NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A DOUBLE BLIND PLACEBO CONTROLLED RANDOMIZED TRIAL OF PF-804 IN PATIENTS WITH INCURABLE STAGE IIIB/IV NON-SMALL CELL LUNG CANCER AFTER FAILURE OF STANDARD THERAPY FOR ADVANCED OR METASTATIC DISEASE

NCIC CTG Protocol Number: **BR.26**

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*(For contact information of study personnel see Final Page.)*
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STUDY ACKNOWLEDGMENT/DISCLOSURE

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

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 will provide copies of the protocol and access to all information furnished by NCIC CTG and Pfizer 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 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 Pfizer and NCIC CTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Pfizer and NCIC CTG 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 NCIC CTG. The study may be terminated at any time by NCIC CTG or Pfizer, with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Pfizer and NCIC CTG and must be kept in confidence in the same manner as the contents of this protocol.

_________________________________ __________________ _________________________
Investigator Date
(printed name and signature)

Protocol Number: NCIC CTG BR.26

CENTRE: ___________________________________________
TREATMENT SCHEMA

This is a multi-centre, prospective double-blinded, placebo controlled randomized (2:1) phase III trial of PF-804 in patients with incurable, non-small cell lung cancer. Patients must have received prior chemotherapy and either erlotinib or gefitinib. Patients must have evidence of disease but measurable disease is not required.

Stratification
- centre
- performance status (0 or 1 vs. 2 or 3)
- tobacco use (never vs. past or present)
- best response to prior EGFR TKI (PD vs. other)
- weight loss (< 5% vs. ≥ 5% or unknown)
- ethnicity (east Asian vs. other)

<table>
<thead>
<tr>
<th>Stage IIIB/IV incurable, NSCLC after failure of standard therapy</th>
<th>R A N D O M I Z E *</th>
<th>ARM A: PF-804 45 mg PO, daily**</th>
<th>Until disease progression or unmanageable toxicity</th>
<th>End of treatment assessment (4 weeks from day 28 of last treatment cycle)</th>
<th>Follow up of disease status and survival (q12 weeks)</th>
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<tr>
<td>ARM B: Placebo 45 mg PO, daily**</td>
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* Randomization will be 2:1 to the active treatment arm
** 1 cycle = 28 days; see section 9.1 for details

Planned Sample Size: 720 patients

Endpoints

**Primary**
- Overall survival (OS)

**Secondary**
- Overall Survival (OS) in KRAS-WT patients
- Overall Survival (OS) in EGFR mutant patients
- Progression Free Survival (PFS)
- Objective Response Rate (RR)
- Time to Response and Response Duration
- Toxicity
- Quality of Life
- Economic Evaluation
- Correlation of tumour and blood markers with outcomes
1.0 OBJECTIVES

This is a double blind, placebo controlled, randomized trial of PF-804 in patients with incurable stage IIIB/IV non-small cell lung cancer after failure of standard therapy for advanced or metastatic disease.

1.1 Primary Objective

- To compare overall survival (OS) between the 2 arms

1.2 Secondary Objectives

- To compare overall survival (OS) in KRAS-WT patients between the 2 arms
- To compare overall survival (OS) in EGFR mutant patients between the 2 arms
- To compare progression-free survival (PFS) between arms
- To compare objective response rates (RR) between arms
- To estimate time to response and response duration
- To evaluate the nature, severity, and frequency of toxicities, between arms
- To compare Quality of Life between the 2 arms
- To determine the incremental cost effectiveness and cost utility ratios for PF-804
- To correlate the expression of tissue and blood markers (at diagnosis) with outcomes and response
2.0 BACKGROUND INFORMATION AND RATIONALE

Lung cancer is the most common cause of cancer-related mortality in developed nations, with an estimated 1.2 million new cases diagnosed each year and 1 million deaths annually worldwide [Jemal 2008]. The majority of patients with non-small cell lung cancer (NSCLC) either present with advanced disease, or develop metastatic disease at some point during their illness and are potentially candidates for systemic therapy. First-line platinum-based chemotherapy is associated with modest improvements in survival and quality of life [NSCLC Meta-Analyses Collaborative Group 2008]. The introduction of newer drugs such as vinorelbine, gemcitabine, pemetrexed, paclitaxel and docetaxel have resulted in further small improvements [Fossella 2003, Schiller 2002 and Scagliotti 2008], although most patients still experience disease progression within a short time, with a median time to progression of approximately four months. At the time of progression many patients maintain a good performance status and may be candidates for further systemic therapy. Randomized trials have established improved survival and quality of life from second-line chemotherapy with either docetaxel or pemetrexed [Shepherd 2000, Hanna 2004].

Recently, a greater understanding of the molecular abnormalities associated with NSCLC has led to the evaluation of new therapeutic targets for NSCLC. Erlotinib, a tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR), has also demonstrated improved survival and symptom control in patients who progressed after one or two lines of prior chemotherapy [Shepherd 2003]. The NCIC CTG BR.21 trial randomized 731 patients to erlotinib 150 mg daily or placebo. The response rate to erlotinib was 8.9%. There were significant improvements in progression free survival (2.2m v 1.8m, HR=0.61, p<0.001) and overall survival (6.7m v 4.7m, HR=0.70, p<0.001) for patients randomized to the erlotinib arm. These improvements were associated with significant improvements in time to symptom deterioration with regards cough (4.9m v 3.7m, p=0.04), dyspnea (4.7m v 2.9m, p=0.03) and pain (2.8m v 1.9m, p=0.04). Correlative sciences research from this trial provided insight into molecular predictors of response and survival following therapy with an EGFR TKI [Tsao 2005]. Despite these advancements in the treatment of NSCLC, the median survival of patients with metastatic NSCLC is still less than one year and there is a strong need for additional and better treatment options.

PF-804 is an orally available, potent, and highly selective irreversible small molecule inhibitor of the human epidermal growth factor receptor HER family of tyrosine kinases (i.e. pan-HER inhibitor): HER-1 (EGFR), HER-2 and HER-4 (HER-3 does not possess kinase activity). PF-804 inhibits the tyrosine kinase activity of the HER family through binding at the adenosine triphosphate (ATP) binding site, which results in covalent modification of a cystine in the ATP binding pocket. PF-804 has significantly improved pharmacokinetic properties (greater bioavailability, longer half-life, larger volume of distribution, and lower clearance) across all species tested (rat, dog and monkey). It exhibited robust anti-tumor effects in at least three different human xenograft models that express and/or over-express HER family members. The irreversible and highly selective properties of PF-804 for the HER kinase family result in sustained suppression of receptor tyrosine kinase activity. The long-lasting inhibition of receptor phosphorylation reduces concern over potentially short plasma half-lives. Furthermore, the low nanomolar potency and irreversible binding of the intended targets reduce the need for high peak plasma levels, which in turn could minimize target-nonspecific toxicities. The observed safety profile is consistent with other reversible small molecule EGFR TKIs and anti-EGFR monoclonal antibodies. The clinical data show encouraging activity in heavily pre-treated patients with advanced NSCLC after failure of prior treatment with reversible EGFR inhibitors. Evidence of activity is reflected by disease control in half of the patients and observation of durable partial responses in 4 of 42 evaluable patients. Mechanisms of activity in this population remain to be elucidated, but clear efficacy signals have been detected in subtypes of patients known to be resistant to reversible EGFR TKIs (patients with tumors having exon 20 insertion mutations). Clinical trials of PF-804 are ongoing or planned in patients with advanced NSCLC in the frontline and 2nd/3rd line and refractory settings.
Assessment of Quality of Life (QoL) in all patients is an important aspect this trial evaluating a new therapy in heavily pretreated NSCLC patients. Any possible survival gains from new therapies need to be assessed in terms of their QoL impact. Individuals in both arms of the study may show a decline in QoL over time, due to deterioration of their clinical condition from progression of disease and/or the effects of treatment. In particular, the expected toxicities associated with PF-804 (skin and gastrointestinal) may negatively impact the QoL of treated patients. However, it is also possible that the type and severity of toxicity may be moderate in degree or could be offset by beneficial effects of the experimental agent. Thus, a patient perspective of the impact of treatment is felt to be an essential part of this study.

A well validated questionnaire in this patient population is needed, and cultural and linguistic adaptation is essential as this will be a multinational study with Canadian and international centres participating. The EORTC core QoL questionnaire (QLQ-C30) [Aaronson 1993] and lung cancer module (QLQ-LC13) [Bergman 1994] are commonly employed in lung cancer clinical trials, and satisfy these basic requirements [Earle 2004]. It will be possible to compare results of this study to QoL outcomes in other clinical trials performed by the NCIC Clinical Trials Group that also used the EORTC instruments. The EORTC QLQ-C30 and QLQ-LC13 include items that address the main side effects of PF-804, with the only obvious exceptions being questions about skin toxicity. The NCIC Clinical Trials Group Quality of Life Item Bank was searched for appropriate questions and questions will be appended to the EORTC instruments. In the context of a placebo-controlled randomized trial, evaluating the success of subject blinding to study treatment is one means of determining if there has been any bias introduced in the conduct of the trial [Altman 2001]. Clinical cancer trials in which overall survival is the primary outcome may be less subject to such an effect, but for patient reported outcomes such as QoL this is a potential concern. To evaluate subject blinding, all patients enrolled on the study will be asked to indicate which treatment they believe they have received after completing the first cycle of treatment. If the patient indicates either PF-804 or placebo, they will then be asked to indicate what led to that belief. This method of determining subjects' beliefs about their treatment is not expected to influence any other outcomes of the study [Byington 1985].

While targeted agents have shown benefits in multiple tumour sites including lung, colon and renal cell carcinoma, their adoption and governmental funding has been variable. For instance, bevacizumab has received notice of compliance from Health Canada for metastatic colon cancer yet provincial funding has been variable across the country due to an estimated cost-utility ratio of greater than $100,000 per quality adjusted life year gained. Therefore accurate prospective economic data for any targeted agents is invaluable in assisting decision makers regarding funding issues. A prospective economic evaluation will be conducted in participating centres to determine the incremental cost-effectiveness and cost-utility of PF-804 in NSCLC from a government payer perspective, over a lifetime time horizon by prospectively collecting economic and resource utilization information during the trial. As part of the economic evaluation in this study, patient preferences, or utilities, will be measured using the EQ-5D questionnaire [Brooks 1996, Drummond 1997, www.euroqol.org]. The EQ-5D self-administered questionnaire consists of two pages comprising the EQ-5D descriptive system and the EQ Visual Analogue Scale (VAS). The EQ-5D descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and each dimension comprises three levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining one level from each of the five dimensions. The VAS records the respondent's self rated health status on a vertical graduated (0-100) visual analogue scale. The EQ-5D is a validated instrument that has been used in population surveys and clinical trial settings. Analysis will be performed as detailed in the statistical section of the protocol (see section 14).
There is a significant history of correlative sciences research in NCIC CTG lung cancer clinical trials. Analysis of molecular markers in the BR.21 trial provided an important contribution to our understanding of prognostic and predictive variables for patients undergoing therapy with an EGFR TKI [Tsao 2005]. Similarly, this trial will prospectively examine tissue samples to further expand our knowledge of predictive value of molecular variables. It is hypothesized that the expression of markers [such as KRAS, EGFR (FISH for copy number, mutations, SNPs), and met (FISH, mutations, IHC)] may correlate with outcomes and response to therapy. If this proves to be the case, it may be feasible to better define a cohort of patients who are most suitable for therapy with agents such as PF-804. All patients randomized to the trial will have tissue collected (diagnostic samples will be used if available; if not available, a biopsy will be performed). Other assays may be performed if considered appropriate. In addition, tissue, blood, serum and plasma samples will be banked for consenting patients.
3.0 BACKGROUND THERAPEUTIC INFORMATION

PF-804 is an orally available, potent, and highly selective irreversible small molecule inhibitor of the human epidermal growth factor receptor HER family of tyrosine kinases (i.e. Pan-HER inhibitor): HER-1 (EGFR), HER-2 and HER-4 (HER-3 does not possess kinase activity). PF-804 inhibits the tyrosine kinase activity of the HER family through binding at the adenosine triphosphate (ATP) binding site, which results in covalent modification of a cystine in the ATP binding pocket. See the PF-804 Investigator Brochure, for additional details.

3.1 Name and Chemical Information

Laboratory Code: PF-00299804
CAS Name: 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-4-(1-piperidinyl)-, monohydrate, (2E)-
Molecular Formula: C24H25ClFN5O2 • H2O
Physical Description: White to off-white powder

3.2 Chemical Structure

3.3 Mechanism of Action

PF-804 is an orally available, potent, and highly selective irreversible small molecule inhibitor of the human epidermal growth factor receptor HER family of tyrosine kinases (i.e. Pan-HER inhibitor): HER-1 (EGFR), HER-2 and HER-4 (HER-3 does not possess kinase activity). PF-804 inhibits the tyrosine kinase activity of the HER family through binding at the adenosine triphosphate (ATP) binding site, which results in covalent modification of a cystine in the ATP binding pocket.

3.4 Experimental Antitumour Activity

PF-804 results in tumour shrinkage or growth inhibition in a range of human xenograft models that express and/or over express HER family members, including NSCLC.

In NCI-H1975 human lung cancer xenografts (T790M positive) which are resistant to erlotinib, PF-804 results in growth inhibition as well as dose dependant inhibition of phosphorylated erbB1.

3.5 Animal Toxicology

Non-clinical studies have demonstrated the potential targets of PF-804 are the kidney, digestive system, epithelial cells (epithelial atrophy of cornea, esophagus, forestomach, cervix, vagina, and mammary gland, skin reddening and inflammation, alopecia), and liver. Other findings included erythrocytic and granulocytic changes, a slight QTc increase, as well as genetic toxicology effects.
In a dog Purkinje study, PF-804 had no effect on resting membrane potential, action potential amplitude, maximum rate of depolarization (Vmax), or action potential duration at 50% and 90% repolarization, at concentrations up to 10 µM.

PF-804 inhibited the hERG current in a concentration-dependent manner, at concentrations of 0.2, 0.7, 2.3, or 9.3 µM, by 4.5 + 2.1, 26.5 + 12.5, 63.1 + 19.7, or 92.0 + 3.6%, respectively. The IC50 of PF-804 was 1.58 µM (~283 × free Cmax concentration of 2.6 ng/mL on Day 14 of Cycle 1 at 45 mg QD in cancer patients) with a Hill coefficient of 1.4.

In in-vitro genotoxicity studies, PF-804 did not induce microbial mutations or produce a significant increase in chromosomal damage in a 24-hour test without metabolic activation, but in a 3-hour test with and without metabolic activation, PF-804 induced weak reproducible significant increases in chromosomal damage at concentrations > 0.8 µg/mL. An in-vivo micronucleus assay in rats demonstrated no evidence of chromosomal damage at doses up to the maximum tolerated dose of 2000 mg/kg/day.

No fertility studies have been conducted.

The major clearance mechanism in non-clinical species appeared to be through metabolism. Data indicated that PF-804 is unlikely, at all clinical exposures, to inhibit the metabolism of co-administered drugs that are mainly metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4. However, PF-804 may inhibit CYP2D6 at clinical concentrations, which may cause drug-drug interactions with concomitantly administered CYP2D6 substrates. Studies indicate that PF-804 can cross the blood-brain barrier of mice. PF-804 also appears to be a weak substrate of human P-glycoprotein and BCRP efflux in in-vitro cell assays. PF-804 showed a moderate permeability and acidic pH-dependent solubility.

3.6 Clinical Toxicology and Pharmacokinetics - Phase I and II Trials

PF-804 has been administered to over 260 patients in the phase I and phase II clinical trials. Overall, PF-804 is well tolerated. The observed toxicity profile is consistent with other EGFR-directed tyrosine kinase inhibitors. The most common adverse events that have been reported were gastrointestinal disorders (79.1%) and skin-related toxicities (75.5%). Gastrointestinal disorders included diarrhea (70.0%), stomatitis (29.3%), nausea (23.2%) and vomiting (11.8%). Skin-related toxicities included rash (45.6%), dry skin (27.4%) and acneiform dermatitis (21.7%). Most adverse events were mild to moderate. Severe adverse events that have been reported include diarrhea (9.9%), acneiform dermatitis (4.9%) and rash (4.4%).

Evidence of clinical activity in patients with NSCLC after failure of prior chemotherapy and EGFR-directed treatment include the observation of durable partial responses and disease control (PFS 12-13 weeks) in trials A7471001, A7471002 and A7471003.
3.7 Pharmaceutical Data

Supplied: 15 mg tablets are supplied

Dose: The recommended phase II dose of single agent PF-804 is 45 mg, administered once daily, continuously.

Stability: Expiry dates are provided on the investigational product label. Stability may be extended during the conduct of the study. Centres will be informed as such data becomes available and advised as to any required procedures.

Storage: Stored as per labeled conditions.

Route of Administration: Oral.
4.0 TRIAL DESIGN

This is a double blind, randomized phase III trial of PF-804 versus matched placebo in patients with incurable, stage IIIB/IV, non-small cell lung cancer for which they have failed standard therapy for advanced or metastatic disease.

4.1 Stratification

Patients will be stratified by:
- centre
- performance status (0 or 1 vs. 2 or 3)
- tobacco use (never vs. past or present)
- best response to prior EGFR TKI (PD vs. other)
- weight loss (< 5% vs. ≥ 5% or unknown)
- ethnicity (east Asian vs. other)

4.2 Randomization

Patients will be randomized 2:1, and will continue PF-804/placebo until either unmanageable toxicity or progression, to a planned total sample size of 720.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>PF-804</td>
<td>45mg</td>
<td>PO</td>
<td>Until unmanageable toxicity or progression</td>
</tr>
<tr>
<td>B</td>
<td>Placebo</td>
<td></td>
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</tr>
</tbody>
</table>
5.0 STUDY POPULATION

This is a double blind, placebo controlled, randomized trial of PF-804 in patients with incurable stage IIIB/IV non-small cell lung cancer who have failed standard therapy for advanced or metastatic disease.

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 calling for 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 Histologically confirmed diagnosis of non-small cell carcinoma of the lung. Patients must have an adequate histopathology or cytology specimen (see section 13), must consent to release of all specimens for this protocol, and the centre/pathologist must have agreed to submission of the specimens.

5.1.2 Patients must have evidence of disease, but measurable disease is not mandatory. To be considered evaluable for complete or partial response assessment, patients must have at least one measurable lesion as follows:

- X-ray ≥ 20 mm
- Spiral CT scan or physical exam ≥ 10 mm (lymph nodes must be ≥ 15 mm in the short axis)

Measurable lesions must be outside a previous radiotherapy field if they are the sole site of disease, unless disease progression has been documented.

5.1.3 Male or female, 18 years of age or older.

5.1.4 ECOG performance status of 0, 1, 2 or 3 (See Appendix II). Patients with performance status of 3 are eligible providing that the investigator attests that the patient has a reasonable life expectancy (≥ 6 weeks).

5.1.5 Adequate renal and hepatic functions as defined by the following required laboratory values obtained within 14 days prior to randomization. If anemic, patients should be asymptomatic and should not be decompensated.

- Creatinine < 1.5 upper limit of normal
- Total bilirubin < 1.5 upper limit of normal
- ALT (SGPT) < 2.5 times the upper limit of normal.

Note: If clearly attributable to liver metastasis, ALT (SGPT) values < 5 times the upper limit of normal are permitted.
5.1.6 Previous Therapy

Failure of a treatment regimen is defined as the inability to continue a regimen for any reason including, but not limited to, progressive disease, toxicity, or patient request. Up to a maximum of three lines of chemotherapy for advanced/metastatic disease (defined below) and at least one of erlotinib or gefitinib for advanced/metastatic disease (defined below) should have failed.

Exchange of one chemotherapy agent for another within a combination chemotherapy regimen is not considered a new regimen in the following circumstances
- carboplatin is substituted for cisplatin due to nephrotoxicity
- one agent in the combination regimen is changed due to hypersensitivity occurring in the first cycle.

Chemotherapy for Advanced/Metastatic Disease:
Patients must have recovered from any reversible toxic effects and at least 21 days must have elapsed from the last dose and prior to randomization (14 days from the last dose for chemotherapy regimens administered on a weekly schedule). Further palliative cytotoxic chemotherapy must not be planned.

Patients < 70 years:
- Must have received 1 and up to a maximum of 3 prior chemotherapy regimens (at least one of the three must have been a combination regimen and at least one must have contained platinum).

Patients ≥ 70 years (generally accepted as being at the time of the administration of the first regimen of chemotherapy for advanced disease):
- Must have received 1 and up to a maximum of 3 prior chemotherapy regimens for their disease.
  These may have been single agent chemotherapy regimens and a platinum agent is not required in keeping with current standards of practice.

Adjuvant Chemotherapy: Patients may ALSO have had prior adjuvant therapy for completely resected disease, providing completed at least 12 months prior to randomization. Adjuvant regimens < 12 months prior to randomization and combined chemotherapy/radiation regimens for irresectable locally advanced stage III disease (irrespective of timing), are considered to be for advanced/metastatic disease and constitute one of the 3 permissible regimens. Patients must have recovered from any reversible treatment related toxicities prior to randomization.

EGFR Inhibitor Therapy: Patients may only be enrolled after failure of prior gefitinib or erlotinib for advanced or metastatic disease. Patients who have received adjuvant gefitinib or erlotinib for completely resected NSCLC and who have recurred < 12 months after discontinuing erlotinib or gefitinib are eligible. Patients who received gefitinib or erlotinib for neodjuvant therapy only are not eligible. EGFR inhibitor therapy must have been discontinued at least 21 days prior to randomization.
Patients who discontinued prior gefitinib or erlotinib therapy for severe or life threatening organ toxicity are not eligible. Patients may also have received other EGFR active agents (such as reversible oral agents or monoclonal antibodies or vaccines) in addition to erlotinib or gefitinib but may not have received ANY prior irreversible EGFR inhibitor such as BIBW2992, HKI-272 (neratinib).
Maintenance Therapy: The same chemotherapy or agent/s continued for longer than 4-6 cycles for the purposes of ‘maintenance’ is considered one regimen; if another chemotherapy agent is given with ‘maintenance’ intent, it is considered a second regimen providing that ‘failure’ is documented. Patients who received erlotinib or gefitinib with ‘maintenance’ intent after completion of 1st line chemotherapy are eligible providing that ‘failure’ is documented.

Radiation: Patients may have had prior radiation therapy provided that a minimum of 14 days has elapsed between the end of radiotherapy and randomization onto the study. (Exceptions may be made however, for low dose, non-myelosuppressive radiotherapy – please call the NCIC CTG at 613-533-6430 PRIOR to randomization if questions arise about the interpretation of this criterion). Patients must have recovered from any acute toxic effects from radiation prior to randomization.

Previous Surgery: Previous surgery is permitted provided that wound healing has occurred and at least 14 days have elapsed (major surgery).

5.1.7 Patient able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires. The baseline assessment must already have been completed. Inability (illiteracy, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

5.1.8 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.

5.1.9 Patients must be accessible for treatment and follow-up. All randomized patients must be followed and treated at participating centres. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.10 In accordance with NCIC CTG 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 receiving concurrent treatment with other experimental drugs or anti-cancer therapy.
5.2.2 Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects). Patients with a significant cardiac history, even if controlled, should have a LVEF > 50%.

5.2.3 Patients with untreated brain or meningeal metastases are not eligible (CT scans are not required to rule this out unless there is a clinical suspicion of CNS disease). Patients with treated CNS disease who have radiologic or clinical evidence of stable brain metastases, with no evidence of cavitation or hemorrhage in the brain lesion, are eligible providing that they are asymptomatic and do not require corticosteroids (must have discontinued steroids at least 1 week prior to randomization).

5.2.4 Patients with active or uncontrolled infections, or with serious illnesses or medical conditions which would not permit the patient to be managed according to the protocol, including
- Severe dry eye syndrome
- Keratoconjunctivitis sicca
- Sjogren’s syndrome
- Severe exposure keratopathy
- Disorders that might increase the risk for epithelium-related complications (e.g., bullous keratopathy, aniridia, severe chemical burns, neutrophilic keratitis)
- Uncontrolled inflammatory gastrointestinal diseases (Crohn's, ulcerative colitis etc)
- Prior pneumonitis/ILD secondary to EGFR inhibitors

5.2.5 Mean QTc with Bazett's correction > 470msec in screening ECG or history of familial long QT syndrome.

5.2.6 Drugs that are highly dependent on CYP2D6 for metabolism are prohibited, since PF-804 is a potent CYP2D6 inhibitor in in vitro assays. These inhibitors or inducers are prohibited from 7 days prior to randomization until the end of treatment with PF-804. These include: S-metoprolol, propafenone, timolol, amitriptyline, clomipramine, desipramine, imipramine, paroxetine, haloperidol, risperidone, thioridazine, codeine, flecainide, mexiletine, tamoxifen, venlafaxine. Lidocaine may be used with clinical monitoring (including telemetry). Opiates such as morphine, oxycodone, dihydrocodeine, hydrocodone, and tramadol can be used as substitutes to replace codeine. Use of these opiates should be monitored for altered analgesia during treatment with PF-804 as they may be partly metabolized by CYP2D6. If PF-804 is administered with drugs which are P-glycoprotein (P-gp) substrates and have a narrow therapeutic index, monitoring for exaggerated effect and/or toxicities is recommended.

5.2.7 Pregnancy or inadequate contraception. Women must be post-menopausal, surgically sterile, or use two reliable forms of contraception. Women of child-bearing potential must have a pregnancy test taken and proven negative within 7 days prior to randomization. Men must be surgically sterile or use a barrier method of contraception.
6.0 PRE-TREATMENT EVALUATION  
(See Appendix I)

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History and Physical Exam including:</strong></td>
<td></td>
</tr>
<tr>
<td>history, height, weight, performance status, clinical tumour measurements</td>
<td>within 14 days prior to randomization</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>CBC, differential</td>
<td>within 14 days prior to randomization</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, LDH, albumin</td>
<td>within 21 days prior to randomization</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
</tr>
<tr>
<td>CT scan chest and upper abdomen, other scans to document disease</td>
<td>within 21 days prior to randomization</td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>Within 12 weeks prior to randomization</td>
</tr>
<tr>
<td>pregnancy test</td>
<td>within 7 days prior to randomization</td>
</tr>
<tr>
<td>urinalysis</td>
<td>within 14 days prior to randomization</td>
</tr>
<tr>
<td>ECG to exclude prolonged QTc</td>
<td>within 14 days prior to randomization</td>
</tr>
<tr>
<td>blood, serum and plasma sample for banking and correlative studies</td>
<td>within 14 days prior to randomization</td>
</tr>
<tr>
<td>archival tissue for banking</td>
<td>within 14 days prior to randomization</td>
</tr>
<tr>
<td>Biopsy if no archival tissue</td>
<td>within 14 days prior to randomization</td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td></td>
</tr>
<tr>
<td>baseline toxicity evaluation (to document residual toxicity from previous therapy and baseline symptoms)</td>
<td>within 24 hours before first treatment</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30 + QLQ-LC13 + trial specific checklist.</td>
<td>within 14 days of randomization</td>
</tr>
<tr>
<td><strong>Health Economics</strong></td>
<td></td>
</tr>
<tr>
<td>Health Utilities Index (EQ-5D)</td>
<td>within 14 days of randomization</td>
</tr>
</tbody>
</table>

1 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).
2 Optional
3 MUGA or ECHO, only for patients with significant cardiac history.
4 Women of childbearing potential only (urine or serum test acceptable).
5 Adverse events to be evaluated using the NCI CTCAE version 4.0.
6 Canada and Australia only
7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done by the NCIC CTG by means of the Mango web-based, password-operated electronic patient allocation system.

To start the Mango Patient Allocation System, go to the NCIC CTG Website. Near the top of the NCIC CTG Website is an icon for accessing Mango. Alternatively, this can be accessed through the following: https://mango.ctg.queens.ca/mango/mango.php.

The userid and password provided to each user by the NCIC CTG must be used to sign on. The userids are not case sensitive, but the passwords are.

At the time of randomization, complete the eligibility checklist electronically in the Mango Patient Allocation System.

If there is any difficulty in accessing Mango, randomizations may be obtained by calling the NCIC CTG Clinical Trials Assistant at 613-533-6430 or by faxing a complete paper copy of the Eligibility Worksheet to 613-533-2941.

The following information will be required:
• trial code (NCIC CTG BR.26)
• treatment centre and investigator
• date of REB approval for study at participating centre
• patient's initials, hospital number (if permitted by the local REB) and NCIC CTG serial number
• confirmation of the requirements listed in section 5.0, including dates of essential tests and actual laboratory values
• completed eligibility checklist
• stratification parameters
• height and weight

7.2 Stratification

Patients will be stratified by:
• centre
• performance status (0 or 1 vs. 2 or 3)
• tobacco use (never vs. past or present)
• best response to prior EGFR TKI (PD vs. other)
• weight loss (< 5% vs. ≥ 5% or unknown)
• ethnicity (east Asian vs. other)
7.3 Randomization

Randomization will be given by the NCIC CTG website.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient’s data be withdrawn. 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.
8.0 TREATMENT PLAN

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

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

8.1 Treatment Plan

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>PF-804</td>
<td>45 mg daily</td>
<td>PO</td>
<td>Until unmanageable toxicity or progression</td>
</tr>
<tr>
<td>B</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.1.1 PF-804/Placebo Administration

Patients will be instructed to take PF-804/placebo drugs orally with approximately 240 ml of water whilst in an upright position. The tablet should be swallowed whole and not chewed, crushed or divided. Patients should take their medication no less than 2 hour prior to the consumption of a meal (defined as ≥ 500 Kcals) or more than 2 hours after a meal has been ingested. Patients will be instructed to take their medication at approximately the same time each morning.

Whilst on study, the daily treatment schedule should be maintained whenever possible. If a patient misses their scheduled dose of PF-804/placebo this will not be made up and they should take their next dose at the scheduled time. Missed doses must be documented on the appropriate CRF and diary card.

8.1.2 Premedication

Nausea and vomiting: Patients will not be routinely pre-medicated, when taking PF-804/placebo, for nausea and vomiting. However, if a patient experiences nausea and/or vomiting, anti-emetics should be introduced and could be used prophylactically for subsequent cycles.

All pre-medications must be recorded on the patient’s case report form.
8.1.3 **Blinding / Unblinding**

PF-804 and matching placebo are identical in appearance as are the bottles in which they are provided. Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician. Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind must first be discussed with the NCIC CTG. For any treatment code unblinding, the reason and parties involved must be documented in the patient’s medical record. Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the patient. The NCIC CTG must be notified as soon as possible of any emergency situation in which the drug code was broken. See List of Contacts for details.

8.1.4 **Dose Adjustments (Both Arms)**

The expected adverse events of PF-804 are: skin toxicity (including hand-foot syndrome), diarrhea, cheilitis, fatigue, stomatitis, vomiting, paronychiae, anorexia, dysgeusia, abdominal pain, headache, epistaxis, VTE, nausea, dehydration, abnormal liver and renal function tests and ocular toxicity. For other reported adverse events please consult the most recent Investigator’s Brochure (IB).

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) (see Appendix V).

The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

The dose levels of PF-804/placebo are 45 mg (kit contains 3 x 15 mg tablets per day), 30 mg (kit contains 2 x 15 mg tablets per day and 15 mg (kit contains 1 x 15 mg tablets per day). Doses of PF-804/placebo may not be escalated after a dose reduction for toxicity.
Diarrhea Management and Dose Adjustments:

Patients should be provided with clear instructions on the management of diarrhea as indicated in the table below.

<table>
<thead>
<tr>
<th>Grade of Event</th>
<th>Management / Next Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Loperamide*** 4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night the patient may take 4 mg of loperamide every 4 hours. Fluid intake of ± 2 L should be maintained to avoid dehydration. PF-804/placebo should be continued.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Loperamide*** as above. If not improved to ≤ grade 1 within 24 hrs, hold PF-804/placebo until grade 1 and resume at same dose. Fluid intake of ± 2 L should be maintained to avoid dehydration. Monitor patient closely and consider intravenous hydration. If diarrhea recurs, reduce 1 dose level.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Loperamide*** as above. Hold* until &lt; grade 2 – resume at 1 dose level lower**. Fluid intake of ± 2 L should be maintained, intravenously if necessary. Consider octreotide or other management of diarrhea. Consider hospitalization if does not improve to grade 2 within 24 hours.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Off protocol therapy.</td>
</tr>
</tbody>
</table>

* Patients requiring a hold of > 3 weeks should go off protocol therapy.
** See section 8.1.4 for dose levels.
*** Other regimens may be used if centre practice.

Rash Management and Dose Adjustments:

Use of an alcohol-free, thick emollient cream on dry areas is suggested, beginning at start of treatment, to reduce development of pruritis. Avoidance of sunbathing or tanning is required, and the use of a sunscreen during times of anticipated sun exposure of SPF-15 or higher, preferably containing zinc oxide or titanium dioxide, is advised.

Patients should be provided with clear instructions on the management of rash as indicated in the table below.

<table>
<thead>
<tr>
<th>Grade of Event</th>
<th>Management / Next Dose</th>
</tr>
</thead>
</table>
| Grade 1        | • Topical 1% to 2.5% hydrocortisone cream and/or clindamycin 1% gel should be considered ***
                  • If no improvement after 2 weeks, treat as for grade 2. |
| Grade 2 or asymptomatic grade 3 | • Add hydrocortisone 2.5% or clindamycin 1% gel, or pimecrolimus 1% cream is advised; PLUS doxycycline 100 mg BID or minocycline 100 mg BID; ***
                  • If no improvement after two weeks, consider dose reduction ± dose hold |
| Symptomatic Grade 3 | • Consider dose reduction
                  • Consider methylprednisolone ***
                  • If no improvement after 2 weeks, hold until recovery ≤ grade 2 and the restart at a one dose level dose reduction ** |
| Grade 4        | • Off protocol therapy. |

* Patients requiring a hold of > 3 weeks should go off protocol therapy.
** See section 8.1.4 for dose levels.
*** Other regimens may be used if centre practice.
Ocular Toxicity, Management and Dose Adjustments:

<table>
<thead>
<tr>
<th>Grade of Event</th>
<th>Management / Next Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>No action</td>
</tr>
</tbody>
</table>
| Grade 2***     | • Preservative free artificial tears, ointments, and /or other therapies as clinically indicated.  
                 • If no recovery to ≤ grade 1 within 2 weeks, hold PF-804/placebo until ≤ grade 1 and then reduce ** one dose level. |
| Grade 3***     | • Hold PF-804/placebo until ≤ grade 1 and then resume at a 1 dose level reduction **.  
                 • Preservative free artificial tears, ointments, and /or other therapies as clinically indicated. |
| Grade 4        | Off protocol therapy    |

* Patients requiring a hold of > 3 weeks should go off protocol therapy.
** See section 8.1.4 for dose levels.
*** Ophthalmology exam within 2 weeks to include slit-lamp and fundoscopic exam recommended

Interstitial Lung Disease (ILD):
If a patient experiences unexplained acute or progressive respiratory symptoms (for example, dyspnea, cough and fever), PF-804/placebo should be interrupted pending investigation for ILD. If ILD is diagnosed, PF-804/placebo should be discontinued and the patient should receive treatment for ILD as appropriate.

Other toxicity:

<table>
<thead>
<tr>
<th>Grade of Event</th>
<th>Management / Next Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ Grade 1</td>
<td>Symptomatic care – no change in dose</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Treat symptomatically. If the adverse event doesn’t immediately resolve to ≤ grade 1, then hold PF-804/placebo until grade 1 and resume at same dose. If adverse event recurs, consider dose reduction.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold* until &lt; grade 2 – resume at 1 dose level lower**</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Off protocol therapy</td>
</tr>
</tbody>
</table>

* Patients requiring a hold of > 3 weeks should go off protocol therapy.
** See section 8.1.4 for dose levels.

8.1.5 Duration of Therapy
Treatment will continue until criteria for the removal from protocol treatment have been met (see section 12.1).

8.1.6 Patient Compliance
Treatment compliance will be monitored by review of the patient diary.

8.2 Concomitant Therapy

8.2.1 Permitted
• Patients may receive ongoing supportive and palliative care (e.g. pain control) as clinically indicated throughout the study.
• Patients who develop urgent local complications in previously documented sites of disease may receive palliative radiation therapy. Continuation on protocol therapy, if medically appropriate, will be determined by discussion with the NCIC CTG and investigators.
8.2.2 **Not Permitted**

- Other anti-cancer treatment at time of registration to this trial or while patient is taking PF-804/Placebo.

- Other investigational therapy.

- Drugs that are highly dependent on CYP2D6 for metabolism are prohibited, since PF-804 is a potent CYP2D6 inhibitor in in vitro assays. These inhibitors or inducers are prohibited from 7 days prior to randomization until the end of treatment with PF-804/placebo. These include: S-metoprolol, propafenone, timolol, amitriptyline, clomipramine, desipramine, imipramine, paroxetine, haloperidol, risperidone, thioridazine, codeine, flecainide, mexiletine, tamoxifen, venlafaxine. Lidocaine may be used with clinical monitoring (including telemetry). Opiates such as morphine, oxycodone, dihydrocodeine, hydrocodone, and tramadol can be used as substitutes to replace codeine. Use of these opiates should be monitored for altered analgesia during treatment with PF-804/placebo as they may be partly metabolized by CYP2D6.

- If PF-804/placebo is administered with drugs which are P-glycoprotein (P-gp) substrates and have a narrow therapeutic index, monitoring for exaggerated effect and/or toxicities is recommended.
## 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

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical Exam including:</td>
<td></td>
</tr>
<tr>
<td>• weight, performance status</td>
<td>day 1 each cycle ¹</td>
</tr>
<tr>
<td>• clinical tumour measurements</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>• CBC, differential</td>
<td>day 1 each cycle ¹</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
</tr>
<tr>
<td>• serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, LDH ², albumin</td>
<td>day 1 each cycle ¹</td>
</tr>
<tr>
<td>Radiology ³</td>
<td></td>
</tr>
<tr>
<td>• CT scan chest [upper abdomen if involved]</td>
<td>At the end of cycle 1 and 2 and then every second cycle</td>
</tr>
<tr>
<td>• other scans to document disease</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>• ECG</td>
<td>as clinically indicated</td>
</tr>
<tr>
<td>• pregnancy test</td>
<td>at investigator discretion</td>
</tr>
<tr>
<td>• blood, serum and plasma samples for banking and correlative studies</td>
<td>day 1 every second cycle</td>
</tr>
<tr>
<td>Health Economics ⁴</td>
<td></td>
</tr>
<tr>
<td>• Health Utilities Index (EQ-5D)</td>
<td>day 1 cycle 2 and each subsequent cycle</td>
</tr>
<tr>
<td>• Resource Utilization Assessment</td>
<td>each cycle</td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
</tr>
<tr>
<td>• EORTC QLQ-C30 + QLQ-LC13 + trial specific checklist.</td>
<td>day 1 cycle 2 and each subsequent cycle</td>
</tr>
<tr>
<td>• Subject blinding question</td>
<td>Day 1 cycle 2</td>
</tr>
<tr>
<td>Patient Drug Administration Diary</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Adverse Events ⁵</td>
<td>Patients must be evaluated continuously for adverse events.</td>
</tr>
</tbody>
</table>

¹ 1 cycle = 28 days, more frequently if clinically indicated.
² Optional
³ To ensure comparability, the baseline imaging and subsequent imaging 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). Bone scans do not need to be repeated routinely except to confirm CR or PR (mandatory, positive scans only) or as clinically indicated.
⁴ Canada and Australia only
⁵ Adverse events will be recorded and graded according to the NCI CTCAE Version 4.0 (Appendix V)
### 9.1.1 Evaluation During Protocol Treatment for Patients Continuing on PF-804 AFTER Unblinding

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical Exam including:</td>
<td></td>
</tr>
<tr>
<td>• As per local clinical practice</td>
<td>Once every 12 weeks</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>• CBC, differential</td>
<td>Once every 12 weeks or more frequently if clinically indicated</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
</tr>
<tr>
<td>• Serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, LDH (^1), albumin</td>
<td>Once every 12 weeks or more frequently if clinically indicated</td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
</tr>
<tr>
<td>• CT scan chest [upper abdomen if involved]</td>
<td>As per local standard of care.(^3)</td>
</tr>
<tr>
<td>• other scans to document disease</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>• ECG</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>• Pregnancy test</td>
<td>At investigator discretion</td>
</tr>
<tr>
<td>Adverse Events (^2)</td>
<td>Patients must be evaluated for AEs considered possibly, probably or definitely related to protocol treatment and SAEs must be reported as per section 11.</td>
</tr>
</tbody>
</table>

\(^1\) Optional

\(^2\) Adverse events will be recorded and graded according to the NCI CTCAE Version 4.0 (Appendix V)

\(^3\) RECIST 1.1 measurements not required
### 9.2 Evaluation After Protocol Treatment

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History and Physical Exam including:</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• weight, performance status, clinical tumour measurements</td>
<td>each visit</td>
</tr>
<tr>
<td>• clinical tumour measurements</td>
<td>every 12 weeks until PD</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>• CBC, differential</td>
<td>4 week follow up only</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>• serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, LDH&lt;sup&gt;2&lt;/sup&gt;, albumin</td>
<td>4 week follow up only</td>
</tr>
<tr>
<td><strong>Radiology</strong>&lt;sup&gt;1,6&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• CT scan chest [upper abdomen if involved]</td>
<td>every 12 weeks until PD</td>
</tr>
<tr>
<td>• other scans to document disease</td>
<td></td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>• blood, serum and plasma samples for banking and correlative studies&lt;sup&gt;6&lt;/sup&gt;</td>
<td>4 week follow up if not done at off treatment</td>
</tr>
<tr>
<td>• ECG</td>
<td>as clinically indicated at 4 week follow up only</td>
</tr>
<tr>
<td>• pregnancy test</td>
<td>at investigator discretion</td>
</tr>
<tr>
<td><strong>Health Economics</strong>&lt;sup&gt;3,6&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Health Utilities Index (EQ-5D)</td>
<td>4 week follow up then every 12 weeks until PD</td>
</tr>
<tr>
<td>• Resource Utilization Assessment</td>
<td>Note: Final EQ-5D Questionnaire and Resource Utilization Assessment must be completed within 2 weeks of PD. Complete at 4 week visit after off treatment ONLY if not already completed within 2 weeks of PD.</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30+ QLQ-LC13 + trial specific checklist</td>
<td>4 week follow up and then every 12 weeks until PD</td>
</tr>
<tr>
<td>Note: Final QoL Questionnaire must be completed within 2 weeks of PD. Complete at 4 week visit after off treatment ONLY if not already completed within 2 weeks of PD.</td>
<td></td>
</tr>
</tbody>
</table>

| Adverse Events<sup>4</sup> | Patients must be evaluated for adverse events at each visit. |

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1 To ensure comparability, the baseline imaging and subsequent imaging 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). Bone scans do not need to be repeated routinely except to confirm CR or PR (mandatory, positive scans only) or as clinically indicated.

2 Optional

3 Canada and Australia only.

4 Adverse events will be recorded and graded according to the NCI CTCAE Version 4.0 (Appendix V).

5 For patients continuing on PF-804 after unblinding, only a 4 week follow up is required after discontinuation of PF-804 (4 weeks after last day of last treatment cycle).

6 Not applicable for patients continuing on PF-804 after unblinding.
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].

10.1.3 Evaluable for Quality of Life Assessment. All patients who have completed the quality of life questionnaire are evaluable for quality of life.

10.1.4 Evaluable for Subject Blinding Assessment. All patients who have completed the subject blinding questionnaire are evaluable for subject blinding analyses.

10.1.5 Evaluable for Health Utilities: All patients who have completed the baseline health utilities assessment questionnaire and at least one other health utilities assessment questionnaire are evaluable.

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 Tumours) 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 x-ray, and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are measurable only if identifiable soft tissue components meet these requirements. 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).

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 (LD)], 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 section 10.2.4).

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 all *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 PET scans before CR can be accepted.

*Partial Response (PR):* at least a 30% decrease in the sum of measures (LD for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum LD. Non target lesions must be non-PD. Confirmation of response is not required as this is a randomized study.

*Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of LD on study.

*Progressive Disease (PD):* at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded on study (including baseline) AND an absolute increase of ≥ 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 ± 75% 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.
### Target Lesions

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
<th>Best Response for this category also requires</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td>Normalization of tumour markers, tumour nodes &lt; 10mm</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Not all evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD/ not all evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD/ not all evaluated</td>
<td>No</td>
<td>SD</td>
<td>documented at least once &gt; 4 wks. from baseline</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Any</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Any</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

### Non target lesions ONLY

<table>
<thead>
<tr>
<th>No Target</th>
<th>CR</th>
<th>No</th>
<th>CR</th>
<th>Normalization of tumour markers, tumour nodes &lt; 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Target</td>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>Non-CR/ non-PD</td>
<td></td>
</tr>
<tr>
<td>No Target</td>
<td>Not all evaluated</td>
<td>No</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>No Target</td>
<td>Unequivocal PD</td>
<td>Any</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>No Target</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

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 start of treatment (or randomization for randomized studies) 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 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).

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 Tumour Markers. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

10.5.7 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

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

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 NCIC CTG SAE form. The term ‘reportable SAE’ is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to NCIC CTG.

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 serious adverse event occurring after this 30-day period which is 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 judgment 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.

Note: Adverse events which are unequivocally related to the underlying malignancy or disease progression are NOT reportable Serious Adverse Events. These include such adverse events as admission for pain control, palliative care or paracentesis of malignant effusions. However, all deaths within 30 days of the last dose of protocol therapy must be reported as a Serious Adverse Event.
11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported as follows:

Within 24 hours: Submit Serious Adverse Event Report Form by Electronic Data Capture (EDC). If EDC is not available, FAX to:

Alexander Montenegro, Study Co-ordinator, or
Dr. Penny Bradbury, Physician Co-ordinator
NCIC Clinical Trials Group
FAX: 613-533-2941

OR in accordance with local procedures for centres outside of Canada.

Within 7 days: Submit Final Serious Adverse Event form (signed by the investigator and updated as much as possible).

11.3 Reporting Malignancies or Myeloid Dysplasia

Malignancies or myeloid dysplasia that are unexpected AND related to protocol treatment in the opinion of the investigator must be reported as Serious Adverse Events as described in section 11.0 and 11.2 within 15 working days of when diagnosis is known to the investigator. Other malignancies occurring or recurring during the trial, which are considered unrelated or expected should only be reported on the case report form.

11.4 NCIC CTG Responsibilities for Reporting Serious Adverse Events to Health Canada and Regulatory Authorities

The NCIC CTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) and local country sponsors (for submission to applicable regulatory authorities) 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 can not be ruled out).

11.5 NCIC CTG Reporting Responsibility to Pfizer

Pfizer will be notified of all protocol reportable serious adverse events (Section 11.1) within one working day of receipt by NCIC CTG.

11.6 Pfizer Reporting Responsibilities

Pfizer will notify NCIC CTG of all Safety Letters / Safety Updates from other studies with PF-804 reported to regulatory authorities.

11.7 Reporting Serious Adverse Events to Local Research Ethics Boards

NCIC CTG will notify all 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 as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Drug Brochure. The date of REB Submission for SAEs and SUs will need to be entered into the NCIC CTG trial BR.26 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.
For this purpose, the REB submission template letter provided by NCIC CTG should be used. Please note:

- this letter must be either printed on institutional letterhead or contain the centre identification/REB name;
- the date of REB submission must be provided;
- this form must be signed by one of the approved participants (according to the participants list) for this trial.

The submission of these 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 notice will be regarded as delinquent.
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 judgment of the investigator, affects assessments of clinical status to a significant degree, and requires discontinuation of protocol therapy.
- Unacceptable toxicity as defined in section 8.0.
- Tumour progression or disease recurrence as defined in section 10.0.
- Clinical Progression (CP): clinically significant deterioration in performance status, analgesic use or pain, maintained for at least 2 weeks believed to be related to progression of malignancy.
- Request by the patient.
- Pregnancy.

12.2 Therapy After Protocol Treatment is Stopped

Treatment after disease progression has been documented and all protocol therapy has been discontinued is at the discretion of the investigator.

12.3 Follow-up Off Protocol Treatment

Refer to section 9.2 and Appendices I and IV for details of follow up and required investigations.

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.
13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

Central radiology review may be conducted.

13.2 Central Pathology Review

There will be no central pathology review for this study.

13.3 Correlative Studies

A detailed Correlative Studies Manual will be provided at centre activation, which will include details on sample preparation, handling and shipping.

13.3.1 Tissue Collection

The collection of tissue is a mandatory part of this trial. Biopsy will be required if no block is available. If feasible, investigators are encouraged to consider an additional biopsy of accessible tumour tissue prior to enrolment (i.e., after EGFRI exposure). If more than one block is available, all blocks should be submitted and clearly identified as initial, post chemotherapy, post EGFRI etc.

Specimens will be carefully banked as part of the NCIC CTG tissue/tumour bank at Queen’s University in Kingston, Ontario. Tumour blocks are the preferred material to collect, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

The tissue may be used by researchers now or in the future to better understand the nature of cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. 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 the surgical/ histology number and/or patient initials. Material issued to researchers will be identified by a coded number only.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen’s Department of Pathology to pathology departments for a representative tumour block.

Testing 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 is collected will be aware of this retrieval and will have given their consent.
High priority assays include \textit{KRAS} mutations and EGFR mutations in exon 18-21. In addition, other mutations will be screened for using a mass-spectrometry based mutation analysis platform. RT-PCR, immunohistochemistry and FISH may also be performed if tissue is available exploring EGFR, HER2, MET, IGF1R, PTEN and HGF.

13.3.2 \textit{Blood / Serum / Plasma Banking}

Blood, serum and plasma samples will be collected and banked for planned and future studies from all patients. Samples will be taken at baseline and every second cycle until off treatment.

Potential studies include: \textit{KRAS} mutations, EGFR mutations and SNPs, serum EGFR extracellular domain (ECD), serum HER2 ECD, E-cadherin ELISAs, TGF-a and HGF.
14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This is a randomized, double blind, placebo controlled study of PF-804 in patients with non-small cell lung cancer who have failed chemotherapy (at least one prior regimen, but no more than three prior regimens) and an EGFRI for advanced or metastatic disease. Patients will be randomized to receive either PF-804 (ARM A) or placebo (ARM B) in a 2:1 ratio using the dynamic minimization method.

The primary objective is to assess the effect of PF-804 by comparing overall survival between ARM A and ARM B among all randomized patients. Secondary analyses will be conducted in KRAS-WT type patients.

14.2 Sample Size and Power

The sample size for this study is determined to compare overall survival between patients randomized to ARM A and patients randomized to ARM B. The median survival of patients on the placebo arm was estimated to be 4 months.

In order to have 90% power to detect a 33% improvement with PF-804 (i.e. from 4 months to 5.3 months) using a 1-sided 2.5% level significance test, we need to observe a minimum of 581 deaths before the final analysis. Assuming that we would enter a total of 28 patients a month, the required number of deaths would be observed by accruing 720 patients over 26 months and following all of them for at least 6 months after accrual is closed. The final analysis will be performed when 581 deaths are observed. The total duration of the trial is estimated to be around 34 months. The sample size was not adjusted for interim analysis outlined in section 14.3.1 as the futility analysis will not inflate type I error, the significance level for final test will remain as 2.5%.

In BR.21, 85% of patients with tissue and successful KRAS assays were KRAS-WT. Not all patients will have usable tissue, and not all assays will be successful. A conservative estimate is that at least 390 patients will have successful assays and be KRAS WT. If 345 deaths are observed in these patients we will have 85% power to detect a 40% improvement in OS (i.e. HR=0.71).

14.3 Endpoints and Analysis

Overall survival, which is defined as the time from the randomization to the death of any cause, is the primary endpoint of this study. Patients who are alive at the time of final analysis will be censored at their last contact date. All randomized patients will be included in the analysis of overall survival. A Kaplan-Meier curve for proportions of survival in each treatment arm will be displayed. The 95% confidence intervals for the median survival will be computed using the method of Brookmeyer and Crowley. In the primary analysis, the two treatment arms will be compared using the log-rank test stratified by ECOG PS (0, 1 vs. 2+), and ethnicity (East Asian vs. other), (stratification factors) as well as patient’s KRAS status (mutated vs. unknown vs. WT) at baseline. The effect of other stratification factors, study centre and other potential prognostic factors on overall survival will be assessed using Cox regression. The Schoenfeld residual plots will be used to check the model assumption for the Cox regression. As a robust analysis, Log-rank test will also be performed without adjusting those stratification factors in test the difference between 2 treatment arms. Sensitivity analyses will be conducted exploring the impact of subsequent anti-cancer therapies. Similar analyses will be conducted in the KRAS-WT population.
Progression free survival (PFS) is one of the secondary endpoints. It is defined as the time from randomization to the first observation of disease progression or death due to any cause. A patient who stops treatment with study drug and goes on to receive alternative therapy for NSCLC, prior to documentation of disease progression, will be censored on the date alternative therapy began. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All analyses for overall survival will be similarly performed for progression free survival.

Patients will be evaluable for objective tumour response if they have at least one measurable lesion at baseline and have at least one disease assessment after baseline. In addition, patients who develop PD prior to this time will also be considered evaluable for response. The response rate will be estimated as the proportion of patients evaluable for response who meet the criteria of complete or partial response. A Cochran-Mantel-Haenszel test will be used to compare tumour response rate between arms adjusting all stratification factors of ECOG PS and ethnicity plus patient’s KRAS status at baseline.

Duration of response will be calculated for all patients achieving a PR or CR. Duration of PR/CR is defined as the time from first objective status assessment of CR/PR to the first time disease progression is documented or death among those who have achieved a PR or CR. A patient who stops treatment with all study drugs and goes on to receive alternative therapy for NSCLC, prior to documentation of disease progression, will be censored on the date alternative therapy. If a patient has not progressed or died, the duration of response will be censored on the date of the last known alive date. Summary statistics for duration of response will be presented by treatment arm.

All patients who receive at least one dose of PF-804/placebo will be included in the safety analysis. Descriptive summary tables will be presented on safety parameters by treatment arm. Toxicity rates will be compared between treatment arms using the Fisher’s Exact Test or Chi-square test, as needed. There will be safety monitoring by the NCIC CTG Data Safety Monitoring Committee (DSMC) every 6 months.

Safety and efficacy data will be correlated with compliance as documented by pill counts recorded on the CRF.

14.3.1 **Interim Analyses**

An interim analysis will be performed when around 300 events (disease progression or death) have occurred. A futility test would close the trial if the observed HR for PFS is > 0.67. Otherwise, the trial would continue to full accrual. If the true HR for PFS is 0.57 (i.e. increase in PFS for placebo from a predicted 2 months to 3.5 months) we will have 90% power to continue to final analysis. The study will not be stopped at the IA for efficacy. The projected analysis time is when around 360 patients are accrued to the trial. The significant level for the final analysis will be 0.025.

14.3.2 **Quality of Life Analyses**

The quality of life (QoL) of patients will be assessed using EORTC QLQ-C30 [Aaronson 1993] and the lung cancer module (QLQ-LC13) questionnaires plus additional study specific questions.
The EORTC QLQ-C30 is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100. The QLQ-LC13 lung cancer module ([Bergman, 1994]) includes questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The validity and reliability have been studied by the EORTC Study Group on Quality of Life. The EORTC QLQ-C30 and module will be scored according to the EORTC QLQ-C30 Scoring Manual, and analyzed accordingly.

The primary end point of the QoL analysis is defined as the time from randomization to deterioration in the following three common lung cancer symptoms: cough (Question 1 in QLQ-LC13), dyspnea (Question 8 in QLQ-C30), and pain (Questions 9 and 19 in QLQ-C30). Patients will be considered as deteriorated for a given symptom if their change score from baseline was 10 points or worse at any time-point after baseline. For each symptom, all patients who have a baseline and at least one follow-up QOL assessment for this symptom will be included in the time-to deterioration analysis. Patients will be censored at the time of the last QOL questionnaire completion if they had not deteriorated before that. The log-rank test will be the primary method to compare the time to deterioration in each symptom between the two treatment arms. The Hochberg procedure ([Hochberg 1988]) will be used to adjust the P values of the log-rank tests for these three comparisons. In addition, NCIC CTG specified QoL response analysis ([Osoba 2005]) will also be performed.

14.3.3 Subject Blinding Analyses

The proportion of subjects who correctly and incorrectly determine whether they are on PF-804 or placebo will be compared.

The self-reported factors affecting subjects’ response to the first ‘yes/no’ question will be tallied, and compared between those who correctly and incorrectly determined that they were on PF-804 or placebo.

14.3.4 Economic Analyses

The purpose of the NCIC CTG economic evaluation is to determine the incremental cost-effectiveness and cost-utility of PF-804 from a government payer perspective, over a lifetime time horizon by prospectively collecting economic and resource utilization information during the clinical trial. The objectives are:

a) determine an incremental cost effectiveness ratio reported as a cost per life-year (LY) gained of PF-804 vs. best supportive care (BSC). A cost-effectiveness analysis will be conducted. The mean overall cost per patient for each of the two study treatment arms will be calculated to determine the addition cost per life-year gained.

b) determine an incremental cost utility ratio in cost per quality-adjusted life-year (QALY) gained of PF-804 vs. BSC. A cost-utility analysis will be conducted. Preference weights for comparator arms will be determined through the US Valuation of the EuroQol EQ-5D Health States, with EQ-5D scores taken directly from the study database. Quality-adjusted survival in the two treatment arms will be generated by multiplying the utility value by the amount of time spent in that utility state. The mean incremental cost per QALY in the study will be calculated. [S. Valuation of the EuroQol EQ-5D Health States, December 2005.]
The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Major drivers of medical care costs, namely hospitalization, chemotherapy and survival, will be varied ± 20%, to examine the impact on the base-case incremental cost effectiveness ratios (ICERs). Bootstrapping and the development of a cost-effectiveness acceptability curve will also be conducted.

In addition to the planned NCIC CTG analyses, Pfizer will conduct standard analyses to support regulatory submissions where applicable.

14.3.5 Correlative Studies

For all patients, tumour tissue as well as baseline and serial whole blood, serum and plasma will be collected and banked.
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 NCIC Clinical Trials Group, NHMRC CTC, ALTG and Pfizer 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.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.

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 Clinical Trials Group of the NCIC and the NHMRC Clinical Trials Centre under the auspices of the Australasian Lung 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 the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the NCIC CTG physician and study coordinator, and approval of the study chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.
16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Institution Eligibility for Participation

Selected member centres in good standing of the NCIC CTG are eligible to participate in this study. Any centre joining the NCIC CTG is required to sign a Participating Centre Study Agreement and have Standard Operating Procedures regarding the conduct of clinical trials.

The NCIC CTG will submit via fax to Health Canada for each participating Canadian centre prior to local activation a completed Health Canada Clinical Trial Site Information Form.

16.2 Investigator Qualifications

For all investigators (principal investigators and co-investigators) the following documentation must be on file with the NCIC CTG:

- A current curriculum vitae, updated and submitted within two years at the time of randomization.
- Documentation indicating completion of training in the protection of human research participants (e.g. NCI U.S. Completion Certificate).
- Completion of the required NCIC CTG GCP training modules.

For the principal investigator only:

- A Health Canada Qualified Investigator Undertaking Form must be completed and signed by the principal investigator of the study at participating Canadian centres and received by the NCIC CTG central office before that centre can be locally activated.

16.3 REB (Research Ethics Board) Approval for Protocols

Each participating centre will have on file with the NCIC CTG central office, as part of its membership/ agreement documents, a description of its ethics review process and composition of its REB.

**REB Composition (Canada)**

Membership of a REB approving this protocol must be consistent with Canadian regulatory requirements, summarized as follows:

- at least 5 members;
- majority of members are Canadian citizens or permanent residents;
- includes 2 members whose primary expertise and experience are in a scientific discipline with broad experience in the methods and areas of research to be approved (1 of these is from a medical discipline);
- includes 1 member knowledgeable in ethics;
- includes 1 member knowledgeable in Canadian laws relevant to the biomedical research to be approved;
- includes 1 member whose primary experience and expertise are in a non-scientific discipline;
- includes 1 member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the NCIC CTG or the centre where the clinical trial is to be conducted.
A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation to the following may be included in the signed local ethics approval document:

- The membership of the Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations;
- The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice; and
- The Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified investigator named at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

This documentation must be received by the NCIC CTG central office before the centre can be locally activated.

**Initial Approval**
Member centres wishing to participate in a trial are required to obtain full board local ethics approval of the protocol and consent form (see below) by the appropriate REB.

**Annual Re-Approvals**
Annual re-approval must continue until NCIC CTG informs you that they are no longer required.

**Amendments/Administrative Updates**
All amendments or administrative updates to the protocol must undergo review by local REBs. Amendments/administrative updates will be circulated to all participating sites in a standard format with clear instructions regarding REB review. If full board approval of an amendment is required it will be specified.

Amendments will be reviewed and approved by Health Canada prior to central implementation of the amendment, and by REBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects. Amendments will be distributed with Health Canada REB attestation forms which must be completed. For each amendment NCIC CTG will collect documentation of REB approval, a completed REB attestation form, and the date the amendment is locally activated.

**REB Refusals**
If an REB refuses to approve this protocol (or an amendment/administrative update to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to Health Canada.

**Serious Adverse Events, Safety Updates, Investigator Brochure Updates and Product Monograph Updates**
During the course of the study serious adverse events, safety updates, investigator brochure updates or product monographs may be sent to you for reporting to your REB. The date of REB submission for these documents will need to be entered into the NCIC CTG trial BR.26 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.
16.4 Informed Consent

**Informed Consent Document**
The REB of an institution must approve the consent form document which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB approval.

It is essential that the consent form contain a clear statement which gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the NCIC CTG and other agencies as necessary. The consent form must include all ICH-GCP consent elements. In addition, the consent form should include all elements required by NCIC CTG policy, and centres receiving funding from NCEHR, SSHRC and/or CIHR should include elements from the Tri Council Policy Statement (TCPS).

Informed consent forms that do not contain all ICH-GCP required elements will require an amendment and will lead to the delay of local activation. A complete list of the elements required by regulations, guidelines and NCIC CTG policy can be found by accessing the NCIC CTG website at [http://www.ctg.queensu.ca/private/ethics/consent_RE_Checklists.html](http://www.ctg.queensu.ca/private/ethics/consent_RE_Checklists.html).

**Consent Process/Patient Eligibility**
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.

16.5 Retention of Patient Records and Study Files

ICH Good Clinical Practice guidelines apply to NCIC CTG studies. It is the responsibility of NCIC CTG to inform the investigator/institution as to when trial related records no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

NCIC CTG will notify all the trial investigators/institutions and all the regulatory authorities if clinical development of an investigational product discontinues or when trial related records no longer need to be retained.

16.6 Centre Performance Monitoring

This trial is eligible for inclusion in the Centre Performance Index. There are minimum standards for performance.

Data is to be submitted by electronic data capture (EDC) according to the schedule in Appendix IV (Documentation for Study).
16.7 **On-Site Monitoring/Auditing**

In addition to the routine review of case report forms and supporting documents sent to the central office, NCIC CTG site monitoring will be conducted at participating centres in the course of the study as part of the overall quality assurance programme. The monitors/auditors will require access to patient medical records to verify the data, as well as pharmacy, essential document binders, standard operating procedures (including electronic information) and ethics documentation.

Your site may be subject to an inspection by regulatory authorities and audits by NCIC CTG, Pfizer, or NCIC CTG designated organisations.

16.8 **Case Report Forms**

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection (including SAE reporting unless indicated otherwise on the BR.26 website) except Quality of Life and Health Utilities. For details of accessing the EDC system and completing the on-line forms please refer to the "Data Collection Guidebook" posted on the BR.26 area of the NCIC CTG web-site (www.ctg.queensu.ca).

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


Byington R.P.,Curb J.D., Mattson, M.E. Assessment of double-blindness in the conclusion of the β-blocker heart attack trial, JAMA 1985; 253 (12): 1733-1736


## APPENDIX I - PATIENT EVALUATION FLOW SHEET

<table>
<thead>
<tr>
<th>Required Investigations</th>
<th>Prestudy</th>
<th>Day 1 of each cycle (Every 28 days)</th>
<th>Follow up Visit (4 weeks from day 28 of last treatment cycle)</th>
<th>12-Weekly</th>
<th>On PF-804 after unblinding 12 weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History and physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>ECOG Performance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical tumour measurements</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test (if applicable)</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hematology</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biochemistry</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, LDH (optional), albumin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scan of chest and upper abdomen&lt;sup&gt;4&lt;/sup&gt;</td>
<td>X</td>
<td>X&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other scans to document disease</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVEF</td>
<td>X&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>as clinically indicated</td>
<td>as clinically indicated</td>
<td></td>
<td>as clinically indicated</td>
</tr>
<tr>
<td>Blood, serum and plasma for banking and correlative studies</td>
<td>X</td>
<td>X&lt;sup&gt;8&lt;/sup&gt;</td>
<td>X&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archival tissue for banking or biopsy if no archival tissue</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuously graded and recorded according to CTCAE V.4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Questionnaires</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life – (EORTC QLQ C-30, LC-13 and trial specific checklist.)</td>
<td>X</td>
<td>X&lt;sup&gt;10&lt;/sup&gt;</td>
<td>X&lt;sup&gt;11&lt;/sup&gt;</td>
<td>X&lt;sup&gt;11&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Health Utilities Index (EQ-5D)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>X</td>
<td>X&lt;sup&gt;10&lt;/sup&gt;</td>
<td>X&lt;sup&gt;11&lt;/sup&gt;</td>
<td>X&lt;sup&gt;11&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Resource Utilization Assessment&lt;sup&gt;14&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X&lt;sup&gt;11&lt;/sup&gt;</td>
<td>X&lt;sup&gt;11&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Subject Blinding Question</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Drug Diary</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Continued on next page...*
1. Not required at 4 week follow up visit or after if PD previously documented.
2. Pregnancy test is only required for women of child bearing potential and should be repeated at investigator’s discretion.
3. Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
4. Include upper abdomen at baseline. Thereafter repeat CT chest. Repeat abdomen if involved Bone scans do not need to be repeated routinely except to confirm CR and PR (mandatory for positive scan only) or as clinically indicated.
5. Radiologic assessment to be done at the end of the cycle 1 and 2 and then every second cycle (e.g. at cycles 4, 6, 8, etc.)
6. Required every 12 weeks until PD.
7. MUGA or ECHO only for patients with significant cardiac history.
8. Required day 1 of every SECOND cycle.
9. 4 week follow up if not done at off treatment.
10. Day 1 cycle 2 and each subsequent cycle.
11. 4 week follow up then every 12 weeks until PD, Quality of Life Questionnaire and Resource Utilization Assessment must be completed within 2 weeks of PD. Complete at 4 week visit after off treatment ONLY if not already completed within 2 weeks of PD.
12. Last question on QoL questionnaire, to be completed only on Day 1 cycle 2.
13. To be completed daily by the patient. To be collected and reviewed for compliance each cycle.
14. Canada and Australia only
15. For patients continuing on PF-804 after unblinding: 12 weekly review during PF-804 treatment and 4 week follow up post discontinuation of PF-804 only.
16. As per local standard clinical practice.
17. Patients must be evaluated for adverse events considered possibly, probably or definitely related to protocol treatment and SAEs must be reported as per section 11.
APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

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

<table>
<thead>
<tr>
<th>ECOG (Zubrod)</th>
<th>Karnofsky</th>
<th>Lansky*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Description</td>
<td>Score</td>
</tr>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>1</td>
<td>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.</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.
APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

General and Drug Accountability

Investigational product (PF-804/placebo) should be stored in a secure area according to local regulations and under the storage conditions stipulated on the investigational product label. It is the responsibility of the Investigator to ensure that investigational product is dispensed only to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Drug accountability logs will be supplied on the BR26 website. Accountability will be maintained and each kit will be treated as a unit dose containers (i.e. bottles and/or pills will not be shared between patients).

The health care professional will determine the appropriate kit (45 mg, 30 mg or 15 mg) to dispense to the patient at the beginning of each cycle. This information will be recorded on the Drug Dispensing Log. The health care professional will instruct the patient that all dispensed bottles must be returned at each follow-up visit, at which time a tablet count will be conducted to assure patient dosing compliance.

Destruction and Return of Investigational Product

• Patients must return all unused study medication and empty containers to the investigator or pharmacist. Returned study medication and empty containers should be kept at the centre until a monitor has visited the center and completed drug accountability on the patient returns.
• All unused or returned study medication, after accountability and reconciliation should be destroyed locally. Destruction of study medication must not take place without accountability and reconciliation by the monitor and the completion of a drug return/disposal form. A copy will be kept with the centre files.
• At the end of the study, it must be possible to reconcile delivery records with records of usage/returned stock by completion of the study drug accountability form. Any discrepancies must be accounted for. At the end of the study, after the monitor has completed drug accountability a copy will be kept with the centre files.

Distribution

Drug will be distributed by NCIC CTG or designee to each participating centre. Start up supplies will be dispatched upon receipt at NCIC CTG or designee of all required regulatory documentation including copies of REB approval and the REB-approved consent form. Full details regarding drug reordering will be supplied at study initiation and will involve the use of the NCIC CTG website.
Follow-up is required for patients from the time of randomization and will apply to all randomized patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except Quality of Life and SAE reporting. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Randomization and Data Management Guidebook" posted on the BR.26 area of the NCIC CTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial are as follows:

<table>
<thead>
<tr>
<th>Form</th>
<th>Timing</th>
<th>To be Submitted Electronically</th>
<th>Supporting Documentation Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Report</td>
<td>Within 2 weeks of randomization</td>
<td></td>
<td>Copies of signed consent form and tissue banking consent, relevant pathology (all centres), and radiology reports</td>
</tr>
<tr>
<td>Banking</td>
<td>Within 2 weeks of randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Report &amp; Resource Utilization Assessment</td>
<td>Every 28 days***</td>
<td>Within 2 weeks of end of cycle</td>
<td>Relevant radiology reports♦♦</td>
</tr>
<tr>
<td>End of Treatment Report</td>
<td>End of Treatment</td>
<td>Within 2 weeks of end of treatment</td>
<td></td>
</tr>
<tr>
<td>4 Week Follow Up Report &amp; Resource Utilization Assessment</td>
<td>4 weeks from day 28 of last treatment cycle♦</td>
<td>Within 2 weeks of follow-up visit</td>
<td></td>
</tr>
<tr>
<td>Correlative Studies</td>
<td>See sections 6.0 and 9.0</td>
<td>To be submitted with the corresponding Reports</td>
<td></td>
</tr>
<tr>
<td>Follow-up Report &amp; Resource Utilization Assessment♦♦</td>
<td>Every 12 weeks until PD (4 week follow up/ End of Treatment Report)</td>
<td>Within 4 weeks of follow-up visit</td>
<td>Relevant radiology reports♦♦</td>
</tr>
<tr>
<td>Short Follow-up Report♦♦</td>
<td>Every 12 weeks after progression</td>
<td>Within 4 weeks of follow-up visit</td>
<td></td>
</tr>
<tr>
<td>Death Report♦♦</td>
<td>When patient dies*</td>
<td>Within 4 weeks of patient’s death</td>
<td>Copy of post mortem report if performed</td>
</tr>
<tr>
<td>Relapse/Disease Progression Report♦♦</td>
<td>Upon disease progression</td>
<td>Within 4 weeks of progression</td>
<td>Relevant radiology and pathology reports</td>
</tr>
<tr>
<td>Serious Adverse Event Report Form</td>
<td>At time of event and reported to NCIC CTG</td>
<td>Within 1 working day**</td>
<td></td>
</tr>
</tbody>
</table>

* It is the investigators responsibility to investigate and report the date and cause of death of any patient entered into this trial.
** See Section 11.0 Serious Adverse Event Reporting for details.
*** Every 12 weeks for patients continuing on PF-804 after unblinding and Resource Utilization Assessment is not required.
♦ 4 weeks from last day of last treatment cycle for patients continuing on PF-804 after unblinding.
♦♦ Not required for patients continuing on PF-804 after unblinding.
♦♦♦ Only required for patients continuing on PF-804 after unblinding if patient dies before being permanently removed from PF-804 treatment or within the four week follow up period.
The **PAPER CRFs** to be used in this trial are as follows:

<table>
<thead>
<tr>
<th>Paper Form</th>
<th>To be Completed</th>
<th>Due in NCIC CTG Central Office</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life (EORTC QLQ-C30 + QLQ-LC13 + trial specific checklist)*</td>
<td>See sections 6.0 and 9.0</td>
<td>Mail as soon as the corresponding report (i.e. baseline report, treatment report) has been submitted electronically</td>
</tr>
<tr>
<td>Health Utilities Index (EQ-5D)</td>
<td>See sections 6.0 and 9.0</td>
<td>Mail as soon as the corresponding report (i.e. baseline report, treatment report) has been submitted electronically</td>
</tr>
</tbody>
</table>

* Not required for patients continuing on PF-804 after unblinding.
APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
VERSION 4.0 (CTCAE)

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) for adverse events and serious adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page: http://ctep.cancer.gov/reporting/ctc.html. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.
APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

Quality of life data are collected for research purposes, and will usually not be used for the patient’s individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization or pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.
2. Pretreatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

*It defeats the whole purpose of the assessment if it is delayed until the patient feels better!*

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

*If yes,* mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.
If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed not to coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.
Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: **BR.26**

This **page** to be completed by the Clinical Research Associate

---

### Patient Information

<table>
<thead>
<tr>
<th>NCIC CTG Patient Serial No:</th>
<th>Hospital No:</th>
<th>Patient Initials:</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________</td>
<td>______________</td>
<td>________________</td>
</tr>
</tbody>
</table>

* (if permitted by REB)  

<table>
<thead>
<tr>
<th>Institution:</th>
<th>Investigator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________</td>
<td>___________________________</td>
</tr>
</tbody>
</table>

---

Scheduled time to obtain quality of life assessment: please check (3)

☐ Prior to randomization

*During treatment:*

☐ Day 1 cycle 2   ☐ Day 1 cycle 3   ☐ Day 1 cycle 4   ☐ Day 1 cycle 5   ☐ Day 1 cycle 6

☐ Day 1 cycle 7   ☐ Day 1 cycle 8   ☐ Day 1 cycle 9   ☐ Day 1 cycle _____

*Off Treatment (until PD):*

☐ at time of progression (must be completed at PD, unless done within 2 weeks of PD)

☐ at week 4  

then  ☐ wk 12   ☐ wk 24   ☐ wk 36   ☐ wk 48   ☐ wk 60   ☐ wk 72   ☐ wk 84   ☐ wk 96   ☐ wk ______

Were ALL questions answered?  ____ Yes  ____ No  

If no, reason: ____________________________________________

Was assistance required?  ____ Yes  ____ No  

If yes, reason: ____________________________________________

Where was questionnaire completed:  ☐ home   ☐ clinic   ☐ another centre

Comments: ________________________________________________

---

Date Completed:  __ __ __ __ - __ __ __ - __ __

**yyyy  mmm  dd**

*PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.*

---

**NCIC CTG use only**

Logged: _____  

Study Coord: _____  

Res Assoc: _____  

Data Ent’d:  

Verif:  

_____ - _____ - _____  

_____ - _____ - _____  

_____ - _____ - _____  

_____ - _____ - _____  

_____ - _____ - _____  

_____ - _____ - _____
European Organization for Research and Treatment of Cancer (EORTC)

**Quality of Life Questionnaire (BR.26)**

We are interested in some things about you and your health. Please answer all the questions *yourself* by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best *single* response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you need to stay in a bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Have you had pain?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhea?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you.

<table>
<thead>
<tr>
<th>Question</th>
<th>Number Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>29. How would you rate your overall health during the past week?</td>
<td>Very Poor</td>
</tr>
<tr>
<td></td>
<td>Excellent</td>
</tr>
<tr>
<td>30. How would you rate your overall quality of life during the past week?</td>
<td>Very Poor</td>
</tr>
<tr>
<td></td>
<td>Excellent</td>
</tr>
</tbody>
</table>
Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

<table>
<thead>
<tr>
<th>During the past week:</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. How much did you cough?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you cough blood?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Were you short of breath when you rested?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Were you short of breath when you walked?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Were you short of breath when you climbed stairs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Have you had a sore mouth or tongue?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Have you had trouble swallowing?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Have you had tingling hands or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Have you had hair loss?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Have you had pain in your chest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Have you had pain in your arm or shoulder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Have you had pain in other parts of your body?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, where?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Did you take any medicine for pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 No</td>
<td>2 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, how much did it help?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>44. Have you had sore skin?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Have you had itchy skin?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Has your skin affected your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please answer the next question on day one before your SECOND CYCLE of treatment ONLY

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you think you were receiving PF-804 (i.e. active drug)?</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Why? (please tick all applicable items)

- [ ] The effects my treatment had on my cancer
- [ ] The effects my treatment had on my symptoms
- [ ] The side effects I experienced
- [ ] Other (please specify) ________________________________

Please fill in your initials to indicate that you have completed this questionnaire: ______________

Today's date (Year, Month, Day): ________________________________

Thank you.
APPENDIX VII - HEALTH UTILITIES ASSESSMENT

Introduction

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, progression free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations
- to evaluate the extent of change in health benefits of an individual, group, or population across time
- to evaluate new treatments, technologies, and patient management strategies
- to support approval of new drug applications or patient management strategies
- to try to provide the best value for health care dollars within and across diseases and health
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

Health utilities data are collected for research purposes, and will not be used for the patient’s individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.
The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, eg: psychological distress, social disruption, symptoms, side-effects, et cetera.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule (4 week follow up then every 12 weeks until PD. Final questionnaire must be completed with in 2 weeks of PD. Complete at 4 week visit after off treatment ONLY if not already completed within 2 weeks of PD).

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If...

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.
There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

D. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic.
6. **Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)**

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.
Health Utilities Questionnaire – ENGLISH

NCIC CTG Trial: **BR.26**

This **page** to be completed by the Clinical Research Associate

**Patient Information**

NCIC CTG Patient Serial No: ___________ Hospital No.: ___________ Patient Initials: ___________ (first-middle-last)
Institution: ___________________________________________ Investigator: ______________________________

Scheduled time to obtain health utilities assessment: please check (✓)

☐ Prior to randomization

During chemotherapy:

☐ Day 1 cycle 2  ☐ Day 1 cycle 3  ☐ Day 1 cycle 4  ☐ Day 1 cycle 5  ☐ Day 1 cycle 6
☐ Day 1 cycle 7  ☐ Day 1 cycle 8  ☐ Day 1 cycle 9  ☐ Day 1 cycle _____

Off Treatment (until PD):

☐ at time of progression (must be completed at PD, unless done within 2 weeks of PD)
☐ at week 4
then  ☐ wk 12  ☐ wk 24  ☐ wk 36  ☐ wk 48  ☐ wk 60  ☐ wk 72  ☐ wk 84  ☐ wk 96  ☐ wk ______

Were **ALL** questions answered?  ☐ Yes  ☐ No  If no, reason: ______________________________________

Was assistance required?  ☐ Yes  ☐ No  If yes, reason: ______________________________________

Where was questionnaire completed:  ☐ home  ☐ clinic  ☐ another centre

Comments: ____________________________________________________________________________________
_____________________________________________________________________________________________

Date Completed:  __ __ __ __ - __ __ __ - __ __

**PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.**

**NCIC CTG use only**

Logged: _______ Study Coord: _______ Res Assoc: _______ Data Ent’d: _______ Verif: _______

_______-____-____  _______ - ____-____  _______ - ____-____  _______ - ____-____  _______  _______
Health Questionnaire

*(Canadian English version)*

© 1990 EuroQol Group. *EQ-5D™ is a trade mark of the EuroQol Group*
By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

© 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group
To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.
APPENDIX VIII - 6TH EDITION OF THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 6th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org/cstage/CSManual010400.pdf). These staging criteria should be used for new trials.
## LIST OF CONTACTS

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<tr>
<td>(including eligibility questions and protocol management)</td>
<td>Alexander Montenegro Study Coordinator NCIC CTG Email: <a href="mailto:amontenegro@ctg.queensu.ca">amontenegro@ctg.queensu.ca</a> or WenLing Liu Study Coordinator NCIC CTG Email: <a href="mailto:wliu@ctg.queensu.ca">wliu@ctg.queensu.ca</a> or: Dr. Penny Bradbury Physician Coordinator NCIC CTG Email: <a href="mailto:pbradbury@ctg.queensu.ca">pbradbury@ctg.queensu.ca</a></td>
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