. Multi-leaf collimators or custom shaped blocks for field definition are acceptable.

Treatment Planning

IMRT planning is encouraged in participating institutions that have completed a formal recognized accreditation process for this technique (ie: RPC/IROC Lung Thorax Phantom). VMAT planning is permitted in accredited centres that use this technique routinely for lung radiotherapy planning. For 3D-conformal RT, the PTV should be treated with any combination of coplanar or non-coplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements should be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. Treatment plan used for each patient will be based on an analysis of the dose volume histogram (DVH) of the PTV and critical normal structures. Each field will be treated daily.

Heterogeneous Dose Calculations

Heterogeneity corrections shall be utilized in dose calculations. Superposition/convolution and Monte Carlo are acceptable algorithms in this study. Institutions will need to complete a feasibility questionnaire and Lung Thorax Phantom accreditation to be eligible for this study.

Dose Prescription and Variations

All patients will be planned to receive 60 - 63 Gy in 30 daily fractions (200 - 210cGy each) over a period of 6 weeks (five treatment days per week), concurrent with chemotherapy. Plans should aim to cover 100% of the PTV with at least 95% of the prescribed dose. Alternatively, coverage of 95% of the PTV with 100% of the prescribed dose will be also acceptable.(4) It will not be a considered a deviation if : $\geq 99\%$ of the PTV receives $\geq 93\%$ of the prescribed dose, and no more than 2cm^3 of the PTV exceed 120% of the prescribed dose.

Deviations

Minor deviation: (*Deviations of this magnitude are not desirable, but are acceptable*)

$\geq 95\%$ of the PTV receives $\geq 93\%$ of the prescribed dose, or no more than 2 cm^3 of the PTV exceed 120-125% of the prescribed dose.

Major deviation: (*Doses in this region are not acceptable*)

More than 1 cm^3 of tissue outside the PTV receives $\geq 120\%$ of the prescribed dose, or $< 95\%$ of the PTV receives $\geq 93\%$ of the prescribed dose, or 2 cm^3 of the PTV exceed 125% of the prescribed dose.

8.1.2 Review of RT Plans

All RT plans will be reviewed and approved locally at the centres by the treating radiation oncologists. Drs. T. Tsakiridis, M. Wierzbicki and J. Wright will be available to offer support with cases where it is difficult to meet the required constraints.

8.2 Chemotherapy

All patients will be planned to receive 2 cycles of Cisplatin- or Carboplatin-based chemotherapy concurrent with RT. Options include: i) Cisplatin combinations with Etoposide or Vinorelbine or ii) Carboplatin combinations with Etoposide or Paclitaxel, the latter of which may be followed by 2 cycles of consolidation chemotherapy of Carboplatin-paclitaxel. Patients will be stratified to the two chemotherapy (Cisplatin-based vs. Carboplatin-based) treatment approaches. These systemic therapy options are standard of care in most North American institutions. Available data do not support the use of consolidation chemotherapy with cisplatin-based chemotherapy and there is no strong evidence of benefit of consolidation chemotherapy overall (76-78). However, the Carboplatin- Paclitaxel regimen is still administered concurrently and with 2 cycles of consolidation therapy in many U.S. and some Canadian institutions.

Hydration and polyantiemetic regimens will be used as per local institution guidelines.

Complete blood counts (CBC) with a differential and a chemistry battery (including creatinine, Na, K, Cl and Mg) should be measured prior to each dose of cisplatin or carboplatin. CBC should be measured prior to each dose of vinorelbine and Liver Function Tests (LFTs) should be

routinely monitored in patients treated with either etoposide or paclitaxel. These are typically routine practices and such data will not be collected for study purposes.

8.2.1 Chemotherapy Details

i) Cisplatin-based regimens

Cisplatin - Etoposide combination: Cisplatin 50mg/m² will be administered intravenously with fractions 1, 6, 21 and 26 of radiotherapy. Etoposide 50mg/m² will be administered intravenously on fractions 1-5 and 21-25. This translates into cisplatin administration on days 1, 8, 29 and 36 of therapy and etoposide on days 1-5 and days 29-33 of therapy. The Cisplatin-Etoposide combination is a 4 week cycle.

Cisplatin-Vinorelbine combination is recommended as follows: Cisplatin 80mg/m² with fractions 1 and 16 of radiotherapy. Vinorelbine 12.5-15.0 mg/m² will be administered on fractions 1, 6, 11, 16, 21, and 26. This translates into cisplatin administration on days 1 and 22 of therapy and vinorelbine on days 1, 8, 15, 22, 29 and 36 of therapy, or as per institutional practice.

In the above regimens, Cisplatin may be substituted with weekly Carboplatin at the discretion of the treating medical oncologist.

Dose modifications or omissions for chemotherapy will be determined as per institutional standard of care. Switching from cisplatin to carboplatin, after Cycle 1, due to chemotherapy toxicity, is permitted. Metformin therapy will not be altered in those situations as it is not altered routinely in diabetic patients that undergo standard CRT for NSCLC and are treated with the drug. Of note, recent pre-clinical studies examined the potential of Metformin to reduce cisplatin-induced nephrotoxicity. They detected an anti-oxidant effect of Metformin in cisplatin treated kidneys but no clear nephron-protective effect (79).

ii) Carboplatin-paclitaxel regimen

Concurrent with Radiation

Patients will receive paclitaxel (50 mg/m² IV) and carboplatin (AUC-2 IV) weekly on days 1, 8, 15, 22, 29, and 36 from start of chemo-radiotherapy, administered intravenously, and weekly concurrent with thoracic radiation.

Consolidation Chemotherapy, when used, will be delivered in two 21-day cycles of consolidation treatment beginning 28-42 days after completion of radiation therapy with paclitaxel (200 mg/m²) and carboplatin (AUC 6) administered intravenously on day 1 of each cycle.

Dose Calculation

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.

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

Intravenous delivery

Chemotherapy will be administered 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.

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. 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.

8.3 Management of Chemo-Radiotherapy (CRT) Toxicity

In this study, the occurrence of all Grade 3 and higher adverse events, according to NCI-CTCAE v4.03, will be recorded. Toxicities related to CRT should be treated as per institutional guidelines.

Pneumonitis, esophagitis, bone marrow toxicity, telangiectasia and skin pigmentation are potential side effects of chest RT. RT induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy.

Pneumonitis

It is essential to spare as much normal lung tissue as possible in order to avoid symptomatic lung injury. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥ 20 Gy, usually within the first six months after initiation of treatment. Symptomatic radiation pneumonitis should be treated with oral prednisone as per routine practice.

Esophagitis

Esophageal complaints are common with concurrent CRT. Rates of 5-13% of acute and 3-6% late radiation esophagitis have been reported with CRT(80-83). Esophageal injury can be reduced by limiting the volume of esophagus that receives high dose RT or the mean esophageal

dose (84). Esophagitis does not constitute a reason to interrupt or delay RT 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 or other supportive care approaches should be used for symptomatic relief. Occasionally, narcotics may be required. Since radiation esophagitis may frequently be associated with reflux esophagitis, Ranitidine or other H2 blocker or H+/K+ pump inhibitors may help relieve symptoms. Approaches to management of esophagitis are listed in Table 3 below.

Acute esophagitis may persist for 4-6 weeks. If Grade 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted.

There is no evidence that Metformin contributes to radiation toxicity or specifically esophagitis. In the event that patients develop severe esophagitis that will necessitate interruption of RT or chemotherapy, efforts should be made for patients to remain on their routine medical treatment and maintain oral Metformin intake at 2000mg per day. Patients with limited oral intake should receive routine dietician support to utilize oral nutrition supplements to maintain caloric intake. Discontinuation of Metformin intake will be permitted for brief periods of time (5–7 days) in the event that patient's oral caloric intake is limited.

Dietician support should be utilized during re-escalation of Metformin dose as oral caloric intake improves. In general, the following should be considered in titrating up Metformin dose in these cases: Restart Metformin treatment at 1000mg / day (500 mg BID) when oral caloric intake increases to 1000 calories and escalate by 500 mg per week.

Table 2. Suggestions for Management of Radiation Esophagitis

1. Fluconazole 100 mg PO q day until the completion of radiation
2. Mixture of: 2% viscous lidocaine: 60cc; sucralfate (1gm/cc): 10cc. Administer 15-30cc PO q3-4 hours prn. (Contraindication: patients on Dilantin, Cipro, Digoxin)
3. Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as Omeprazole) until the completion of RT.
4. Grade 4 esophagitis: hold RT + chemotherapy until Grade 2 or less. It is expected that a significant number of patients will experience Grade 3 esophagitis.

8.4 Anti-cancer therapy post CRT

Immunotherapy

Health Canada recently approved durvalumab, which is a PD-L1 inhibitor, for patients with locally advanced NSCLC (85). This agent is given after the completion of CRT. It is anticipated that many patients on ALMERA will be offered this medication by their oncologist. Patients on ALMERA will be permitted to receive durvalumab in accordance with Health Canada

specification and monograph. It is recognized that PD-L1 inhibitors are associated with their own unique set of side effects.

9. FOLLOW-UP ASSESSMENT

Refer to Appendix III: Schedule of Study Assessments and Evaluations

9.1 Assessment during Treatment

Toxicity will be assessed every two weeks (Week 4, 6, and 8) during the concurrent CRT treatment period during routine clinic appointments.

9.3 Follow-up Assessment

Toxicity will be assessed at 3 month intervals during the first year of the study (3, 6, 9 and 12 months from the date of randomization). In addition, patients will be followed for disease progression and survival, assessed every 3 months for up to 12 months. During scheduled follow up visits patients will undergo a physical examination (including measurement of weight) and imaging evaluation of the chest with CT scans. Since PFS will likely be determined by the follow up CT scans, every effort should be made to pre-book the CT scans at Weeks 13, 26, 39 and 52 to ensure that the follow up appointments and clinical assessments take place within a 1-2 week window from the CT scan date. Additional investigations, such as X-rays or bone scans, will be left to the discretion of the treating radiation oncologist.

A fasting blood sample will be drawn from patients who have provided consent to the correlative studies at baseline, weeks 4 and 8 and at month 6. (*See Appendix IV. Correlative Studies*).

After the first year, only survival data will be collected for up to one additional year.

10. CORRELATIVE STUDIES

Patients accrued to this study will also be asked to provide additional consent to obtain bio-specimens for future biomarker studies. A separate consent form will be used for participation in this part of the study. Participation to this part of the study will be encouraged but refusal of participating patients to do so will not constitute ineligibility. (*see Appendix IV. Correlative Studies*).

11. ADVERSE EVENTS

This study will be conducted in accordance with Health Canada regulatory requirements and ICH Good Clinical Practice guidelines. Adverse events (AEs) and Serious Adverse Events (SAEs) data will be reported and collected.

11.1 Adverse Event Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient who is administered a drug or biologic (medicinal product) or using a medical device; the event does not necessarily have a causal relationship with this treatment or usage. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Each AE is to be classified by the Investigator as serious or non-serious.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e., subject at immediate risk of death),
- requires inpatient hospitalization or prolongation of existing hospitalization, except pre-planned hospitalizations required as part of a standard procedure or cancer treatment,
- results in a persistent or significant disability or incapacity,
- results in congenital anomaly/birth defect
- is an important medical event that may not result in death, be life threatening or require hospitalization, but may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent other outcomes specified in the above definition of SAE

An AE is **unexpected** when the nature or severity of the AE is not consistent with the applicable product information (i.e., Investigator’s Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). An AE is considered to be associated with the use of the drug if the attribution is classified as “Possible”, “Probable” or “Very Likely”.

11.2 Attribution Definitions

<i>Not Related</i>	An AE which is not related to the use of the study drug.
<i>Doubtful</i>	An AE for which an alternative explanation is more likely (e.g. concomitant medication, concomitant disease), and/or the relation with time suggests that a causal relationship is unlikely.
<i>Possible</i>	An AE which might be due to the use of the study drug. An alternative explanation (e.g., concomitant medication, concomitant disease) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
<i>Probable</i>	An AE which might be due to the use of the study drug. The relationship in time is suggestive (e.g., confirmed by a de-challenge). An alternative explanation is less likely (e.g., concomitant medication, concomitant disease).

Very Likely	An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation (e.g., concomitant medications, concomitant diseases). The relationship in time is very suggestive (e.g. it is confirmed by a de-challenge and a re-challenge).
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11.3 Adverse Event Reporting Criteria

All AEs will be described and graded according to the NCI-CTCAE, version 4.03. For each event, the highest severity grade attained since the last assessment period will be reported. If a CTCAE score does not exist, the investigator should assess the event as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (causing death) to describe the maximum intensity of the AE.

Adverse events related to disease progression and the toxicities related to standard cancer treatment in this patient population (e.g., surgery, chemotherapy and radiotherapy) are expected with great frequency, but bear no relationship to the study drug and therefore only AEs assessed as Grade 3 or higher will be documented for the purpose of this trial. Deaths due to recurrent cancer are also expected and will not be reported as SAEs for the purpose of this trial. Deaths will be monitored by OCOG and will not require reporting to Health Canada.

AEs are to be recorded within the electronic CRF. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, grade, action taken with respect to the Metformin, corrective treatment or therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was related to the investigational product.

11.4 Adverse Event Reporting Period

The AE reporting period for this clinical trial begins from the time of randomization and ends 30 days after the last treatment (concurrent CRT with or without consolidation +/- Metformin). Patients who discontinue the study treatment for a study related adverse event including an abnormal laboratory value must be followed for 30 days or until resolution or stabilization of the event, whichever comes first. In the case of an SAE, the patient will be followed until clinical recovery or until progression has been stabilized or judged to be chronic or the condition is unlikely to resolve because of the subject's underlying disease.

In addition, any known untoward event of Grade 3 or greater severity that occurs subsequent to the AE reporting period that the Investigator assesses as Possible, Probable or Very Likely related to the study drug should also be reported.

11.5 Serious Adverse Event Reporting to OCOG

Adverse events considered to be **SERIOUS and UNEXPECTED and RELATED** (that is, attributed as *Possibly, Probably, or Very Likely*) to the protocol treatment, must be reported by the Investigator to OCOG within 24 hours from the time when the clinical centre personnel

became aware of the event, using the SAE Form accompanied by relevant source documentation. All other SAEs should be reported to OCOG within 5 days from the time when the clinical centre personnel became aware of the event.

Follow-up SAE reports must be submitted to OCOG when new information becomes available and not later than 5 days after the clinical centre personnel became aware of the event. If an ongoing SAE changes in its intensity (Grade) or relationship to the investigational product, a follow-up SAE report should be sent immediately.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately, the Investigator is to report the event to OCOG within 24 hours of notification of the event.

The occurrence of SAEs and follow-up information related to SAEs will be documented by the clinical centre using the OCOG SAE Form. Relevant source documentation should be included. Forms and source documentation must be submitted by confirmed facsimile transmission (fax) and the original mailed to OCOG.

SAE FACSIMILE TRANSMISSION:

1-905-575-2639

SAE MAILING ADDRESS:

OCOG Safety Desk
Juravinski Hospital,
G Wing, 1st Floor
711 Concession Street,
Hamilton, ON Canada
L8V 1C3

11.6 Serious Adverse Event Reporting to Health Canada

OCOG, acting as Sponsor, will be responsible for notifying Health Canada, Therapeutics Products Directorate, Office of Clinical Trials in an expedited manner of adverse events which are considered **SERIOUS and UNEXPECTED and RELATED** to the protocol treatment (or for which a causal relationship with the protocol treatment cannot be ruled out). For each event reported to Health Canada, OCOG will inform the Data Safety Monitoring Committee (DSMC). Follow-up of SAEs as documented and submitted by the clinical centre on the SAE form will be forwarded to Health Canada by OCOG, where applicable.

11.7 Reporting SAEs to Local Research Ethics Boards

Investigators will be notified by OCOG of all SAEs that were reported to Health Canada and will be instructed to notify their local REB of the same, as per local REB requirements. The submission of these events by the investigator to their local REB should be completed upon

receipt and not later than 30 days from the date of the correspondence from OCOG.

The Investigator will be responsible for reporting SAEs occurring at their local site to their local REB, as per local REB requirements.

12. STUDY OUTCOMES

12.1 Primary Outcome

Progression Free Survival (PFS) at 12-months is the primary outcome for this study. PFS illustrates loco-regional disease control (LRC) and freedom from distant metastasis. LRC is shown to be an excellent early marker of overall survival (OS) by many studies of NSCLC patients treated with CRT including recent analyses of RTOG studies by Machtay et al (86). PFS will be evaluated at scheduled clinic appointments using follow up CT imaging of chest or by unscheduled CT scans of the abdomen and pelvis, CT or MRI of the head or nuclear medicine bone scan if clinically indicated. PFS duration will be defined from the date of randomization until the date of objective progression (loco-regional or distant), defined below, or death due to any cause. Any patient alive and progression-free at the time of data analysis will be censored on the last objective evaluation date. Any patient who withdraws from the study or is removed prior to 12 months will be considered as having an event for the primary analysis.

Detection of a clear loco-regional failure in a single CT scan will be adequate to conclude a failure event. Loco-regional failure will be determined based on standard RTOG-WHO criteria and progression events will be recorded according to criteria shown in Table 3 (86). In this approach, all patients are assumed to have LRC at the time of randomization. Supraclavicular lymph node progression will be considered loco-regional progression. Pleural or pericardial effusions, if cytologically positive would be considered distant progression (metastasis). Any new clinical or radiographic evidence of extra-thoracic disease (including pathologically enlarged upper neck lymph nodes) will be considered distant progression.

All PFS outcomes will be reviewed by an independent central adjudication committee, who will remain blinded to treatment allocation. (See Section 20.3)

Table 3. RTOG criteria for determination of Loco-Regional failure.

Local – Regional failure events will be recorded if one of the following conditions is satisfied:

- Enlargement by >25% in the bi-dimensional product of two dimensions of a measurable index (Pre-treatment lesion)
- For a non-measurable lesion, estimated enlargement by > 25% of tumour bulk, after taking into account post-radiation pneumonitis/fibrosis
- The development of severe tumour-related local-regional complications such as post-obstructive pneumonia and/or hemoptysis if these clinical events cannot be attributed to radiation toxicity and/or intercurrent disease

- Appearance of a new malignant lesion within the radiation field or at the edge of the field
- Positive biopsy and/or surgical specimen after radiotherapy showing viable NSCLC cells

12.2 Secondary Outcomes

(1) Overall survival

Overall survival will be defined from the date of randomization until the date of death due to any cause. Any patient who is alive at the time of data analysis will be censored on the last date the patient is confirmed to be alive.

(2) Time to loco-regional progression

Time to loco-regional progression is defined from the date of randomization until the date of confirmed loco-regional progression. Patients who die or who have distant metastases without evidence of loco-regional progression will be considered as having a competing risk on the day of death/distant progression. Time to loco-regional progression will be evaluated using a competing risk analysis.

(3) Distant progression-free survival

Distant progression-free survival is defined from the date of randomization until the date of distant progression, or death due to any cause. It is hypothesized that any patient deaths in this population without evidence of distant progression likely resulted from unobserved distant progression, hence, deaths will be considered an event and not a competing risk. Patients with loco-regional progression will continue to be followed for distant progression. Any patient alive and without a distant progression at the time of data analysis will be censored at the last objective evaluation date.

(4) Toxicities

Adverse events will be summarized using the NCI CTCAE v4.03 guidelines.

13. STATISTICAL CONSIDERATIONS

13.1 Sample Size Justification

Currently, due to the influence of PET staging, there is no reliable historical control for PFS or OS in locally advanced NSCLC. Therefore, there is need for efficacy studies to be randomized rather than single arm. Preliminary evidence of efficacy would be needed prior to embarking on a large, phase III randomized trial which could require in excess of 600 patients and 5 years to accrue.

Therefore, we will utilize a phase II screening trial as proposed by Rubinstein et al (87., 88). Based on prior studies (17), (Section 1.4), it is estimated that patients in the control treatment

arm will have 12-month PFS of approximately 45%. A clinically meaningful improvement for the use of Metformin is defined as an improvement in the 12-month PFS of 20% or greater (from 45% to 65%). Given that time to PFS is subject to various biases, the primary analysis will be based on the 12-month PFS rate, with the time to PFS analysed as a supportive analysis. Using a PFS rate at a specified time point is known to reduce the impact of any bias which can occur from lead time bias in un-blinded studies. Therefore, a Fisher's exact test will be performed with the outcome defined as a binary variable based on 12-month PFS. Using the recommendations of Rubinstein et al(83, 84), a 1-sided, $\alpha=0.20$, test would have over 80% power to distinguish between 12-month PFS rates of 45% and 65% with 42 patients in each arm (84 patients total). For this analysis, any patient who withdraws from the study, or otherwise is removed from the study prior to 12-months, will be considered as having an event. Supportive analyses will be performed to examine the impact of this imputation, including a time-to-event analysis using Kaplan-Meier estimation and after excluding patients who are removed from the study prior to 12-months. To account for an estimated 10% of patients who may drop out or be lost-to-follow-up, the total sample size for this study will be increased to 94 patients, or 47 in each arm. Note that for the time to event supportive analysis, a one-sided, log-rank test would have over 83% statistical power to detect a difference between arms, which would result in 12-month PFS of 45% versus 65%, at the $\alpha=0.10$ level of significance, assuming patients are recruited over 18 months with a further 12 months of follow-up.

As this is a phase II study, no formal interim analysis will occur. Given the short duration of accrual (18 months) relative to the time required to observe 12-month PFS, it is unlikely that a sufficiently large early efficacy signal could be observed at an interim analysis upon which an intervention on the trial would have any noticeable effect. Additionally, if the experimental arm appears superior at an interim analysis, continued accrual is warranted to gather increased information for the planning of a phase III study, whereas, if the results were to appear futile, sufficient information would be required to convince others of these results so that future studies of Metformin in this population are not performed. It is noted that the Data Safety Monitoring Committee (DSMC) will meet at least twice annually to review any safety concerns; therefore, these findings assume that no safety issues are observed as would be expected.

13.2 Feasibility

Over the last three years approximately 30-40 locally advanced NSCLC patients per year were treated with standard concurrent CRT at the Juravinski Cancer Centre (JCC). It is assumed that roughly 10 of these patients will be eligible and consent to this study each year, and similar numbers will be recruited at each participating centre. Therefore, it is expected that 94 subjects can be recruited to this study within 18-24 months.

13.3 General Statistical Methods

Descriptive statistics, such as the mean, median, proportion and frequency, will summarize patient, tumour, treatment and outcome characteristics. No formal comparison will be performed between patients randomized to each treatment arm. If substantial differences are observed between treatment arms, supportive analyses may be performed to evaluate the effect of any difference. Time-to-event analyses will use the Kaplan-Meier method. Supportive analyses will be performed including Cox or logistic regression, adjusting for baseline strata. Tables, plots and listings will be presented as appropriate to better interpret study results. 95% confidence intervals will be constructed for outcomes of interest. Results will be presented for each arm separately.

AE information will be presented for all AEs recorded, all grade 3 or higher AEs and all AEs deemed at least possibly attributable to treatment. The number and proportion of patients with each AE will be presented. A listing and tabular presentation of all patient deaths will be presented.

Supportive and secondary analyses will be two-sided and $\alpha=0.05$ will be defined as the statistical level of significance. Given that these are supportive and secondary analyses, results will be interpreted as hypothesis generating rather than confirmatory. Notably, subgroup efficacy, safety and tolerability analyses will be performed which analyzes patients categorized by whether they received post-chemoradiation treatment with a PD-L1 inhibitor. For the primary analysis, if statistical significance is observed, results will be used for the planning of a future, phase III confirmatory randomized controlled trial.

13.4 Evaluation of Biomarkers

Only collection of bio-specimens will take place within this study. Evaluation of biomarkers will be the subject of future studies.

13.5 Analysis Sets

All patients who are randomized will be included in the intent-to-treat (ITT) population. Efficacy analyses will be based on the ITT population.

All patients in the ITT population who receive at least one dose of Metformin will be included in the safety population. Safety analyses will be based on the safety population.

Supportive analyses may be performed on sub-populations, including those patients in the safety population who remain in the study for >1 year, those patients having at least one post-baseline objective response evaluation, or those patients who are deemed compliant to study procedures. All supportive analyses will be clearly defined as supportive analyses.

13.6 Patient Compliance Issues

Loss to follow-up is expected to be minimal (<5%) for this study. All reasonable efforts will be made to limit missing data and loss to follow-up. No imputation for missing data or loss to follow-up will occur.

Accountability logs related to study drug will be maintained by each clinical centre. Drug dispensing records including a pill count of returned study drug will be completed to assess study drug compliance.

14. STUDY SIGNIFICANCE

Locally advanced NSCLC remains a disease with limited treatment options and very poor outcomes despite aggressive CRT. There is an urgent need to improve the response of NSCLC to CRT. Unfortunately, recent efforts with RT dose escalation and introduction of specific targeted therapies were not successful. The present study is based on promising pre-clinical data

indicating that Metformin inhibits growth of NSCLC and sensitizes it to RT and CT. This is supported by retrospective evidence of improved outcomes in a number of tumour sites for diabetic patients treated with Metformin compared to other hypoglycemic agents. Metformin is an economical, well tolerated and widely-used agent that is proven to be safe and to have beneficial metabolic effects in non-diabetic patients. To date, there are no reports of increased toxicity when Metformin is combined with curative CRT. For this, the present screening randomized phase II study is an appropriate first step to investigate, with a simple design, whether Metformin could improve clinical outcomes in NSCLC. If positive, the present study will provide the basis to investigate Metformin definitively in locally advanced NSCLC with a large randomized placebo controlled trial.

15. ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly, Helsinki, Finland 1964 and later revisions or the laws and regulations of the country, whichever provide the greater protection for the study participant.

This clinical trial will be conducted in compliance with the ICH guidelines for Good Clinical Practice and will adhere to national laws and regulations of the country in which the study is performed.

Personnel involved in conducting this clinical trial will be qualified by education, training and experience to perform their respective tasks.

15.1 Informed Consent

OCOG, as Sponsor, will provide each clinical centre with a sample Informed Consent Form (ICF). The ICF used by the local Investigator or designate for obtaining the patient's informed consent must be reviewed and approved by OCOG prior to submission to the appropriate Ethics Committee (Research Ethics Board (REB)) for approval/favourable opinion.

It is the responsibility of the local Investigator or a person designated by the local Investigator and under the Investigator's responsibility, to provide each potential study patient, prior to inclusion in the study, full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. The patient must be informed about their right to withdraw from the study at any time. The patient must be allowed adequate time to make an informed decision.

Prior to a patient's participation in the study, the locally approved written ICF must be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written consent form document and any other written information should be provided to the patient.

Written informed consent will be obtained from all potentially eligible patients prior to commencing any study related procedures. Until the patient has been completely informed of the clinical trial, has freely consented to take part in the study and has signed and dated an ICF that has received documented approval by a licensed REB, no study related procedures can be performed.

15.2 Research Ethics Board (REB)

Prior to the commencement of the study, the Investigator must submit this clinical trial protocol, the ICF document, Product Monograph, recruitment materials/process, patient questionnaires, and any other written information to be provided to study patients to the appropriate REB and is required to forward to OCOG a copy of the written and dated approval/favourable opinion signed by the Chairman with REB composition.

The clinical trial (protocol number, clinical trial protocol title, version number and version date), the documents reviewed (clinical trial protocol, ICF, Product Monograph, etc.) and the date of review should be clearly stated on the written REB approval/favourable opinion.

During the clinical trial, any amendments or modification to the study protocol and/or ICF document, as issued by OCOG, must be submitted to and approved by the local REB. The REB should also be informed of any event likely to affect the safety of patients or the continued conduct of the study.

Annual re-approval is required for as long as the study is open to patient accrual, study participants are being followed and until the data collection and sponsor close-out is completed.

The REB must be informed when the study is closed or has been suspended.

16. RESPONSIBILITIES of the INVESTIGATOR

One Qualified Investigator (QI) will oversee the trial at each clinical centre. The QI undertakes to perform the study in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice and the applicable national regulations and local REB requirements.

The QI may appoint other individuals as he/she deems appropriate to assist in the conduct of the study. All appointed designates will be listed and provided to OCOG (Sponsor). The appointed designates will be supervised by and under the responsibility of the QI.

For the purpose of ensuring compliance with the clinical trial protocol, ICH GCP and applicable regulatory requirements, the QI agrees to permit study monitoring/auditing by or on the behalf of OCOG and inspection by applicable regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records, including source data/documents.

17. STUDY MONITORING and DATA HANDLING

17.1 Data Collection Method

Data collection is the responsibility of the designated clinical trial staff at the clinical centre under the supervision of the local QI. During the study, the QI must maintain complete and accurate documentation for the study. Study Case Report Forms (CRFs) are designed to record the disease status, treatment, intervention, all observations, follow-up and other pertinent data on each enrolled study participant. Data reported on the CRF that are derived from source documents must be consistent with the source documents. All source documents and laboratory reports must be reviewed by the designated clinical trial staff at the participating clinical centre. Adverse events must be graded, assessed for causality and reviewed by the local QI or designate.

Clinical centres will use Electronic Data Capture (EDC) to submit study data to OCOG. Electronic CRFs will be prepared for the data collection requirements except for fields specific to SAEs, pregnancy and patient questionnaires, which will be reported on paper forms. Subjects are to be identified by subject study number, initials and date of birth. Where paper CRFs are utilized data recorded must be neat and legible, to ensure accurate interpretation of the data. Paper CRFs must be completed in ink. A correction, prior to submission of the CRF to OCOG, must be made by striking through the incorrect entry with a single line and entering the correct information beside the incorrect entry. The correction must be dated and initialed by the person making the correction and must not obscure the original entry.

The completed CRF must be promptly reviewed, signed by the QI or designate and dated. For EDC, review and approval/signature by the QI or designate is completed electronically through an EDC tool.

Once the submitted paper CRFs and/or electronic study data are received at OCOG, data verification may result in additional requests to clarify or correct the data. Data queries are tracked and archived electronically.

17.2 Source Document Requirements

According to the ICH guidelines for Good Clinical Practice, each participating clinical centre will maintain appropriate medical and research records for this trial. Source data are original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. The data management team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The OCOG CMC will complete CRF verification by obtaining and reviewing local source documents. The ICF will include a statement by which the patient allows the Sponsor's authorized personnel, the REB, and the regulatory authorities to have direct access to source data which support the data on the CRFs. Such personnel must maintain confidentiality according to privacy legislation. It is the QI's responsibility to ensure source documentation submitted to

OCOG have been de-identified and labeled with study specific identifiers (i.e., study acronym, study subject ID number and subject initials).

17.3 Retention of Study Records

OCOG as sponsor is responsible for adhering to the retention of records as per Health Canada regulations and ICH Good Clinical Practice guidelines. The QI must also maintain confidential study documentation and ensure the retention of these study documents as per national regulations and guidelines. The QI must notify OCOG (sponsor) prior to destroying any essential documents following the completion or discontinuation of the clinical trial. If the QI can no longer ensure retention of the study documentation, the QI is required to inform OCOG (sponsor) to arrange the transfer of the relevant records to a mutually agreed upon designee.

OCOG will be responsible for informing the local QI as to when trial records and documents no longer need to be retained.

18. CONFIDENTIALITY

All information disclosed or provided by OCOG, or produced during the clinical trial, including, but not limited to, the clinical trial protocol, the Product Monograph, the CRFs, operations manuals and the results obtained during the course of the clinical trial, is confidential. The QI at each participating centre and any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of OCOG. This excludes the required REB submission.

19. CLINICAL TRIAL PROTOCOL AMENDMENTS

Investigators should not implement any deviation from, or changes to the clinical trial protocol without written authorization from OCOG (sponsor), prior review and documented written approval from their local Ethics Committee (REB/IRB), unless the safety of the study patient is in jeopardy.

An amendment may require a change to the ICF. The Investigator must receive REB approval/favourable opinion of the revised ICF prior to the implementation of the change.

20. STUDY ORGANIZATION

20.1 Steering Committee

The Steering Committee consisting of the study PI, selected clinical site investigators and OCOG representation will be responsible for the overall conduct of the trial, including the design, execution, analyses, and reporting. In addition, the Steering Committee is also responsible for the assignment of responsibilities to other study committees. The Steering Committee will hold the primary responsibility for publication of the study results. This Committee will convene on a regular basis (at least every 6 months) by teleconference or face to face meetings to monitor

study progress, execution and management and to review the reports from the DSMC. A list of the Steering Committee members is maintained by OCOG.

20.2 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) will consist of individual external to the conduct of the study, and will be composed of experts in the fields of clinical trial methodology and oncology. The DSMC will review accumulating safety data, provided to the Committee through the OCOG CMC, and will meet at the discretion of the Chair, but minimally twice per year.

20.3 Independent Central Adjudication Committee

All PFS events will be adjudicated by a blinded committee at the end of the study. The committee will consist of a group of Oncologists and Radiologists from participating institutions who are not involved with this clinical trial. The committee members will be blinded with respect to the treatment allocation.

20.4 Study Coordination

The OCOG CMC, located at the Juravinski Hospital in Hamilton, ON, Canada is responsible for the overall study management including finance and contracts, implementation of the study protocol logistics, patient allocation, data management, quality assurance and statistical analysis. The CMC is responsible for monitoring study execution, particularly with regard to methodological aspects and ensuring each clinical centre adheres to the study protocol. Web based registration and drug dispensing will be performed by the clinical centres utilizing the CMC's Interactive Registration/Randomization System (IRIS). A secure and confidential electronic study database is maintained by the CMC. Data collection will be performed via an EDC system. The CMC's Online Remote Collection of Clinical Information and Data (ORCCID) system incorporates a clinical database, data query process, visit management tracking and SAE tracking to ensure data is complete, accurate, of high quality and is reported/submitted according to required timelines. Designated personnel at participating clinical centres will be provided with member access to OCOG's website to obtain study documents, operations manuals, monthly status reports and newsletters.

An in-house Ethics & Regulatory Affairs Officer will complete and submit the required applications to Health Canada and facilitate the local REB applications, ensuring required start-up documentation is obtained from each clinical centre prior to centre activation.

The CMC will keep the Steering Committee informed of the study progress and report any problems or issues throughout the course of the study. In addition, the CMC at OCOG will prepare monthly status reports as well as summary information and reports for the various study committees and will provide methodological and administrative support to all study committees, Investigators and other study personnel.

21. SCIENTIFIC REPORTING and PUBLICATION

This clinical trial protocol was developed by the Principal Investigator(s) and study Steering Committee, with the assistance of OCOG.

The Steering Committee is responsible for the scientific reporting, publishing and/or presentation of the study results. Authorship will be determined by the Steering Committee and will be guided by the extent of participation in the development of the protocol, accrual of patients to the study, involvement in the study analysis and the drafting of the final manuscript. Results of the study will be disseminated through publications and presentations at international meetings. Any other publication or presentation related to the study and the results by any investigator or participant must receive prior approval from the Steering Committee. No other publication or presentation is permitted before the primary publication or presentation by the Steering Committee.

The information developed during the conduct of this clinical study is considered confidential.

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APPENDIX I: 7TH EDITION IASLC, TNM STAGING FOR LUNG CANCER

TNM Clinical Classification

T - Primary tumor

- TX Primary tumour cannot be assessed or tumour 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 Tumour 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 Tumour 2 cm or less in greatest dimension
- T1b Tumour more than 2 cm but not more than 3 cm in greatest dimension
- T2 Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features:
- involves main bronchus, 2 cm or more distal to the carina
 - invades visceral pleura
 - associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- T2a Tumour more than 3 cm but not more than 5 cm in greatest dimension
- T2b Tumour more than 5 cm but not more than 7 cm in greatest dimension
- T3 Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour 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 tumour nodule(s) in the same lobe as the primary.
- T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.

N – Regional Lymph Nodes

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

M – Distant Metastasis

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

Stage Grouping

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage 1B	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, T2a,b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

APPENDIX II: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, 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 more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX III: SCHEDULE OF ASSESSMENTS

		Metformin Treatment Period													
Metformin Dose		Dose escalation	2000 mg / day												
			Chemo-Radiotherapy treatment												
Weeks from Randomization	Pre-Trt	1	2	3	4	5	6	7	8	13	26	39	52		
Months from Randomization										3	6	9	12	24	
Informed Consent • main study • correlative studies	X														
Screening Assessment (including fasting blood)	X														
Randomization	X														
Demographics	X														
Cancer Staging	X														
Physical Exam (height, weight, vital signs)	X									X	X	X	X		
ECOG	X														
Routine Clinical Assessments	X				X		X		X	X	X	X	X		
CT-chest & upper abdomen	^a X									X	X	X	X		
FDG PET-Scan (whole body)	^a X														
MRI or CT – brain	^a X														
PFTs	^b X														
<i>(all considered standard)</i>															
Toxicity Assessment (NCI CTCAE)					X		X		X	X	X	X	X		
Correlative Fasting Blood Draws (2 x 10 ml tubes) (isolate and store EDTA Plasma and Buffy Coats)	X				X				X		X				
Collection of Tumour Blocks or Slides	X														
Disease Progression Assessment										X	X	X	X		
Survival										X	X	X	X	X	

- a. Pre-treatment imaging within 8 weeks prior to study randomization. CT chest and upper abdomen and brain imaging within 12 weeks of randomization is acceptable with a PET-CT within 8 weeks of randomization.
- b. PFTs performed within the last 12 weeks prior to study randomization will be accepted. Spirometry alone is acceptable if a complete PFT is performed before initiation of cytotoxic therapy.

APPENDIX IV: CORRELATIVE STUDIES

1. Blood Samples

1.1 Plasma and Buffy Coat Biomarkers

Metformin and fasting glucose, insulin, and plasma lipid profile will be analyzed in EDTA plasma. Apart from a direct anti-tumour effect, Metformin is believed to also inhibit tumour growth by lowering serum glucose and insulin levels in cancer patients, which leads to reduced growth effects of insulin on tumours. This model has gained popularity in the setting of breast cancer (89). However, recent studies suggest that insulin receptor is expressed in NSCLC tumours and may be associated with survival (90). Goodwin et al. observed that Metformin reduced insulin levels and improved insulin resistance and the lipid profile in non-diabetic women with early stage breast cancer (91). Our future biomarker studies will aim to verify whether Metformin therapy has the same metabolic effects in NSCLC patients. These studies will allow us to examine whether those parameters are associated with Metformin response. Evaluation of serum Metformin levels will allow us to examine whether serum Metformin levels associate with outcomes.

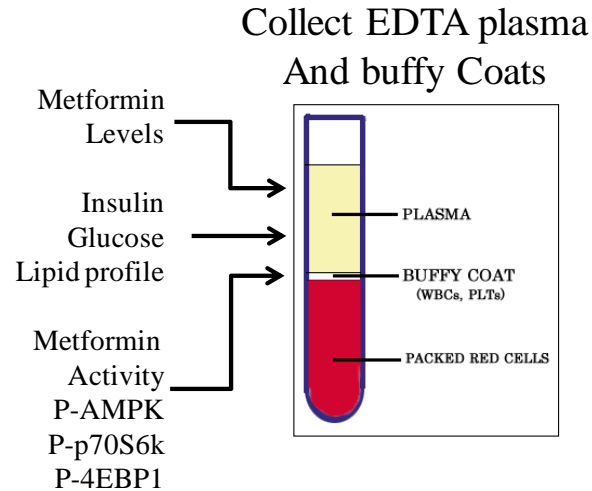
Analysis of molecular markers of Metformin response in circulating cells. Examination of the levels of phosphorylated AMPK, p70^{S6k} and 4EBP1 in circulating blood cells, isolated in buffy coats, will determine whether they can serve as potential pharmaco-dynamic markers in future Metformin studies.

1.2 Blood Sampling

Patients who provide additional consent to obtain blood samples, whether they are randomized to the standard or experimental arm, will provide four fasting (8 hours) blood samples: at Baseline, at Week 4, Week 8 and Month 6 after randomization. These times are selected to examine baseline insulin levels and metabolic parameters and compare them with the effects of Metformin on those parameters at times when the maximum dosing will be achieved (4 weeks) and maintained (8 weeks). Evaluation of the parameters at Month 6 will verify whether plasma levels and the effects of Metformin remain constant over long periods of time. Clinical centres will be provided with blood collection kits.

EDTA plasma preparation: From each patient, 20 ml of blood will be collected into 2 EDTA Vacutainer Lavender top tubes (10 ml each). These will be processed for plasma and Buffy Coat isolation.

For a visual explanation of the layers to be collected from each tube and the intended analysis, see diagram below.



2. Tumour Tissue

We hypothesize that the clinical benefit of Metformin in NSCLC may be associated with specific mutation and/or expression signatures of key genes that participate in the mechanism of action of Metformin and are frequently detected in NSCLC such as p53, LKB1 and K-Ras mutations (92, 93). Although, our preclinical NSCLC model work has not shown dependence of Metformin activity on p53 or LKB1 defects other studies have suggested these concepts (94-96). In addition, our observation of inhibition of Akt by Metformin(58) suggests that Metformin may have activity in tumours with activating K-Ras mutations, which show enhanced PI3k-Akt activity. Therefore, we will collect tumour blocks to examine, i) by DNA extraction and Polymerase Chain Reaction (PCR) and ii) by tissue microarrays and immunohistochemistry (IHC), whether the tumour mutation status and expression levels of p53, LKB1 and K-Ras can serve as predictive biomarkers of Metformin response. Further, depending on the number of cases with adenocarcinoma that will be collected on each arm, we will consider analysis of EGFR mutation and EML4/Alk translocation status. We recognize that the fairly small sample size in this study may prohibit definitive conclusions in the biomarker studies. However, we believe that these studies can provide adequate experimental clues and will guide bio-specimen collection and biomarker analysis in future Metformin trials.

2.1 Collection of Tumour Tissue Blocks

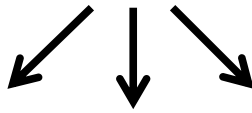
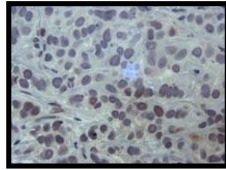
Tumour tissue specimens will be collected from each consenting patient for analysis of LKB1, K-Ras and p53 mutation status and expression. Centres will provide:

1. One H+E stained slide from the block supplied (indicating the presence of tumour).
2. A block of tissue, ideally from a core biopsy. Centres are urged to submit all biopsy tissue available. A portion of the block will be used for DNA extraction and PCR analysis of the mutation status of the markers and the remaining will be used for the creation of tissue microarray to examine by immunohistochemistry the protein levels of each of the markers using specific antibodies. In the event that this will not be possible a 2-3 mm diameter core of tissue punched from the tissue block with a skin punch, containing tumour, will be acceptable and it should be submitted in a plastic tube. The biopsy block or core containing tumour should be labelled with the study name, the pathology identification number, and the

patient Study ID number. Alternatively, we will accept slides. To adequately assess, we will require approximately 15 unstained slides.

3. A copy of the de-identified pathology report. The surgical pathology numbers and information must not be removed from the report. If the EGFR mutation and/or the EML4/Alk translocation status has been determined for this study patient, this information should be copied and provided.

Biopsy tissue blocks



LKB1, K-Ras, p53

3. Shipment of Blood Samples and Tumour Tissue

All collected blood samples will be batch shipped via courier on dry ice to the Juravinski Cancer Centre, Hamilton, ON for analysis. Tissue blocks will be collected at each participating centre and will be batch shipped by courier to the Juravinski Cancer Centre, lab of Dr. T. Tsakiridis.