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CANADIAN CANCER TRIALS GROUP (CCCTG)

A RANDOMIZED PHASE II TRIAL OF SELUMETINIB IN PATIENTS RECEIVING STANDARD PEMETREXED AND PLATINUM-BASED CHEMOTHERAPY FOR THE TREATMENT OF ADVANCED OR METASTATIC KRAS WILDTYPE OR UNKNOWN NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

CCTG Protocol Number: **IND.219**

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to CCTG and AstraZeneca.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG and AstraZeneca to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of AstraZeneca and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to AstraZeneca and CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG or AstraZeneca with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to AstraZeneca and CCTG and must be kept in confidence in the same manner as the contents of this protocol. I will retain all furnished information in confidence, prevent its disclosure to third parties and will not use it, other than for the purposes of the study, during the study and for a period of five years from the expiration or termination of the study. I will ensure that all study personnel receiving this information are informed of the obligations of confidentiality under this agreement and are made subject to these same obligations of confidentiality.

_____ _____

Qualified/Principal Investigator
(printed name and signature)

Date

Protocol Number: CCTG IND219

CENTRE: _____

TREATMENT SCHEMA

This is an open-label, randomized phase II clinical study of selumetinib (intermittent or continuous) in patients with advanced or metastatic *KRAS* wildtype or unknown *KRAS* status, non-squamous non-small cell lung cancer (NSCLC) who are receiving pemetrexed/platinum chemotherapy doublet as a first line palliative treatment.

Sample Size

The total sample size is 140 patients. The estimated accrual is 8-10 patients per month. It is anticipated that the duration of accrual will be 12-15 months.

Eligibility

- Histologically and/or cytologically confirmed stage IIIB or IV non-squamous, *KRAS* wildtype or unknown NSCLC
- Tumour sample available for correlative studies; patient must have provided informed consent for the release of the block.
- At least one measurable lesion as per RECIST 1.1.
- Age $\geq$ 18 years.
- ECOG performance status 0 or 1.
- Previous major surgery is permitted provided $\geq$ 14 days prior to randomization.
- Prior radiation is permitted provided $\geq$ 4 weeks has elapsed between the last dose and randomization.
- Prior adjuvant chemotherapy or combined chemoradiotherapy permitted provided completed at least one year prior to enrolment.
- No prior cytotoxic chemotherapy for advanced/metastatic disease.
- Prior therapy with ALK inhibitors is permitted. No prior treatment with MEK inhibitors or any other tyrosine kinase inhibitor (including EGFR inhibitors of any kind). Patients may have received vaccines, immunotherapy or other agents that are not MEK/tyrosine kinase inhibitors in the adjuvant setting or for advanced or metastatic disease.
- Laboratory tests:
  - Neutrophils $\geq 1.5 \times 10^9$/L
  - Platelets $\geq 100 \times 10^9$/L
  - Creatinine Clearance $\geq$ 50 ml/min
  - Total bilirubin $\leq$ 1.5 x ULN
  - AST and ALT $\leq$ 2.5 x ULN (if liver metastases $\leq$ 5x ULN permissible providing ALP also $\leq$ 6 x ULN)
- No history of other untreated malignancies or malignancies requiring therapy within the past 2 years.
- No symptomatic brain metastases or spinal cord compression. Patients with asymptomatic brain/spinal cord metastasis who are not planned for radiation, or who have been treated and are stable off steroids (or on a decreasing dose) and anticonvulsants are eligible.
- No significant cardiac disease (including uncontrolled hypertension); LVEF $\geq$ 50% for patients with cardiac disease.

- No evidence of:
  - severe or uncontrolled systemic disease;
  - active infection, active bleeding diatheses or renal transplant;
  - significant GI disease or inability to swallow capsules;
  - neuropathy > grade 1;
  - central serous retinopathy or retinal vein occlusion, high intraocular pressure ($\geq$ 21 mm) or uncontrolled glaucoma.
- No contraindications to treatment with standard cisplatin/carboplatin + pemetrexed chemotherapy regimen.
- No:
  - potent inducers or inhibitors of CYP 3A4/5, CYP 2C19 or CYP1A2;
  - large amounts of grapefruit and Seville oranges and other products containing these fruits;
  - vitamin E or multivitamin supplements;
  - excessive sun exposure (must use adequate sunscreen protection).
- Oral anticoagulants permitted with increased INR monitoring if patient cannot be switched to low molecular weight heparin.
- No pregnant or lactating women; women of childbearing potential must have negative urine pregnancy test; use of adequate method of birth control if not sterile.
- Risk benefit for Asian patients must be evaluated (increased exposure and or adverse events possible).

Pre-Treatment Evaluations

- History, physical exam, adverse events / baseline symptoms, hematology, biochemistry, coagulation, pregnancy test, EKG, LVEF (if applicable) and ophthalmology exam (if clinically indicated) within 7 days prior to randomization.
- Chest CT including upper abdomen and other scans / x-rays to document disease within 28 days (35 days if negative).

Treatment

Arm	Selumetinib 75 mg bid PO	Pemetrexed: 500mg/m^2 Cisplatin*: 75mg/m^2 or Carboplatin*: AUC=6	Schedule
A	Days 2-19	Day 1	q 21 days
B	Days 1-21 (continuous)		
C	Not given		
*	Must be specified at the time of randomization. Patients who start on treatment with cisplatin may switch to carboplatin only after discussion with CCTG.		

- Standard chemotherapy administered for 4-6 cycles; should continue with pemetrexed maintenance thereafter.
- May continue with selumetinib alone in absence of disease progression providing that further chemotherapy is not planned.

On Treatment Evaluations

- History and physical exam (weight, performance status, clinical tumour measurements, heart rate and tobacco use): Day 1 each cycle.
- Blood pressure: Weekly in cycle 1, then Day 1 each cycle and as clinically indicated.
- Hematology and biochemistry: Day 1, 8 and 15 for cycles 1 and 2, then Day 1 each cycle.
- INR (if on oral anticoagulants), EKG and ophthalmology exam: As clinically indicated.
- LVEF: Every 12 weeks if performed at baseline; additional assessments as per Section 8.3.2.3.
- Radiology (chest CT including upper abdomen; other scans / x-rays as necessary to follow disease): Every 6 weeks regardless of treatment delays.
- Adverse events: Evaluated continuously.

Duration Of Treatment

Treatment will continue until:

- Patient experiences progression as defined in Section 10.
- Unacceptable toxicity as defined in Section 8.
- Intercurrent illness.
- Patient refuses to continue treatment.

1.0 OBJECTIVES

1.1 Primary Objective

To determine the efficacy, as determined by objective response rate, of selumetinib (intermittent or continuous) in patients with NSCLC not known to have *KRAS* mutation receiving standard pemetrexed and platinum-based chemotherapy compared to chemotherapy alone.

1.2 Secondary Objectives

1.2.1 To assess the tolerability of selumetinib in patients receiving pemetrexed and platinum-based chemotherapy.

1.2.2 To assess the progression free survival of patients receiving selumetinib with pemetrexed and cisplatin to those receiving pemetrexed and platinum-based chemotherapy alone.

1.2.3 To assess whether *KRAS* mutation, other common mutations, or tumour based molecular signatures are predictive of selumetinib effect.

1.3 Exploratory Objective

1.3.1 To explore the feasibility of *KRAS* mutation testing in circulating tumour DNA (ctDNA) and concordance of *KRAS* mutation status between ctDNA and archival tumour tissue.

2.0 BACKGROUND INFORMATION AND RATIONALE

Lung cancer is the leading cause of cancer related mortality worldwide *[Jemal 2008]*. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases *[Rankin 1986]*. Approximately 40% of patients present with advanced NSCLC *[Ramalingam 2008]*, and for patients who present with earlier stage of disease, relapse is common due to early micrometastatic spread *[Winton 2005]*. In this setting the disease is incurable and treatment is palliative in intent. Although the number of treatment options for patients with advanced disease has increased over the past decade, prognosis remains poor, and there is a pressing need for additional therapeutic options *[Shepherd 2002; Schiller 2002; Hanna 2004; Shepherd 2005; Sandler 2006]*.

Cytotoxic chemotherapy is standard of care for patients with advanced NSCLC, and good performance status. In the first line setting, cisplatin based chemotherapy is associated with an absolute increase in overall survival of 10% at one year versus best supportive care (BSC) *[NSCLC Collaborative Group 1995]*. More recently, an additional modest benefit over that of standard combination chemotherapy, with the addition of the anti-angiogenic agent bevacizumab *[Sandler 2006]* or the epidermal growth factor (EGFR) inhibitor cetuximab has been reported *[Pirker 2008]*. In the second line, single agent docetaxel is associated with a superior overall survival (OS) versus BSC (median OS 7.0 months versus 4.6 months, log-rank p=0.047 respectively). Pemetrexed or the EGFR tyrosine kinase inhibitor (TKI) gefitinib provide alternative treatment options to docetaxel, with equivalent survival *[Shepherd 2005; Hanna 2004; Kim 2008]*. In the second or third line setting, the EGFR TKI, erlotinib, has been demonstrated to provide OS and quality of life (QOL) benefits over that of BSC, after one or two lines of chemotherapy (Hazard ratio (HR) 0.70 p<0.001) *[Shepherd 2005; Bezjak 2006]*. More recently, studies have shown platinum based pemetrexed combinations offer superior outcomes for patients with adenocarcinoma, as does pemetrexed maintenance therapy *[Ciuleanu 2009; Paz-Ares 2012; Scagliotti 2014]*. For patients with *EGFR* mutation positive disease, first line therapy with an EGFR TKI (gefitinib or erlotinib) is associated with a superior progression free survival compared with first line cytotoxic chemotherapy and has become a standard first line approach *[Fukuoka 2011; Rosell 2012]*. Despite these advances, the majority of patients with NSCLC die of their disease.

Chemotherapy agents may invoke compensatory activation of the ras-raf-mek pathway and this is postulated to contribute to the emergence of drug resistance (for example, through regulation of downstream transcription factor such as GATA-1 which controls the transcription of genes such as XRCC1 and ERCC1, promoting proliferation and preventing apoptosis). Treatment of drug resistant cells with mitogen activated protein kinase (MEK) inhibitors, or combined treatments consisting of a chemotherapeutic drug and a MEK inhibitor, may be an effective approach to prevent drug resistance.

Conversely, while combinations of paclitaxel and MEK inhibitors have been reported to be synergistic, some data suggest antagonism when MEK inhibitors and platins are given in combination. Cisplatin-induced apoptosis was associated with increased levels of both p53 and the downstream Bax protein as well as activated ERK1/ERK2 levels in a study with neuroblastoma cells. MEK inhibitors blocked apoptotic cell death, which prevented the cisplatin-induced accumulation of p53 and Bax proteins. Other nonclinical data suggest strong schedule dependence suggesting that combined treatment with chemotherapy and MEK inhibitors would be more active following a 48 hour interruption in dosing with a MEK inhibitor, rather than dosing concurrently.

Selumetinib (AZD6244, ARRY-142886) is a potent and selective allosteric MEK inhibitor. A randomized phase II study in patients with *KRAS* mutation-positive NSCLC has been conducted which compared selumetinib plus docetaxel to placebo plus docetaxel. There was a numerically greater increase (not statistically significant) in the primary endpoint of survival. The secondary endpoints of progression-free survival, objective response rate, and patients alive and progression free at 6 months each showed a statistically significant improvement in favour of selumetinib plus docetaxel *[Janne 2012]*. Further, while preclinical studies with selumetinib in combination with docetaxel suggested that intermittent scheduling (docetaxel followed by selumetinib) was active, the randomized phase II study in NSCLC showed activity with continuous administration with intermittent docetaxel.

A candidate predictive gene expression signature for MEK inhibitors in NSCLC has been identified that detects activated KRAS/MEK signaling *[Loboda 2010; Dry 2010; Brant 2013]*. Signature scores indicating high pathway activity were consistently found in both *KRAS* mutant and wildtype tumours. Further testing of the gene expression signature in both of these tumour types may provide evidence of possible benefit for treatment with selumetinib in additional or alternative populations. The assay has been demonstrated to be robust using formalin fixed paraffin embedded (FFPE) tumour tissue *[Brant 2013]* which makes it feasible to test the signature as part of a clinical trial of selumetinib.

In recent years, circulating tumour DNA (ctDNA) has emerged as a minimally invasive biomarker for profiling the tumour genome in multiple solid malignancies, including NSCLC, and as a potential alternative source of tumour DNA for genomic analysis *[Schwarzenbach 2011; Francis 2015; Freidin 2015; Diaz 2014]*. *KRAS* mutations have been detected successfully in ctDNA in patients with advanced NSCLC with > 90% concordance between ctDNA and the tumour tissue *[Saik 2014]*. We are planning to explore feasibility of *KRAS* mutation analysis from ctDNA and its concordance with tumour tissue.

CCTG has undertaken a phase I trial (NCIC CTG IND.215) of selumetinib combined with pemetrexed and cisplatin to evaluate the recommended phase II dose of both an intermittent schedule (selumetinib given on days 2-19 of a 21 day cycle) and continuous selumetinib (continuous selumetinib daily in a 21 day cycle). CCTG is interested in the further exploration of the efficacy in patients with KRAS wildtype or unknown NSCLC and toxicity of these two schedules versus standard pemetrexed/cisplatin (carboplatin) chemotherapy in patients with previously untreated advanced or metastatic non-squamous NSCLC.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Name and Chemical Information

Selumetinib (AZD6244, ARRY-142886) is a potent, selective, allosteric non-ATP competitive inhibitor of MEK.

Chemical Information
6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide: AZD6244 free-base.

3.2 Chemical Structure

Molecular formula $C_{17}H_{15}BrClFN_4O_3$
Relative molecular mass 457.7

3.3 Mechanism of Action

In cancer cells, signaling through the RAS/RAF/MEK/ERK pathway is frequently deregulated due to enhanced mitogenic stimulation at the level of growth factor receptors or activating mutations in RAS or RAF oncogenes. Inhibition of MEK, which lies downstream from these over-activated targets blocks inappropriate signal transduction in the pathway and is anticipated to arrest cancer cell proliferation and growth, offering a promising anti-cancer therapeutic strategy.

AZD6244 inhibits the activity of isolated MEK to phosphorylate ERK2 in enzyme assays with an IC50 of approximately 10 to 14 nM. It is an uncompetitive inhibitor with respect to ATP.

AZD6244 was inactive or only minimally active at 10 μM when tested against EGF receptor, erbB2, p38α, ERK2 and mitogen-activated protein kinase kinase. No significant activity for either AZD6244 or N-desmethyl AZD6244 was detected in a diverse panel of 305 and 336 enzymes, receptors, ion channels and transporters, respectively, at 10 μM. The potency of AZD6244 in inhibiting ERK1 and ERK2 phosphorylation in a diverse panel of cell lines was consistent ranging from 0.0018 to 0.0408 μM. In cell viability assays, IC50 values ranged from < 10 nM to > 10 μM and most of the cell lines that were sensitive to AZD6244 contained either a *BRAF* or *RAS* gene mutation *[Davies 2007; Dry 2010]*.

3.4 Experimental Anti-tumour Activity

AZD6244 has demonstrated potent inhibition of *BRAF* or *KRAS* mutation-positive cell line viability and inhibition of xenograft growth, both as monotherapy and in combination with a number of cytotoxic and targeted anti-cancer agents, including docetaxel. In three xenograft models of a *KRAS* mutation-positive tumour (SW620 colorectal cancer, HCT-116 colorectal cancer and A549a NSCLC), a beneficial effect of the combination of AZD6244 with cytotoxic drugs (e.g. docetaxel and temozolomide) or targeted anti-cancer agents (e.g. gefitinib) was observed when compared with either agent as monotherapy.

3.5 Animal Toxicology

AZD6244 free-base has been acutely dosed as single oral doses up to 300 mg/kg in rats and as bid doses up to 100 mg/kg/dose in cynomolgus monkeys and for up to 29 days, once daily at doses of up to 100 mg/kg/day in rats and bid at doses up to 30 mg/kg/dose in cynomolgus monkeys. However, there appeared to be dose-limited absorption due to the limited solubility of AZD6244.

AZD6244 Hyd-Sulfate has been dosed to mice and monkeys for 6 months bid at doses of up to 20 and 4 mg/kg/dose, respectively. AZD6244 Hyd-Sulfate enhances systemic exposure (3- to 6-fold) to AZD6244 and clear dose-related increases in exposure in mice and monkeys over the dose range studied were seen.

In a battery of safety pharmacology studies with AZD6244 free-base (hERG channel assay and behavioural, cardiovascular, pulmonary and gastrointestinal function/tolerability studies), there were no toxicologically significant findings. While there was some evidence of gastric irritation following a 100 mg/kg dose of AZD6244 in rats in the safety pharmacology study, there was no histopathological evidence of gastric irritation in rats in the 1-month study at this dose level. While minor increases in airway resistance were seen at 100 mg/kg AZD6244 in the respiratory safety pharmacology study, no respiratory abnormalities were apparent in the rat 1-month study at this dose level.

The following have been observed during administration of AZD6244 in toxicology studies: diarrhea, dehydration and electrolyte imbalance; gastrointestinal tract toxicity; inflammatory changes in the liver; tissue mineralization (gastrointestinal mucosa, cornea, kidney, liver, myocardium, skeletal muscle, glandular tissue) associated with changes in plasma inorganic phosphate, calcium and/or albumin; hematopoietic atrophy, anemia, and an associated reticulocytosis. There was evidence of reversibility of most changes, with the exception of tissue mineralization. In vitro assays indicate a potential for phototoxicity (enhanced cytotoxicity in the presence of ultraviolet light).

Reproductive toxicology studies indicate that AZD6244 can affect embryofetal development and survival at dose levels that do not induce maternal toxicity. AZD6244 showed no evidence of mutagenic or clastogenic potential in vitro. AZD6244 produced an increase in micronucleated immature erythrocytes in mouse micronucleus studies, predominantly via an aneugenic mode of action.

3.6 Studies in Humans

As of 31 January 2014, approximately 1940 patients with cancer have received treatment with selumetinib. Full details are described in the current selumetinib investigator brochure.

3.6.1 *Phase I Trials*

Study ARRY-0401 – free-base suspension formulation of AZD6244
Dose-limiting toxicities (DLTs) included grade 3 diarrhea and rash as well as hypoxia. The most frequently reported adverse events (AEs) were rashes (74.2%), diarrhea (58.1%), nausea (54.8%), fatigue (54.8%) and edema peripheral (48.4%). A trend towards elevated serum transaminase levels was observed, and AEs of alanine aminotransferase or aspartate aminotransferase were reported in 19.3 and 33.3%, respectively, of patients across all doses. Adverse events of hypertension were reported in 8.9% of patients, including 7.0% with hypertension or other cardiac conditions at entry to the study. No clinically significant trends in ECG parameters, including QTc, were observed.

Study D1532C00005 – Hyd-Sulfate capsule formulation of AZD6244
DLTs included rash, fatigue and pleural effusion and the 75 mg bid dose was determined to be the maximum tolerated dose of the AZD6244 Hyd-Sulfate capsule formulation.

The most frequently reported adverse events were fatigue (65.7%), dermatitis acneiform (60.0%), diarrhea (54.3%), nausea (48.6%), and edema peripheral (48.6%). Small increases in blood pressure were observed within the first week of continuous treatment with AZD6244; maximal median increases were apparent at after 3 weeks treatment with AZD6244 75 mg bid (systolic +7 mmHg; diastolic +13 mmHg) with improvement within 4 weeks of continuing treatment (to median +1 mmHg and +2 mmHg). Adverse events of left ventricular dysfunction or ejection fraction decreased have been reported in 8.6% of patients receiving AZD6244 75 mg bid in Study D1532C00005. There were no clinically significant changes in pulse rate, blood oxygen saturation, ECG parameters (including QTc) or hematology assessments, and no new clinically significant effects on laboratory parameters were observed.

3.6.2 *Phase II Trials*

Rashes (including the preferred terms dermatitis acneiform, rash, rash maculopapular, rash macular, rash papular, acne and folliculitis), were reported in approximately 70% of patients receiving treatment with AZD6244, and dermatitis acneiform was the most common AE term overall (53.9%). Other commonly reported AEs were diarrhea (49.4%), nausea (32.7%) and vomiting (23.8%). AEs of peripheral edema, periorbital edema or facial edema were reported in 30.9%, 8.6% and 4.1% of patients, respectively. AEs of fatigue or asthenia were reported in approximately 30% of patients in this Phase II population. Dyspnea exertional or dyspnea was reported in 13% of patients and, in individual studies, dyspnea exertional was reported at a higher incidence in the AZD6244 groups than in the comparator chemotherapy groups.

Serious AEs were reported in 23.8% of patients receiving AZD6244 monotherapy. The most frequently reported serious AEs were vomiting (1.5%), diarrhea, erysipelas and pulmonary embolism (in 1.1% patients each). Serious AEs of infections (bacterial sepsis, sepsis, infection, bacterial arthritis) were reported in 2.2% of patients.

3.6.3 *Pharmacokinetic Studies*

The first-in-human study of AZD6244 was conducted using a free-base suspension formulation. The maximum tolerated dose (MTD) was determined as 100 mg bid and subsequent phase II monotherapy studies conducted by AstraZeneca used this dose level and formulation. The pharmacokinetics of the AZD6244 Hyd-Sulfate capsule formulation was explored in Study D1532C00005; a MTD of AZD6244 75 mg bid was determined.

In Study D1532C00005 the estimated oral bioavailability of the Hyd-Sulfate capsule relative to the free-base suspension based on dose-normalized AUC0-24 was determined to be 263% (90% CI = 214 to 322%).

AZD6244 plasma pharmacokinetic parameters were similar after single and multiple dosing, suggesting minimal accumulation over time after bid dosing, consistent with the pharmacokinetic (PK) profile observed. The AZD6244 parameters were approximately dose proportional across the 25 to 100 mg dose range studied.

Circulating plasma concentrations of two metabolites, N-desmethyl AZD6244 and AZD6244 amide, were measured. The mean ratio of N-desmethyl AZD6244 to AZD6244 was ≤ 15%, and N-desmethyl AZD6244 was found to be 3- to 5-fold more potent than AZD6244 in an *in vitro* assay of cell-based ERK phosphorylation. Therefore N-desmethyl AZD6244 is likely to be contributing to pharmacodynamic effects. An investigation of the plasma PK of the AZD6244 amide metabolite was included in Study D1532C00005 in order to further characterize the plasma PK profile and to investigate the concentrations of circulating AZD6244 amide relative to AZD6244. In an *in vitro* assay of cell-based ERK phosphorylation, the AZD6244 amide metabolite was approximately 40- to 50-fold less active than AZD6244, and is therefore unlikely to contribute significantly to biological activity. Concentrations of the AZD6244 amide increased after multiple dosing, with a mean ratio of AZD6244 amide to AZD6244 after multiple dosing of ≤ 8% (maximum 22%).

A food effect study (D1532C00020) involving administration of AZD6244 to patients with advanced solid malignancies under fasting conditions and with a high-fat meal indicated a statistically significant effect of food on the exposure of AZD6244. Glsmean C_{max} and AUC were reduced by 62 and 19%, respectively, under fed conditions.

There is no evidence of a PK interaction between AZD6244 and docetaxel, dacarbazine, erlotinib or temsirolimus.

3.7 Pharmaceutical Data

Supplied:
The drug product consists of a series of plain, blue hydroxypropylmethylcellulose (HPMC) capsules containing 25 mg of AZD6244 (expressed as free-base) for oral administration. AZD6244 capsules are supplied in white high-density polyethylene (HDPE) bottles with foil-lined, induction-sealed, child-resistant closures. The container includes a desiccant canister.

Selumetinib will be supplied as 25 mg blue capsules in bottles of 60 capsules.

Storage:
The capsules should be stored in their original packaging until use. For further information, Investigators should refer to the investigational product label.

3.8 Standard Chemotherapy Agents

Standard chemotherapy agents are used in this protocol but are not supplied. Centres should consult the manufacturers' guidelines for further details.

Participating centres who are not able to access pemetrexed due to provincial funding constraints should contact CCTG for details on assistance from Lilly Canada.

4.0 TRIAL DESIGN

This is an open-label, randomized, phase II clinical study of selumetinib (intermittent or continuous) in patients with advanced or metastatic *KRAS* wildtype or unknown *KRAS* status, non-squamous non-small cell lung cancer (NSCLC) who are receiving pemetrexed/cisplatin or pemetrexed/carboplatin as a first line palliative treatment. This study is being conducted by the Canadian Cancer Trials Group (CCTG), with support from AstraZeneca.

4.1 Starting Doses

The starting doses of pemetrexed and cisplatin or pemetrexed and carboplatin are the standard doses recommended for clinical practice. Dose de-escalation will be permitted in the event of unacceptable toxicity.

Selumetinib starting dose is 75mg bid.

4.2 Randomization

Patients will be randomly assigned to a treatment arm as follows:

Arm	Selumetinib	Pemetrexed/Cisplatin (Carboplatin)
A	Days 2-19	Day 1 q 21 days
B	Days 1-21 (continuous)	
C	Not given	

4.3 Stratification

Patients will be stratified by the type of planned platinum treatment (cisplatin vs. carboplatin).

5.0 STUDY POPULATION

Patients will have histologically and/or cytologically confirmed non-squamous NSCLC with wildtype *KRAS* or unknown *KRAS* status that is metastatic or unresectable and for which standard curative measures do not exist.

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed prior to randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Patients must have histologically and/or cytologically confirmed non-squamous, *KRAS* wildtype or unknown, non-small cell lung cancer that is stage IIIB or IV, metastatic or unresectable and for which standard curative measures do not exist.

5.1.2 All patients must have a formalin fixed paraffin embedded tumour block (from primary or metastatic tumour) available for correlative studies and must have provided informed consent for the release of the block for correlative studies.

5.1.3 Patients must have at least one site of disease which is unidimensionally measurable as follows:

- Measurable disease defined as at least one target lesion that has not been irradiated or has progressed after radiation and can be accurately measured in at least one dimension by RECIST 1.1 criteria.
- Chest X-ray $\geq$ 20 mm
- CT/MRI scan (with slice thickness of < 5 mm) $\geq$ 10 mm → longest diameter
- Physical exam (using calipers) $\geq$ 10 mm
- Lymph nodes by CT scan $\geq$ 15 mm → measured in short axis

5.1.4 Presence of clinically and/or radiologically documented disease (marker positive only patients are not eligible).

All radiology studies must be performed within 28 days prior to randomization (within 35 days if negative).

5.1.5 Age $\geq$ 18 years.

5.1.6 ECOG performance status 0 or 1 (Appendix II).

5.1.7 *Previous Therapy*

Surgery:
Previous major surgery is permitted provided it has been at least 14 days prior to patient randomization and that wound healing has occurred.

Radiation:
Prior external beam radiation is permitted provided a minimum of 4 weeks has elapsed between the last dose and enrollment to the trial. Exceptions may be made for low dose, non-myelosuppressive radiotherapy after consultation with CCTG.

Chemotherapy and systemic therapy:
Prior therapy with ALK inhibitors is permissible. Patients may not have received prior MEK inhibitors or any other tyrosine kinase inhibitor (including EGFR inhibitors of any kind). Patients may have received vaccines, immunotherapy or other agents that are not MEK/tyrosine kinase inhibitors in the adjuvant setting or for advanced or metastatic disease.

Prior adjuvant platinum-based chemotherapy or combined chemoradiotherapy with curative intent is permissible provided completed at least one year prior to enrolment.

No prior cytotoxic chemotherapy for advanced / metastatic disease is permissible.

5.1.8 *Laboratory Requirements*
(must be done within 7 days prior to randomization)

Hematology:

Neutrophils	$\geq 1.5 \times 10^9$/L	
Platelets	$\geq 100 \times 10^9$/L	

Biochemistry:

Creatinine Clearance*	$\geq$ 50 ml/min	
Total bilirubin	$\leq$ 1.5 x ULN	
AST and ALT	$\leq$ 2.5 x ULN	(if liver metastases $\leq$ 5x ULN permissible providing ALP also $\leq$ 6 x ULN)

* *Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by appropriate formula below:*

$$\text{Females: GFR} = \frac{1.04 \times (140 - \text{age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$$

$$\text{Males: GFR} = \frac{1.23 \times (140 - \text{age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$$

5.1.9 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

5.1.10 Patients must be accessible for treatment and follow-up. Patients randomized on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

5.1.11 In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient randomization.

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

5.2.1 Patients with a history of other untreated malignancies or malignancies which required therapy within the past 2 years. Patients with other malignancies of a nature that do not require treatment may be eligible after consultation with the CCTG.

5.2.2 Symptomatic brain metastases or spinal cord compression. Patients with asymptomatic brain/spinal cord metastasis who are not planned for radiation, or who have been treated and are stable off steroids (or on a decreasing dose) and anticonvulsants are eligible.

5.2.3 Patients with significant cardiac disease, including:

- any factors that increase the risk of QTc prolongation or risk of arrhythmic events (e.g. heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age) or mean resting corrected QT interval (QTc) > 470 msec
- uncontrolled hypertension (BP $\geq$ 150/95 mmHg despite medical therapy)
- acute coronary syndrome within 6 months prior to starting treatment
- angina Canadian Cardiovascular Society Grade II-IV (despite medical therapy)
- symptomatic heart failure (NYHA II-IV)
- prior or current cardiomyopathy including but not limited to known hypertrophic cardiomyopathy or known arrhythmogenic right ventricular cardiomyopathy
- atrial fibrillation with a ventricular rate > 100 bpm at rest
- severe valvular heart disease

Patients with cardiac disease, who do not meet the exclusion criteria above, must have a baseline LVEF $\geq$ 50%.

5.2.4 Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

5.2.5 Patients who have neuropathy > grade 1 or other conditions precluding treatment with the standard chemotherapy regimen planned. Consult CCTG for patients with localised neuropathies as such patients may be eligible.

5.2.6 Patients who have significant gastrointestinal disease and who are unable to swallow capsules.

5.2.7 Patients on potent inhibitors or inducers of CYP3A4/5, CYP2C19 and CYP1A2 (must have discontinued within 2 weeks prior to randomization or 3 weeks for St. John's Wort). Patients who do not agree to avoid the ingestion of large amounts of grapefruit and Seville oranges (and other products containing these fruits, e.g. grapefruit juice or marmalade) and not take vitamin E supplements or multivitamin supplements.

Patients who require oral anticoagulants (Coumadin) are eligible provided there is increased vigilance with respect to INR monitoring upon initiation of dosing with selumetinib (see Sections 6 and 9). If medically appropriate and treatment available, the investigator should consider switching these patients to LMW heparin.

5.2.8 Patients with current or past history of central serous retinopathy or retinal vein occlusion, high intraocular pressure ($\geq$ 21mm) or uncontrolled glaucoma (irrespective of IOP). Patients with visual symptoms should undergo ophthalmologic examination prior to randomization.

5.2.9 Pregnant or lactating women. Women of childbearing potential must have a urine pregnancy test proven negative within 7 days prior to randomization. Men and women of childbearing potential must agree to use adequate contraception as described in Section 11.3.1.

5.2.10 Patients who do not agree to avoid excessive sun exposure and use adequate sunscreen protection.

5.2.11 Selumetinib-specific precautions for patients of Asian ethnicity:

Plasma exposure of selumetinib (Cmax and AUC) is higher, at a population level, in subjects of Asian descent by approximately 1.5- to 2-fold in non-Japanese Asians and Japanese subjects, compared with Western subjects. However, there is overlap in the range of exposure experienced by Asian and Western subjects and the higher average plasma exposure was not associated with a change in the tolerability profile of single dose selumetinib.

Investigators should make a clinical judgment as to whether the potential risk of experiencing higher selumetinib plasma exposure and potential adverse events outweighs the potential benefit of treatment with selumetinib.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	• history, height, weight, BSA, performance status, tobacco use • vital signs (blood pressure and heart rate) • documentation of all measurable and non-measurable disease • clinical tumour measurements (if applicable)	within 7 days prior to randomization
Hematology	• CBC, ANC, platelets	
Biochemistry	• serum creatinine • creatinine clearance • bilirubin • alkaline phosphatase • AST, ALT • LDH • total protein • calcium, phosphate • albumin • CPK	
Coagulation[1]	• INR (if applicable)	
Other Investigations	• pregnancy test[2] • EKG • LVEF (if applicable) • ophthalmology exam (if clinically indicated)	
Radiology[3]	• chest CT including upper abdomen (must include adrenals) • other scans/x-rays as necessary to document disease	within 28 days (35 days if negative) prior to randomization
Correlative Studies	• Archival tissue[4] (Mandatory)	must be confirmed available prior to randomization
	• Whole blood and plasma	after registration but before first dose of study treatment
Adverse Events[5]	Baseline adverse event evaluation (to document residual adverse events from previous therapy and baseline symptoms)	within 7 days prior to randomization

1 Required only if taking oral anticoagulants (i.e. Coumadin).

2 For women of childbearing potential only.

3 To ensure comparability, the baseline scans and subsequent scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

4 See Section 17 and laboratory manual(s) for details.

5 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (*Appendix V*).

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the IND.219 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing patients please contact the help desk (link in EDC) or the IND.219 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG IND.219)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- BSA, height and weight
- Stratification factors: *KRAS* known WT vs. unknown *KRAS* status and the type of planned platinum treatment (cisplatin vs. carboplatin)

7.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight. This principle applies to individuals whose calculated surface area is 2.2 m^2 or less. In those rare cases where a patient's surface area is greater than 2.2, the actual surface area or 2.2 may be used.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

7.3 Stratification

Subjects will be stratified by *KRAS* status (known WT versus unknown) and the type of planned platinum treatment (cisplatin vs. carboplatin).

7.4 Randomization

Randomization will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of the data and the follow up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration/randomization.

All randomized patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required.

8.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient randomization.

8.1 Drug Administration

NB: For reporting purposes, each three week period of treatment will be considered "one cycle" and the date of chemotherapy administration is considered "Day 1".

Arm	Selumetinib 75 mg bid PO	Pemetrexed: 500mg/m^2 plus Cisplatin*: 75mg/m^2 or Carboplatin*: AUC 6	Schedule
A	Days 2-19	Day 1	q 21 days
B	Days 1-21 (continuous)		
C	Not given		
* Must be specified at the time of randomization. Patients who start on treatment with cisplatin may switch to carboplatin only after discussion with CCTG.			

Selumetinib is to be taken on an empty stomach - no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing (i.e. take at least 2 hours after a meal and 1 hour before the next meal) with water. The bid doses should be taken approximately 12 hours apart.

Guidelines recommend that first line chemotherapy be administered for no more than 4-6 cycles. All patients receiving standard chemotherapy are considered on study until criteria in Section 12.1 are met. Patients should continue with pemetrexed maintenance (with selumetinib for Arms A and B). Patients who discontinue standard chemotherapy for reasons other than disease progression, may continue with selumetinib alone providing that further chemotherapy is not planned. When further chemotherapy (other than pemetrexed maintenance) or systemic therapy is planned, selumetinib must be discontinued.

Total carboplatin dose (mg) will be calculated according to the Calvert formula:
Carboplatin dose (mg) = (target AUC) x (GFR +25);
GFR = glomerular filtration rate (see Section 5.1.8)

The maximum dose based on a GFR estimate is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used. Please refer to the following link for more information:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm

8.2 Premedication

Patients should receive standard premedication according to the product monograph and local and provincial formulary guidelines:

- Antiemetics (for highly emetogenic chemotherapy)
- Hydration (for cisplatin)
- Vitamin supplementation (for pemetrexed)

Alternatively, standard protocols are available on the Cancer Care Ontario website: https://www.cancercare.on.ca/toolbox/drugformulary.

Initially, premedication for nausea and/or vomiting related to selumetinib is not required, as it is usually self-limiting but can be easily managed with anti-emetic medication such as prochlorperazine or 5-HT3 receptor antagonists at the treating investigator's discretion.

8.3 Dose Adjustments

Dose adjustments for each drug should be performed for toxicity related to that drug.

8.3.1 *Dose Adjustments for Standard Pemetrexed Plus Cisplatin/Carboplatin*

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V).

Investigators must consult the product monographs for each chemotherapy agent, or follow their local or provincial formulary guidelines for dose modifications.

Alternatively, standard protocols are available on the Cancer Care Ontario website: https://www.cancercare.on.ca/toolbox/drugformulary.

8.3.2 *Dose Adjustments for Selumetinib ONLY*

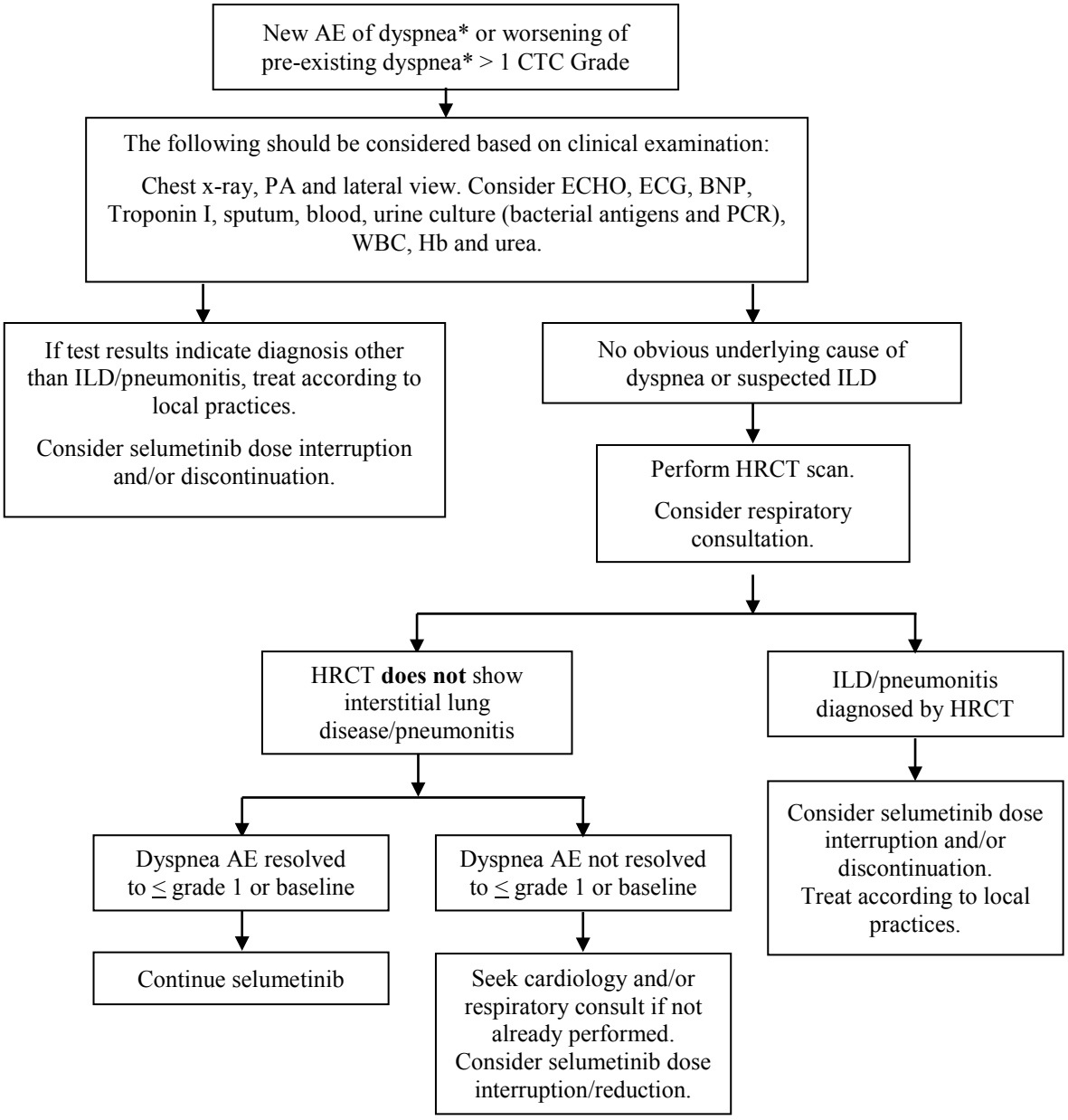
The major adverse events which have been described with selumetinib are diarrhea, nausea, vomiting, stomatitis, rash, fatigue, fever, dyspnea, pneumonitis, edema, hypertension, CPK increases, phosphate increases, falls in LVEF, transaminitis and visual symptoms. The guidelines which follow outline dose adjustments for several of these toxic effects.

If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level. If the patient has several adverse effects which are related to both standard chemotherapy and selumetinib, use the recommended dose adjustment that reduces to the lowest level for both standard chemotherapy and selumetinib.

Dose levels of selumetinib are provided below. A maximum of two dose reductions for toxicity is permitted; if a third is required, the patient must discontinue protocol therapy. If a patient discontinues selumetinib for more than 4 weeks (or more than 6 weeks for asymptomatic reductions in LVEF and for RPED/central serous retinopathy), they are no longer eligible to re-start treatment.

Selumetinib	0 (starting dose)	Dose level-1	Dose level -2
Arm A Intermittent	75 mg bid day 2-19	50 mg bid day 2-19	50 mg od day 2-19
Arm B Continuous	75 mg bid continuously	50 mg bid continuously	50 mg od continuously

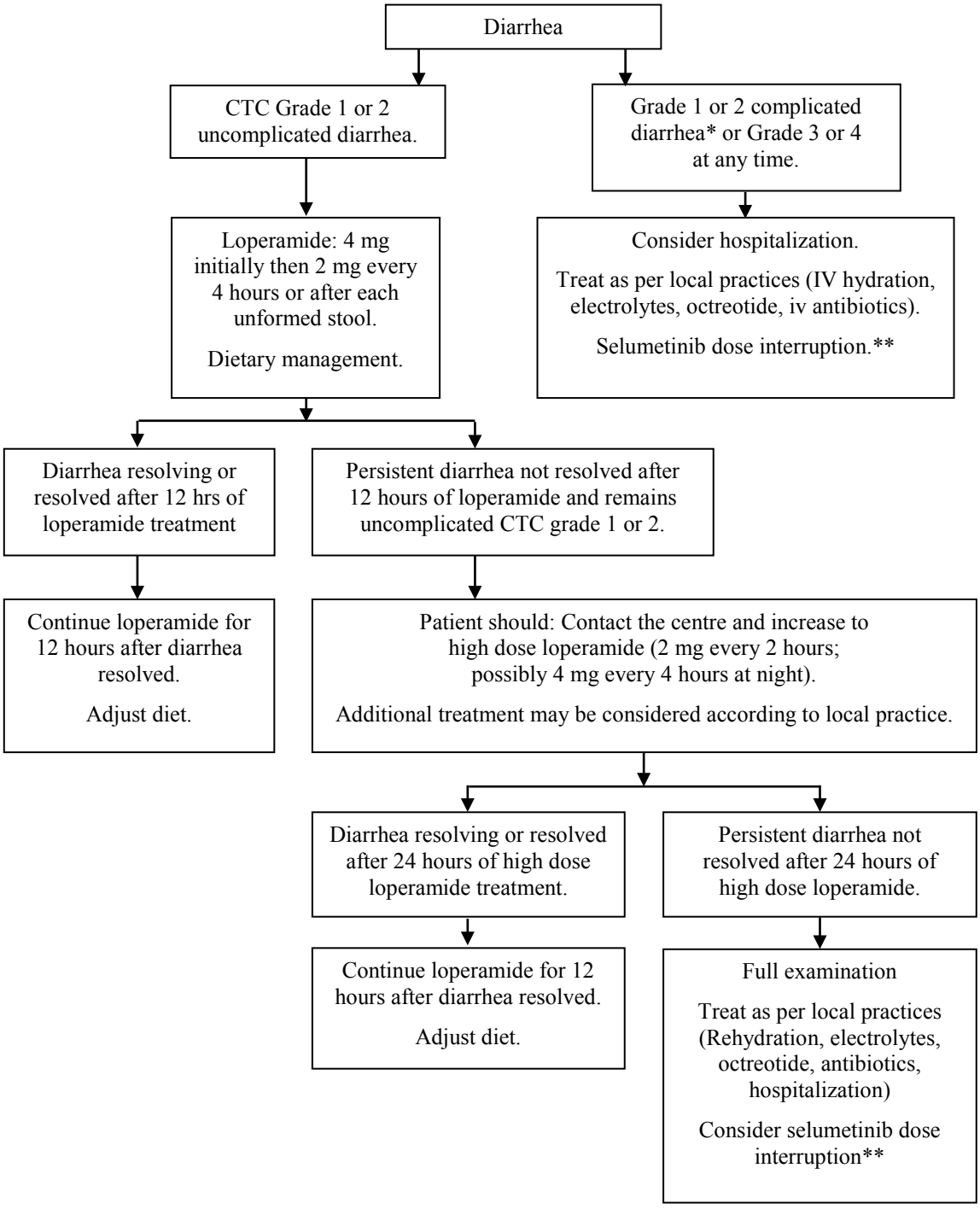
8.3.2.1 *Management of New or Worsening Dyspnea Not Related to NSCLC*



BNP: Brain Natriuretic Peptide
CTC: National Cancer Institute common toxicology criteria
Echo: Echocardiography
Hb: Hemogloblin
HRCT: High resolution computerized tomography
ILD: Interstitial Lung Disease
PA: Posteroanterior
PCR: Polymerase chain reaction
WBC: White blood cells

*** For investigating events of dyspnea that are not considered to be due to disease under study.**

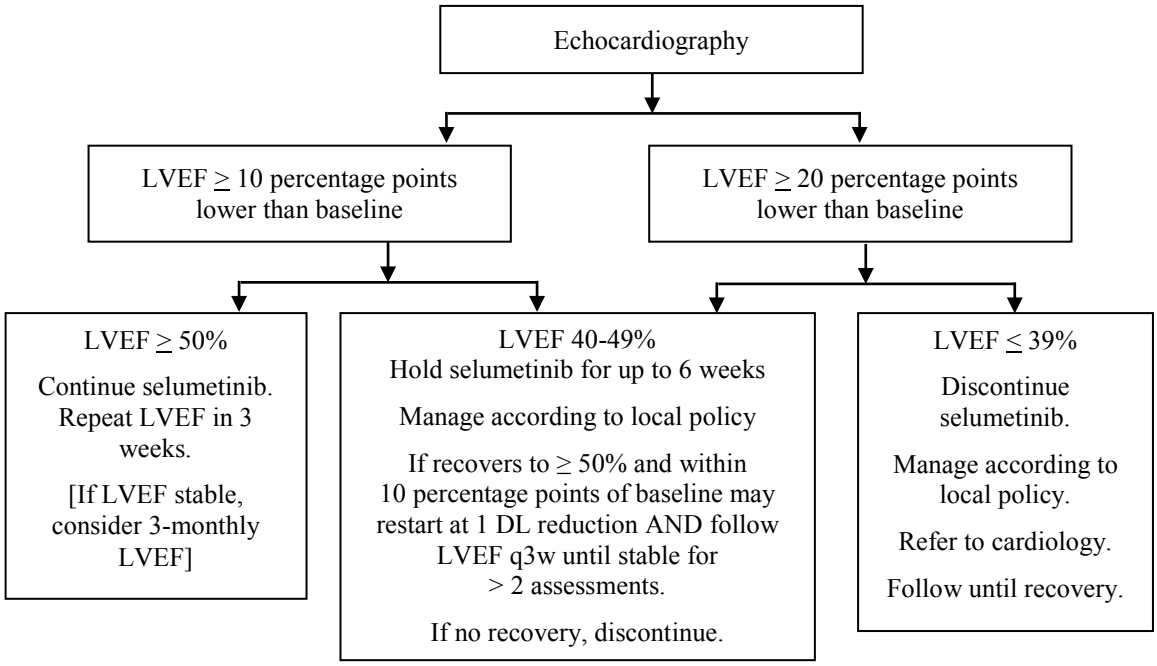
8.3.2.2 *Management of Diarrhea*



* Diarrhea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension

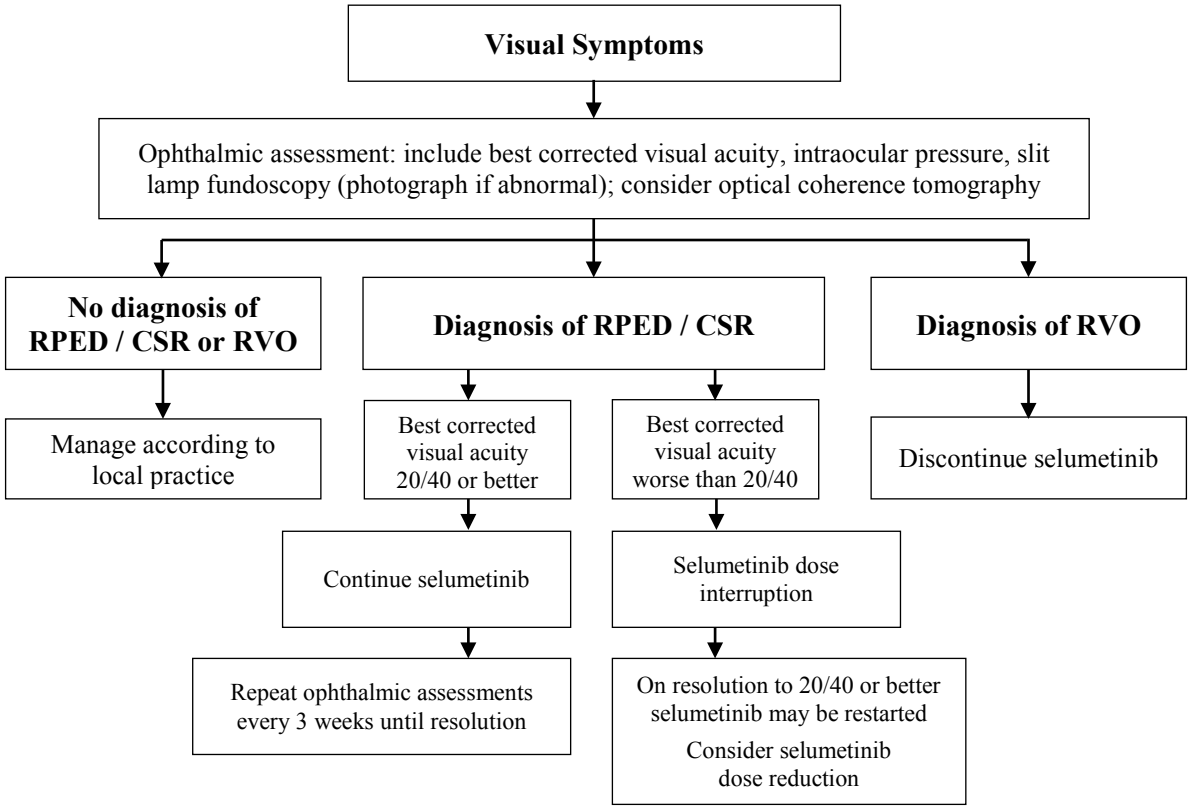
** **Consider interruption or delay of pemetrexed/cisplatin (carboplatin).**

8.3.2.3 *Management of LVEF Changes (if LVEF done at baseline)*



LVEF: Left ventricular ejection fraction

8.3.2.4 *Management of Visual Symptoms*



CSR: Central serous retinopathy
RPED: Retinal pigment epithelial detachment
RVO: Retinal vein occlusion

8.3.2.5 *Management of Rash*

Recommendations to start on day 1 of treatment with selumetinib and for the duration of treatment

- Use skin moisturizer (thick, alcohol-free) at bedtime
- Avoid excessive exposure to sunlight
- Use sunglasses/sunscreen (PABA-free, SPF ≥15; UVA and UVB protection) as needed
- Use of topical retinoids or benzoyl peroxide is not recommended

Grade 1 rashes
Mild or moderate strength topical steroid and/or topical antibiotic

Grade 2 rashes
Moderate strength topical steroid and oral antibiotic

Grade ≥ 3 rashes or
Grade 2 rashes considered by the patient to be intolerable

- Moderate strength topical steroid and oral antibiotic
- (consider broad spectrum/gram negative cover if infection suspected)
- Consider referral to a dermatologist: manage rash per recommendation
- Interrupt selumetinib until rash improves to grade 2 or less

Selumetinib may be restarted at original dose or reduced at the discretion of the investigator

8.3.2.6 Oral care guidelines

- Patients should be encouraged to take responsibility for their own oral care whenever possible to help maintain a clean and pain-free mouth.
- Oral health assessment prior to anti-cancer treatment may be beneficial for dentate patients with poor oral/ dental health.
- Prevention, early diagnosis and management of stomatitis may help reduce the need for dose modification.
  - Smoking and high alcohol intake should be discouraged.
  - Avoidance of painful stimuli (such as spicy food, hot food and drink) may be beneficial.

Recommended Dental Care	Management of Stomatitis
• Brush teeth twice daily twice daily using a fluoride toothpaste and soft toothbrush • in the morning before breakfast • before bedtime, at least 30 minutes after evening meal • the tongue can be gently brushed, if not sore	• Consider treatment at Grade 1 or as soon as the patient experiences sore mouth
• Use dental floss once daily (caution in patients with coagulopathies)	• Saline (0.9% sodium chloride) mouthwash recommended • Use at times other than after tooth brushing
• Use non-alcoholic mouthwash (in patients with a healthy mouth) • Immediately after selumetinib intake • Several times daily according to the instructions	• The following may be considered depending on the patient's clinical condition and local medical practice • oral topical analgesic anaesthesia • topical steroids • antiviral and/or antifungal medication
• Clean dentures thoroughly using a soft toothbrush and a mild denture-soaking solution • in the morning, after overnight soaking • after every meal • before soaking overnight • Dentures should be left out while resting	

8.3.2.7 *Management of Other Toxicity*

Grade of Toxicity	Action	Dose Modification
Grade 2	Treat symptomatically. If persistent and symptomatic, consider short selumetinib dosing holiday of 2-4 days.	None
Grade 3	Hold selumetinib.*	When resolved to ≤ grade 2, restart selumetinib at a one dose level reduction
Grade 4**	Discontinue selumetinib permanently.	

* *Discontinue if not recovered within 21 days.*
** *Discuss with CCTG if isolated hematologic toxicity*

8.4 Duration of Protocol Treatment

Treatment will continue until the criteria for removal from protocol treatment have been met (see Section 12).

8.5 Concomitant Therapy

Permitted:

Patients may receive ongoing supportive and palliative care (e.g. pain control - avoid NSAIDs while receiving pemetrexed) as clinically indicated throughout the study. All supportive medications must be recorded on the electronic case report form as appropriate.

Not Permitted:

- Other anti-cancer treatment.
- Other investigational therapy.
- Patients should avoid the ingestion of large amounts of grapefruit and Seville oranges (and other products containing these fruits (e.g. grapefruit juice or marmalade)).
- Patients should not take vitamin E supplements.
- Patients should avoid excessive sun exposure and use adequate sunscreen protection.
- Potent inhibitors or inducers of CYP3A4/5, CYP2C19 and CYP1A2 are not permitted unless clinically indicated and no alternate therapies are available. Corticosteroids as part of anti-emetic regimens are permitted.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

9.1 Evaluation *During* Protocol Treatment

Investigations		Timing
History and Physical Exam including:	• history • weight • ECOG performance status • clinical tumour measurements • blood pressure • heart rate • tobacco use	Day 1 Each Cycle. Blood pressure weekly cycle 1 and then day 1 each cycle and as clinically indicated.
Hematology[1]	• CBC, ANC, platelets	Day 1, 8 and 15 for cycles 1 and 2; thereafter day 1 each cycle.
Biochemistry[1]	• serum creatinine • creatinine clearance • bilirubin • alkaline phosphatase • AST, ALT • LDH • total protein • calcium, phosphate • albumin • CPK	Day 1, 8 and 15 for cycles 1 and 2; thereafter day 1 each cycle.
Coagulation[2]	• INR (if applicable)	As clinically indicated.
Other Investigations	• LVEF	Every 12 weeks if required at baseline. See section 8 for additional assessments.
	• EKG • Ophthalmology exam[3]	If clinically indicated.
Radiology[4]	• Chest CT including upper abdomen (must include adrenals) • Other scans as necessary to follow known disease	Every six weeks, regardless of any treatment delays.
Adverse Events[5]	Patients must be evaluated continuously for adverse events	

1 Timing of Day 1 Assessments: Pre-treatment blood draws, physical exams, weight and performance status may be done one working day prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). NOTE: Labs do NOT need to be repeated on day 1 cycle 1.

2 Required only if taking oral anticoagulants (i.e. Coumadin).

3 If visual symptoms.

4 To ensure comparability, the baseline x-rays/scans and subsequent x-rays/scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

5 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

9.2 Evaluation *After* Protocol Treatment

All patients will be seen at the end of the last cycle and then 4 weeks after the end of the last cycle date. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2; repeat LVEF and/or ophthalmological assessments may be required) and late toxicities (including second malignancies) and death. For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 3 months until progression (see Appendix I for investigations to be performed). A Death Report will be required for all patients and is due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).

Investigations		Timing
History and Physical Exam including:	• ECOG performance status • clinical tumour measurements (if applicable) • blood pressure • heart rate	Four weeks after completion of protocol treatment
Hematology	• CBC, differential, platelets	Four weeks after completion of protocol treatment Thereafter repeat abnormal labs related to selumetinib until ≤ grade 2 or baseline
Biochemistry	• serum creatinine • creatinine clearance • bilirubin • alkaline phosphatase • AST, ALT • LDH • total protein • calcium, phosphate • albumin • CPK	
Coagulation[1]	• INR (if applicable)	As clinically indicated.
Other Investigations	• LVEF[2]	Every three months until resolution of protocol related toxicity
	• EKG • ophthalmology exam[3]	If clinically indicated.
Radiology[4]	• chest CT including upper abdomen (must include adrenals) • other scans as necessary to follow known disease	*Only for patients with CR, PR or SD ongoing:* every 3 months until PD.
Adverse Events[5]	Four weeks after completion of protocol treatment. All protocol related adverse events must be followed (every 3 months) until resolution to ≤ grade 2 or baseline. Every 3 months thereafter *only if ongoing protocol related toxicity until resolved ≤ grade 2.*	

1. Required only if taking oral anticoagulants (i.e. Coumadin).
2. Only if done at baseline or if patient experienced cardiac toxicity.
3. If visual symptoms.
4. To ensure comparability, the baseline x-rays/scans and subsequent x-rays/scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
5. Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 *Evaluable for adverse events*. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

10.1.2 *Evaluable for response*. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Eisenhauer 2009]*.

10.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee.

10.2.1 *Measurable Disease*. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

10.2.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

10.2.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

10.2.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

10.2.5 *Response*.

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or imaging) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study. Minimum duration of stable disease is 4 weeks.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of $\geq$ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table:
Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	tumour nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	tumour nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.3 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

10.4 Stable Disease Duration

Stable disease duration will be measured from the time of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.5 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

10.5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

10.5.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

10.5.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

10.5.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

10.5.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

10.5.6 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

11.0 SERIOUS ADVERSE EVENT REPORTING

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

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events, regardless of whether they are unexpected or related to protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported in an expedited manner. Any late deaths related to protocol treatment or other serious adverse event occurring after this 30-day period which is unexpected and related to protocol treatment must also be reported in an expedited manner (see Section 11.2 for reporting instructions).
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the IND.219 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.
Within 7 days:	Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

IND.219 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2411

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the IND.219 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

11.3 Other Protocol Reportable Events – Pregnancy/Exposure Reporting

11.3.1 *Pregnancy Prevention*

Women of childbearing potential (WOCBP) and males who are enrolled in the trial must be informed of the requirement to use contraception as outlined in eligibility criterion 5.2.9. Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

11.3.2 *Pregnancy Reporting*

The investigator is required to report to the sponsor any pregnancy occurring in female participants and female partners of male participants. Pregnancies occurring up to 6 months after the completion of treatment with selumetinib and pemetrexed and cisplatin must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy, using the CCTG Pregnancy Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812 / safety-desk@ctg.queensu.ca).

If the pregnancy results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

11.3.3 *Exposure Reporting (non-study participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non-study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure, using the CCTG Exposure Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812 / safety-desk@ctg.queensu.ca).

If the exposure results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

11.5 CCTG Reporting Responsibility to AstraZeneca and Lilly

AstraZeneca and Lilly will be notified of all serious adverse events reported to Health Canada for selumetinib and pemetrexed respectively. CCTG as sponsor will determine regulatory reportability in Canada.

11.6 AstraZeneca Reporting Responsibilities

AstraZeneca will report all selumetinib regulatory reportable serious adverse events from non-CCTG trials (Safety Updates) to Health Canada and also provide to CCTG within the timelines outlined in the contract. CCTG will review these events to determine which meet the criteria (serious, unexpected, drug related) for IND.219 investigator distribution.

11.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial IND.219 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial IND.219 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0.
- Tumour progression as defined in Section 10.0.
- Request by the patient.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Duration of Protocol Treatment

(see Section 10.0 for response definition)

- Patients who progress (treatment failure) will go off all study agents at the time progression is documented clinically and/or radiographically.
- All other patients should continue treatment with standard pemetrexed chemotherapy (with selumetinib for Arm A and B) in the absence of unacceptable toxicity.

12.3 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment

See Section 9.2.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

At the conclusion of the trial, a central review of x-rays and/or scans may be carried out if any responses have been claimed. For purposes of reporting, the results of both local and central radiology reviews will be included.

13.2 Central Pathology Review

There will be no central pathology review for this study.

13.3 Correlative Studies

Details of tissue collection for this study are found in Section 17.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This is an open-label, randomized, phase II clinical study of selumetinib (intermittent or continuous) in patients with advanced or metastatic *KRAS* wildtype or unknown status, non-squamous non-small cell lung cancer (NSCLC) who are receiving pemetrexed/cisplatin or pemetrexed/carboplatin as a first line palliative treatment. A minimization procedure will be used to allocate patients after stratification by *KRAS* status (wildtype versus unknown) and planned platinum treatment (cisplatin versus carboplatin). Before the interim analysis, patients will be allocated with equal probability to one of three treatment arms: pemetrexed/cisplatin (or carboplatin) and intermittent selumetinib (Arm A), pemetrexed/cisplatin (or carboplatin) and continuous selumetinib (Arm B) or pemetrexed/cisplatin (or carboplatin) alone (Arm C). The trial may be stopped after interim analysis (see Section 14.4). If the trial is not stopped, subsequent patients will be randomized to the selected selumetinib arm and Arm C in a 3:1 ratio to ensure that the final analysis includes Arm A (or B) and Arm C in a 2:1 ratio.

14.2 Primary Endpoints and Analysis

The primary endpoint is response rate, defined as proportion of patients with CR or PR among all patients evaluable for response (definition in 10.1.2). Sensitivity analysis will also be performed with response rate defined as proportion of patients with CR or PR among all patients randomized. A stratified Cochran–Mantel–Haenszel (CMH) test will be the primary method to compare the response rates between Arm B (or A) and Arm C in the final analysis. The lower 80% asymptotic confidence limit (one-sided) for the difference of response rate between continuing selumetinib arm and Arm C will also be calculated based on asymptotic method.

Secondary endpoints include toxicity, progression free survival and overall survival, gene expression signatures/profiles and/or *KRAS* codon subtypes in tumour that may influence response. Because of the small sample size, analyses for most of these secondary endpoints will be descriptive. Dose intensity and dose modifications will be calculated for each drug, and progression free survival and overall survival will be summarized by the median and associated confidence intervals and described by Kaplan-Meier curves.

14.3 Sample Size and Duration of Study

The response rate of patients on the chemotherapy alone arm (Arm C) is expected to be 30%. Assuming that Arm B is chosen at the interim analysis, with 120 patients randomized overall, with 80 patients on Arm B and 40 on Arm C, we would be able to detect an 18% difference in response rate between two arms (from 30% to 48%) with a one-sided alpha = 0.2 and beta = 0.2.

The 20 patients who are randomized to the Arm A (or B) discontinued at the interim analysis will not be included in the final analysis but will be summarized separately. Assuming the trial goes to full accrual, it is anticipated that 140 patients will be enrolled in approximately 12 months with 6 months follow up time after the end of accrual before and after the interim analysis, it will take 24 months to complete the trial.

14.4 Interim Analysis

An interim analysis will be performed at a total accrual of 60 patients (20 per arm). If both Arm A and Arm B have 4 or more responses (PR+CR), one arm will be chosen for further study based on response efficacy and toxicity data.

If only one of Arm A or B have 4 or more responses, that arm with less than 4 responses will be discontinued. The remaining Arm will progress to full accrual. The data from the discontinued Arm will not be included in the final analysis.

If both Arm A and Arm B have less than 4 patients with response, the trial shall stop because the chance to have a positive trial is low.

The above decision rule was derived by testing the null hypothesis that the true response rate of a selumetinib arm is 10% or less versus the alternative hypothesis that the true response rate of a selumetinib arm is 30% or higher. Therefore, a selumetinib arm would be discontinued at interim analysis if its true response rate is much worse than expected. With 20 patients included in the analysis, the exact alpha and beta levels of the above stopping rule are 0.13 and 0.11, respectively.

14.5 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigator meetings. Toxic effects will be categorized using the CTCAE. The worst event for each patient in each category or subcategory will be described. Both events related and unrelated to treatment will be captured.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results

CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

16.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

16.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/exposure. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children
In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/legal guardian.

For reporting an exposure, the parent/guardian is required to sign an "exposure follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

16.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

16.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

AstraZeneca has reserved the right to audit participating centres. Audits may only be conducted after consultation with CCTG.

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "EDC Generic Data Management Guidebook" posted on the IND.219 area of the CCTG web-site (www.ctg.queensu.ca).

17.0 CORRELATIVE STUDIES

17.1 Laboratory Correlative Studies

17.1.1 *Tumour Tissue (Mandatory)*

The collection of representative tumour tissue is an important part of this trial and is mandatory for participation in the study for the evaluation of *KRAS* and other common mutations, as well as gene expression signatures/profiles and/or KRAS codon subtypes. Samples may be tested for gene fusions involving the *ALK, ROS* and RET genes. As the clinical relevance of these tests has not yet been determined and standard mutation assessment (e.g. EGFR mutations) is done as part of usual care, there are no plans to inform centres or patients of the results.

Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial, and may also include patient initials or unique identifiers and the pathology identification number.

Testing specifically for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

All patients on whom tumour samples are collected will be aware of this retrieval and will have given their consent.

17.1.2 *Blood Samples (Mandatory)*

Whole blood and plasma for *KRAS* mutations analysis in ctDNA will be collected from all patients at baseline. Other mutations may also be evaluated.

PLEASE REFER TO THE LABORATORY MANUAL FOR COMPLETE INSTRUCTIONS.

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study (within 7 days prior to randomization, or as noted)	Day 1 each cycle	Weekly cycles 1 and 2 then Day 1 each cycle	Every 6 weeks	4 weeks after end of last treatment cycle, then every 3 months until PD / death
History and Physical Exam[1]					
Weight	X	X			
Performance status	X	X			4 weeks only
Tobacco use	X	X			
Blood pressure	X	X	X[2]		4 weeks only
Heart rate	X	X			4 weeks only
Clinical tumour measurements	X			X	X (if applicable)
Hematology and Biochemistry[1]					
CBC, ANC, platelets	X	X	X		X[5]
Creatinine, creatinine clearance, bilirubin, ALP, AST, ALT, LDH, total protein, calcium, phosphate, albumin, CPK	X	X	X		X[5]
Coagulation					
INR[3]	X	As clinically indicated			
Radiology[4]					
Chest CT including upper abdomen (must include adrenals) Other scans / x-rays as necessary to document disease	X (within 28 days prior to randomization or 35 if negative)			X[6]	Every 3 months if patient is off treatment with CR, PR or SD
Other Investigations					
Pregnancy test[7]	X				
EKG	X	As clinically indicated			
LVEF	X[8]			X[9]	X[10]
Ophthalmology exam (if clinically indicated)	X	As clinically indicated			
Correlative Studies					
Archival tissue (all pts)	X				
Whole blood and plasma for ctDNA	X				
Adverse Events					
Baseline symptoms/ adverse events[11]	X	Continuously			X[5]

1 Timing of Day 1 Assessments: Pre-treatment blood draws, physical exams, weight and performance status may be done one working day prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). NOTE: Labs do NOT need to be repeated on day 1 cycle 1.

2 Blood pressure weekly in Cycle 1, then Day 1 each cycle and as clinically indicated.

3 Required only if taking oral anticoagulants (i.e. Coumadin).

4 To ensure comparability, the baseline x-rays/scans and subsequent x-rays/scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

5 Required at 4 weeks. To be done additionally every three months thereafter (Follow-up Report) if ongoing related grade > 2 adverse events even if patient came off treatment with progressive disease.

6 Maintain schedule even if cycles are delayed.

7 Women of childbearing potential only.

8 Required for patients with cardiac disease.

9 Required every 12 weeks if performed at baseline. See section 8 for additional assessments.

10 Repeat every 3 months to follow toxicities even if patient came off treatment with progressive disease.

11 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution

Selumetinib will be supplied by AstraZeneca and distributed by Bay Area Research Laboratory.

All other agents are commercially available and should be dispensed from the centre's pharmacy. (Note: Lilly Canada may provide assistance with pemetrexed if needed. Contact CCTG.)

Drug Labelling

Drug supplies for this study will be labelled in accordance with Health Canada regulations.

Initial Drug Supply

Once a centre is locally activated (following receipt and review of all required documentation), the CCTG will authorize start-up supplies of selumetinib to be shipped directly to the centre. Drug will be shipped to the centre within 3 working days of local activation. Drug accountability and drug re-order forms for each agent will be included with drug shipments and are also available on the trial website.

Drug Ordering (Re-Supply)

Fax a copy of the re-order form to the distributor. Please allow sufficient time for shipment of drug.

Drug Accountability

The investigational products are to be prescribed only by the investigator and co-investigators on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained accounting for the receipt of the investigational product and for the disposition of the product (Drug Accountability Log).

Drug Destruction

Expired/used study drug may be destroyed as per local standard operating procedures. Destruction of expired/used drug must be documented on the Drug Accountability Log and a copy of the destruction certificate kept on file in the pharmacy. Instructions for return or destruction of unused drug will be supplied at the time of expiry and at trial closure.

** PLEASE NOTE**
DRUG FROM THIS SUPPLY IS TO BE USED ONLY
FOR PATIENTS RANDOMIZED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating centre.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see Section 11.0 for details regarding SAE reporting). For details about accessing the EDC system and completing the on-line Case Report Forms, please refer to the Data Management Guidebook posted on the IND.219 are of the CCTG web-site (www.ctg.queensu.ca).

Electronic Case Report Form	To be Completed/Submitted Electronically:	Supporting Documentation to be submitted using Supporting Document Upload Tool[2]
BASELINE REPORT	Due within 2 weeks of patient randomization. Note: Eligibility Checklist must be completed at time of randomization to confirm eligibility.	Copy of main consent signature page(s); relevant pathology and radiology reports. Documentation of *KRAS* status (if applicable).
TREATMENT REPORT	To be completed every 3 weeks (i.e. after each cycle). Due within 2 weeks of end of cycle. This form documents treatment, adverse events, investigations and response assessment for each cycle.	Relevant radiology reports. Patient Diary. LVEF, EKG reports (if applicable).
CORRELATIVE STUDIES	See Section 17. To be completed and submitted with the tumour tissue at time of Baseline Folder completion.	Archival Tissue Submission Forms and Request for Payment Form.
END OF TREATMENT REPORT	To be completed when patient permanently discontinues treatment. Due within 2 weeks of end of protocol treatment.	
4 WEEK POST TREATMENT REPORT	To be completed once on all patients, 4 weeks after going off protocol treatment. Due within 2 weeks after contact with patient.	Relevant radiology reports.
FOLLOW-UP REPORT	Continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing treatment related toxicities (until resolved to ≤ grade 2; repeat LVEF and/or ophthalmological assessments may be required) and late toxicities (including second malignancies). For patients who go off protocol treatment with response or stable disease ongoing, Follow-up Report to be completed every 3 months until relapse/progression. Due within 2 weeks after contact with patient. An additional follow-up report may be required at the time of final analysis to capture survival and therapy information since last report. Due within 2 weeks after contact with patient	Relevant radiology reports.
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
DEATH REPORT	Required for all patients[1]. Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT (SAE) REPORT	All reportable serious adverse events must be reported as described in Section 11.0. Preliminary CCTG Serious Adverse Event Report due within 24 hours. Updated CCTG Serious Adverse Event Report due within 7 days.	All relevant test reports; admission, discharge summaries/notes.

1 It is the investigator's responsibility to investigate and report the date/cause of death of any patient. Any death that is *thought to be treatment related* must also be reported as a Serious Adverse Event as described in Section 11.

2 Supporting documents should be submitted using the Supporting Document Upload Tool. For instructions on this tool, see Power Point Presentation available on the IND.219 webpage.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

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

LIST OF CONTACTS

PATIENT RANDOMIZATION
All patients must be randomized via the web-based, password-operated electronic data system at the CCTG web page before any treatment is given.

	Contact	Tel. #	Fax #
STUDY SUPPLIES Data Management Guidebook, Protocol, Safety Information Electronic Case Report Forms.	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*	613-533-6430	613-533-2411
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Pamela Brown-Walker Study Coordinator CCTG Email: pbrown-walker@ctg.queensu.ca or: Dr. Greg Korpanty Email: gkorpanty@ctg.queensu.ca		
STUDY CO-CHAIRS	Barbara Melosky Email: bmelosky@bccancer.bc.ca	604-877-6000 x 2017	604-877-0585
	Penelope Bradbury Email: penelope.bradbury@uhn.ca	416-946-4501	
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Greg Korpanty Senior Investigator, CCTG or Pamela Brown-Walker Study Coordinator, CCTG	613-533-6430	613-533-2411
DRUG ORDERING	See Appendix III and trial website (www.ctg.queensu.ca) for details and contact information		