Early Stage Non-SCLC

- BRC.2 Intergroup trial ECOG 1505
- BRC.2/E NCIC CTG
- BRC.5 Intergroup trial CALGB 140503
NCIC CTG Trial BRC.2 – Schema

ELIGIBLE:
- Resected IB-III A
- ≥ Lobectomy
- No prior chemo
- No planned XRT
- No h/o CVA/TIA
- No ATE w/in 1 yr
- No therapeutic anticoagulation

STRATIFIED:
- Stage (IB*, II, IIIA-N2, IIIA-T3N1)
- Histology (Squam vs other)
- Gender
- Chemo regimen*

Chemotherapy x 4 cycles

Chemotherapy x 4 cycles
Plus
Bevacizumab
X 1 year

* Choice of: cisplatin plus either: vinorelbine, docetaxel, gemcitabine or pemetrexed
Trial Objectives

Primary Objective:

• To evaluate overall survival

Secondary Objectives:

• To evaluate DFS, toxicity
• To explore blood, tissue markers of benefit
• To explore association of smoking with outcome

BRC.2E – To evaluate cost effectiveness of adjuvant chemotherapy +/- bevacizumab
A prospective economic analysis of NCIC CTG BRC.2/E (ECOG 1505)

Primary objective:

• to determine the incremental cost effective ratio of adding bevacizumab to platin-based chemotherapy in the Canadian pts enrolled to the study.

• Activated in March, 2008
NCIC CTG BRC.5 (CALGB 140503)

A Phase III Randomized Trial of Lobectomy versus Sublobar Resection for Small (≤ 2cm) Peripheral Non-Small Cell Lung Cancer

NCIC CTG Study Chair: Jean Deslauriers
Physician Coordinator (PC): Ralph Meyer
Study Coordinator (SC): Cathy Davidson
Lead Group: CALGB
Participating groups: NCIC CTG, RTOG, ACOSOG, SWOG
CALGB 140503 - NCIC BRC-5

T<sub>1</sub>N<sub>0</sub> lung cancer ≤ 2cm

RANDOMIZATION

Lobectomy

Limited resection (Wedge or segmental)

Stratification: Tumor size (< 1cm, 1-1.5cm, 1.5-2.0cm)
Histology (Sq. cell, AdenoCa, Other)
Smoking status (Never, Former, Current)
Study Objectives of CALGB 140503 – NCIC BRC-5

• Primary
  – Non inferiority in DFS after sublobar vs lobar resection.

• Secondary
  – Non inferiority of OS after sublobar resection.
  – To determine differences in PFTs (spirometry) at 6 months.
# LIMITED RESECTION TRIAL, NCIC-CTG-BRC-5

## ACCRUAL SUMMARY *

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<tr>
<th>STATUS</th>
<th># PTS</th>
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<tr>
<td>Pre-registered (not randomized)</td>
<td>212</td>
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<tr>
<td>Randomized to lobectomy</td>
<td>155</td>
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<tr>
<td>Randomized to limited resection</td>
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* Target accrual of 692 randomized patients
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<tr>
<th>COUNTRY</th>
<th># PTS (%)</th>
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<td>USA</td>
<td>222 (72%)</td>
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<tr>
<td>Canada</td>
<td>76 (25%)</td>
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<td>Australia</td>
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Advanced Disease

• BR.29 – First line study

• BR.26 – Third and subsequent lines

• IND 2011 – Second line
BR.24: Progression Free Survival (30mg Cohort)

Median: Cediranib: 5.6 months
Placebo: 5 months
HR 0.77 (p = 0.13 95% C.I. 0.56 to 1.08.)
NSCLC
Stratified by:
Centre
Stage III B vs IV
Gender
Weight loss:
<5% vs 5-10% vs UNK
Prior Adjuvant Rx

AZD2171 @ 20mg
Paclitaxel/carboplatin
for 4 – 6 cycles

Placebo @ 20 mg
Paclitaxel/carboplatin
for 4 – 6 cycles
Randomise/Stratify
Gender/Stage/Weight loss/Centre/Adjuvant Rx

Safety analysis after 50 pts accrued
1A on first 260 pts for PFS after 170 events
Minimum HR for continuing < 0.7

Continue to full Phase III accrual
Endpoint: OS (HR 1.33, 25% risk reduction)
Total N = 750
Interim Analysis (n=260)

- HR for PFS: 0.89 (95% CI 0.66-1.20)
- Trial halted and unblinded
- Data locked June 2012
- Final analysis performed
Final Results

- 306 enrolled patients
- Median age 62
- Male 55%
- PS 0 / 1 = 26 / 74%
- Adeno / Squam / Other = 64 / 13 / 23%
Toxicity

• Stat. Sign. increased Gr 3 +
  – HTN (15 vs 3 %)
  – Anorexia (7 vs 1 %)
  – Diarrhea (16 vs 1 %)

• 2 possibly related deaths
  – hemorrhage
  – leukoencephalopathy
Efficacy (n = 306)

- Increased ORR with cediranib
  - 52 vs 34 % (p = 0.001)

- Median PFS
  - 5.5 vs 5.5 m (HR 0.91, 95 % CI 0.71-1.18)

- Median OS
  - 12.2 vs 12.1 m (HR 0.95, 95 % CI 0.69 – 1.30)
OS by treatment arm

NCIC CTG TRIAL BR.29
K-M Curve for Overall Survival

SUMMARY STATISTICS:
Log-Rank test for equality of groups: p=0.6598
Median for Placebo: 12.12
-95% C.I. (11.07, 15.47)
Median for Cediranib: 12.19
-95% C.I. (9.10, 18.04)
Hazard Ratio of Cediranib/Placebo: 0.932
- 95 % C.I. (0.681, 1.275)
NCIC BR26

- A double blind placebo controlled randomized trial of PF-00299804 (PF-804) in patients with incurable stage IIIB/IV non-small cell lung cancer who have failed standard therapy for advanced or metastatic disease
PF-804

- Irreversible inhibitor of EGFR, Her2 and Her4, small molecule TKI
- Safety profile consistent with other small molecule EGFR TKIs
- Evidence of activity in patients treated with prior chemotherapy and reversible EGFR TKI
  - PR in 4/42, disease control in half of patients
- Currently under evaluation or planned studies in first line, 2nd/3rd line and refractory settings
Stage IIIB/IV NSCLC
1 or 2 prior chemo
Prior EGFR therapy

Strata
Centre
PS (0,1 v 2/3)
Smoking (never v past v present)
Response to prior EGFR therapy (PD v other)
Weight loss

PF-804
Primary outcome
Overall survival
Placebo

Treatment to progression
Objectives

• **Primary objective**
  – Overall survival

• **Secondary objectives**
  – Overall survival in K-RAS WT
  – PFS
  – Response rate
  – Assessment of toxicity
  – Limited PK assessment
  – Cost effectiveness evaluation
  – Tissue and blood correlative analysis

  • *EGFR* mutation, *EGFR* copy number, K-RAS, met
  • *EGFR* KRAS PCR (blood)
Statistical considerations

- 90% power, one sided $\alpha$ 0.025, HR 1.33 (OS 4m v 5.3m)
- Assumptions 28 patients per month over 26 months. Requires 720 patients and 640 deaths
- Primary analysis is stratified logrank test
- One interim analysis (still finalising details)
A RANDOMIZED PHASE II STUDY OF REOLYSIN IN COMBINATION WITH STANDARD SALVAGE THERAPY (DOCETAXEL OR PEMETREXED) VERSUS STANDARD SALVAGE THERAPY ALONE FOR PATIENTS WITH PREVIOUSLY TREATED ADVANCED OR METASTATIC NON SMALL CELL LUNG CANCER

NCIC CTG IND. 211

Study Chair: Don Morris
Trial Committee: Victor Cohen, Frances Shepherd
Physician Coordinator (PC): Lesley Seymour
Statistician: Dongsheng Tu
Study Coordinator (SC): Lynn McIntosh
Trial Background & Rationale

- REOLYSIN (reovirus) is a non attenuated environmental dsRNA virus
- Preclinical *in vitro* and *in vivo* data has shown both as a monotherapy and in combination with cytotoxics promising activity in both solid and liquid tumours
- Extensive toxicicology studies in non-human primates suggestive of minimal toxicity
- Possible synergy with microtubule poisons
- MTD in human trials have never been reached
- To date over 350 pts treated within 15 plus clinical trials
NCIC CTG Trial IND 211 – Schema

Pts with one prior platinum based doublet regimen (unless > 70 yrs)

N=150

Squamous NSCLC or Non-Squamous NSCLC pts who have had 1st line Pemetrexed

Docetaxel 175mg/m² plus Reolysin day x 3

Docetaxel 75mg/m²

Pemetrexed 500 mg/m² plus Reolysin daily x 3

Non-Squamous NSCLC

Pemetrexed 500 mg/m²
Trial Objectives

Primary Objective:
- PFS

Secondary Objectives:
- ORR
- OS
- Progression rate at 3 months
- Exploratory: Circulating tumour cell enumeration, KRAS and EGFR status correlation with outcome,
Pemetrexed and Reolysin

- As pemetrexed and reolysin has never been studied in human trials, an additional 6 patients will participate as a “lead in” group to look for toxicity (three centres)
Statistics

- 150 patients (approx 38 patients per arm)
- PFS for docetaxel or pemetrexed alone in the second line setting estimated to be 4.5 months
- 90% power to detect a PFS difference between the combined groups of 4.5 to 7.7 months (HR 0.59), 2 sided alpha of 0.1
- 6-8 patients per month
- 21 month overall accrual
CONVERT NCIC CTG BR.28

- Concurrent ONce-daily VERSus Radiotherapy Twice-daily in LD SCLC
Once daily Thoracic Irradiation

D1   D3   D22  D24  D43   D45  D64   D66
RT 66Gy/45D/33F

Twice daily Thoracic Irradiation

D1   D3   D22  D24  D43   D45  D64   D66
RT 45Gy/19D/30F

SD, PR, CR → PCI
If < SD
→ No PCI

Registration
Randomisation
Restage

Chemotherapy
Radiotherapy

CONVERT STUDY
Mesothelioma
NCIC CTG IND. 207

A Phase II Study of PF-03446962 in Patients with Advanced Malignant Pleural Mesothelioma

Study Chairs: Paul Wheatley-Price
              Quincy Chu

Physician Coordinator (PC): Penny Bradbury
Study Coordinator (SC): Linda Hagerman
Trial Background & Rationale

- PF-03446962 is a fully human anti-ALK-1 antibody (Activin-receptor like kinase-1)
- ALK-1 is located on endothelial cells, and is required for the development of vasculature, and is expressed in the vasculature of most tumours, including MPM
- Ligands are from the TGFβ family, with downstream activation/phosphorylation of Smad 1/5/8
- In the SCID chimera/M24met model, PF-03446962 significantly reduced CD31 staining (a human endothelial cell marker)
Trial Background & Rationale

- Phase 1 - 39 patients with advanced solid tumours
- Recommended phase 2 dose was 10mg/Kg
- The most common adverse events include constitutional symptoms (fatigue), elevations in lipase and amylase, and thrombocytopenia

- Currently no standard of care for patients with MPM after failure of 1\textsuperscript{st} line platinum-based chemotherapy
- Rationale: Assess efficacy of PF-03446962 in the second line setting of patients with advanced MPM
Non-randomized, open-label, multi-centre phase II trial of PF-03446962 in patients with advanced malignant pleural mesothelioma, previously treated with cytotoxic therapy

**Stage I of accrual:** 16 response evaluable patients. If \( \geq 2 \) objective responses \( \rightarrow \) proceed to stage II

**Stage II of accrual:** Accrue an additional 10 evaluable patients

Note: If <2 responses, evaluate ALK expression

**Estimated accrual:** 2-3 patients/mo. over 24 months
IND.207 Objectives

Primary Objective

• To assess the efficacy of PF-03446962 given by IV infusion Day 1 of 2 week cycle in patients with advanced malignant pleural mesothelioma and previously treated with cytotoxic therapy

Secondary Objectives

• To assess the toxicity, safety and tolerability of PF-03446962
• To assess duration of response or stable disease, stable disease rate, progression-free, median and overall survival rates
• To collect tissue and blood for correlative studies
Main entry criteria

- Histologic / cytologic confirmed advanced MPM
- ECOG PS 0 or 1 (ECOG 2 at investigator discretion)
- Measurable disease
- Tumour block from primary or metastatic tumour available, or undergo a biopsy prior to registration
- Stage II patients must have accessible tumour lesion for fresh biopsy
- One, but no more than one, prior platinum based combination chemotherapy regimen

**Drug Administration**

- PF-03446962 IV infusion over 1 hour, every 2 weeks