The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small cell lung cancer and brain metastases

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CLINICAL PROTOCOL

PHASE 3, RANDOMIZED, OPEN-LABEL STUDY OF THE EFFICACY AND SAFETY OF PF-02341066 VERSUS STANDARD OF CARE CHEMOTHERPAY (PEMETREXED OR DOCETAXEL) IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) HARBORING A TRANSLOCATION OR INVERSION EVENT INVOLVING THE ANAPLASTIC LYMPHOMA KINASE (ALK) GENE LOCUS

Compound:	PF-02341066
Compound Name (if applicable):	N/A
US IND Number (if applicable):	73,544
Protocol Number:	A8081007
EudraCT Number:	2009-012595-27
Phase:	Phase 3

Document History

Document	Version Date	Summary of Changes
Amendment 13	31 December 2012	Modifications have been made to this global amendment based on Amendment 11(France only), eg, updated safety information about Hy's Law cases). As the primary endpoint of the study was recently met, a reduced schedule of assessments for ongoing patients in Arm A has been provided. The total number of OS events required to conduct the final OS analysis has been revised. Detailed description of patients of child bearing potential language as an inclusion criteria and detailed contraception guidelines were introduced to ensure consistency with updated Pfizer protocol. Text was added or replaced to ensure consistency with updated Pfizer protocol template language especially with respect to medication error, and SAE reporting for Oncology studies after the active safety reporting period was clarified. Use of prophylactic antiemetics and concomitant acetaminophen/paracetamol was clarified. Prohibited medications by topical administration added. Pregnancy testing in response to IRBs/IECs and/or local regulations was clarified. Reporting of local cardiologist manual ECG overread was clarified. Requirements for data retention were revised in consistency with the updated Pfizer protocol template language. Corrections of typographical errors/omissions and other administrative inconsistencies were made throughout the protocol.

Amendment 12	22 October 2012	Withdrawn
Amendment 11	21 March 2012 (Country Specific; France Only)	Modifications were made for French sites only: safety information about Hy's Law cases provided and dose modification rules were revised for patients with drug-related ALT increases.
Amendment 10	09 November 2011	Planned interim analysis removed and study design assumptions revised after consultation and approval by the US Food and Drug Administration. As a result, sample size requirement has been updated. Time to tumor response was added as a secondary endpoint. Duration of survival evaluation period was extended. Revised monitoring guidance for Hy's Law and new safety and monitoring guidance for complex renal cysts development was added. Added language regarding the Internal Oncology Business Unit Safety Data Monitoring Committee. Text modified in some sections to ensure compliance with the Sponsor protocol template.
Amendment 9	12 January 2011	Dose modifications for crizotinib updated; dose administration guidelines for docetaxel and pemetrexed updated; safety guidelines for potential cases of drug-induced liver injury added; washout for palliative radiation changed.
Amendment 8	5 August 2010	Additional safety monitoring for the potential AEs of pneumonitis were added and an exclusion criterion to exclude patients with known interstitial fibrosis or interstitial lung

		disease was added.
Amendment 7	22 June 2010	The patient-reported VSAQ-ALK was included, additional ECG monitoring was added for patients with QTc >500 msec, modifications of the eligibility criteria (which included cutoffs for hemoglobin and platelet counts) were included, washout period for cardiovascular (CV) or cerebrovascular events was decreased, hypertension exclusion criteria was deleted, all available scans were required to be reviewed by a third-party radiology laboratory, a treatment delay to up to 42 days without requiring discontinuation was now allowed; and metabolites of crizotinib were to be evaluated, if possible.
Amendment 6	8 March 2010 (Country Specific: Ireland Only)	Modifications were made for Ireland sites only to require all patients for Irish sites to have a MUGA test at scheduled times during the study.
Amendment 5	18 February 2010 (Country Specific: France Only)	Modifications were made for French sites only to require all patients in France to have both MUGA scans (or echocardiograms) and ophthalmology examinations at scheduled times during the study.
Amendment 4	26 January 2010	Update to pemetrexed dosing administration and contraception requirements based on approved packet insert.
Amendment 3	21 December 2009 (Country Specific: Japan)	Modifications were made for Japanese sites only regarding eligibility criteria.
Amendment 2	23 November 2009	RECIST version 1.0 changed to version 1.1; CTCAE criteria changed from version 3.0 to version 4.0;

		primary endpoint changed from ORR to PFS, as well as update to interim analysis timelines; randomization block design updated; survival follow up period revised; tumor assessments will now be based on calendar and not cycle; toxicity management for pemetrexed and docetaxel updated; wound healing timelines added; administration for PF-02341066 can now be with or without food; dose modification section for PF-02341066 updated based on safety database.
Amendment 1	3 August 2009	Protocol was updated based on feedback from a Special Protocol Assessment completed by the Federal Drug Administration (FDA). Specific changes were to central laboratory requirements for ALK testing; entry criteria modifications; survival analysis modifications; PK requirements updated; sample size for ECG substudy modified; independent radiology review requirements modified.
Original protocol	22 May 2009	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country Health Authorities, Institutional Review Boards, and Independent Ethics Committees

PROTOCOL SUMMARY

Indication

PF-02341066 is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of one prior chemotherapy regimen in patients with tumors harboring a translocation or inversion event involving the ALK gene locus.

Background and Rationale:

Non-small cell lung cancer (NSCLC) is the most common fatal malignancy in the United States accounting for nearly 30% of all cancer related deaths[1], and a frequent cause of mortality throughout the world. In 2007 there were 1.5 million new lung cancer cases diagnosed worldwide, with broad regional distribution.[2]

Approximately 85% of lung cancer is histologically defined as non-small cell and the remaining 15% as small cell. The majority of patients with NSCLC present with inoperable locally advanced (Stage IIIB) or metastatic (Stage IV) disease for which no curative treatment is available. In newly diagnosed patients, with good performance status, platinum-based doublet-combination chemotherapies are associated with a median overall survival (OS) of 7.4 to 9.9 months.[3, 4, 5, 6, 7, 8] With the addition of bevacizumab to chemotherapy, the resultant median OS was 12.5 months.[9] Three drugs (docetaxel, pemetrexed and erlotinib) have been approved by the FDA for patients with NSCLC after previous treatment with at least one prior chemotherapy regimen. The median progression-free survival (PFS) for these drugs ranged from 2.2 months for erlotinib[10] to 2.9 months for docetaxel or pemetrexed.[11]

An inversion within chromosome 2p resulting in the formation of a fusion gene product comprising portions of the echinoderm microtubule associated protein-like 4 (EML4) gene and the ALK gene was discovered in 2007 in NSCLC cell lines and archived clinical specimens.[12] A subsequent series of published studies indicated that EML4-ALK inversion events included 7 fusion variants, each comprised of the same portion of the ALK C-terminal kinase domain and each resulting in expression of catalytically active kinase fusion protein variants.[13, 14, 15, 16, 17] EML4-ALK fusion variants were demonstrated to transform NIH-3T3 fibroblasts [12]. Expression of EML4-ALK specifically in lung alveolar epithelial cells in transgenic mice demonstrated numerous bilateral lung adenocarcinomas with 100% penetrance only a few weeks after birth, confirming the potent oncogenic activity of the fusion kinase.[18] Although EML4 is the predominant fusion partner, other less common partners as well as yet unknown partners have also been reported [[19, 20, 21] and J. Iafrate, personal communication].

Collectively, a series of studies utilizing archived NSCLC specimens across a broad set of ethnicities indicated that the incidence of EML4-ALK inversion events ranged from 2-7% (mean 3.5%).[12, 13, 14, 15, 16, 17] A detailed review of these studies indicates that the prevalence of EML4-ALK inversion events in lung cancer is approximately 6,000 patients/year in the U.S. and up to 40,000 patients/year world wide.[12, 13, 14, 15, 16, 17] However, there are limitations to this estimation such as a small dataset (1500 tumor samples) and the different

methodologies used across studies.[12, 13, 14, 15, 16, 17] This collective group of studies also indicated that the vast majority of EML4-ALK fusion events were observed in lung adenocarcinoma specimens compared with squamous or small cell histologies.[12, 13, ,15, 16, 17] A subset of the studies also established a statistically significant correlation of EML4-ALK fusion events with never or light smoking status although some independent studies demonstrated inversion events were also observed in patients with a smoking history and/or reported that smoking status was not a statistically significant cofactor.[12 ,13, 16, 22] In addition, EML4-ALK is rarely coincident with EGFR, HER2, or KRAS mutations, indicating it is a distinct disease subtype.[22]

PF-02341066 is a selective ATP-competitive small-molecule inhibitor of c-Met/Hepatocyte Growth Factor Receptor (HGFR) and ALK tyrosine kinases and their oncogenic variants (eg, c-Met/HGFR mutant variants or ALK fusion proteins). Consistent with these mechanisms of action, PF-02341066 dose-dependently inhibits phosphorylation and kinase target dependent functions of c-Met/HGFR, ALK, and selected variants in tumor cells both in vitro and in vivo. PF-02341066 also exhibits potent and selective growth inhibitory activity against a subset of tumor cells exhibiting amplification of the c-Met/HGFR gene locus (IC_{50} value range = 30-120 nM) or translocation/inversion of the ALK gene locus (ie, EML4-ALK or NPM-ALK fusion variants; (IC_{50} = value range 40-450 nM). In addition, PF-02341066 demonstrates antitumor efficacy in mice implanted with xenografts of human tumors containing activated c-Met/HGFR or NPM-ALK, providing further rationale for study in clinical trials in molecularly selected patient populations.

An ongoing Phase 1 trial (A8081001) evaluating PF-02341066 as an oral single agent is being conducted to investigate safety, pharmacokinetics and pharmacodynamics in patients with advanced cancer (excluding leukemias). This trial includes a dose escalation component followed by a dose expansion component in a selected cohort of molecularly-defined patients referred to as the enriched population. During the dose escalation phase, PF-02341066 was administered under fasting conditions QD or BID on a continuous schedule. The objectives of the dose escalation component of the trial were to establish the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), and pharmacokinetics (PK) of PF-02341066 in patients with advanced cancer. Enrollment for the dose escalation part of the trial is complete and 37 patients have been dosed. Three DLTs have been observed including Grade 3 ALT increase in 1 patient at 200 mg QD and Grade 3 fatigue in 2 patients at 300 mg BID. The MTD was determined to be 250 mg BID administered in a continuous daily dosing regimen. The most common treatment-related adverse events were nausea, emesis, diarrhea, and fatigue, which were primarily Grade 1-2 in severity. Nausea and emesis were independent of dose or duration of treatment and were effectively managed using I.V. or oral anti-emetics. Treatment-related sight disturbances were observed in 6 patients and occurred at doses of 200 mg BID or above. All of these visual events were Grade 1 in severity and were reversible upon discontinuation of PF-02341066.

As of 15 May 2009, there were 31 patients enrolled in the enriched population cohort of the ongoing Phase 1 trial examining patients with tumors harboring c-Met amplification/gene mutation or EML4-ALK fusion variants. There are 27 NSCLC patients enrolled in this trial,

25 in the enriched population cohort and 2 in the dose escalation portion. These patients had a median of 3 previous treatments (range 1-7) with the majority exhibiting a previous treatment best response of stable disease (SD) or progressive disease (PD). In the ongoing Phase 1 trial, 10 EML4-ALK patients have currently experienced a PR (including 3 unconfirmed at the time of data cut-off). All PRs had occurred at the time of their first or second post-dose scan. The duration of response has ranged from 2+ to 23+ weeks. One of the responding patients experienced progressive disease as of the data cut-off date. In addition, 5 patients have/had stable disease as their best response (duration 8+, 8+, 16, 20 and 40 weeks). Ten patients have not yet had a post-dose scan and 4 patients had a best response of PD. There has also been 1 confirmed PR in a patient with inflammatory myofibroblastic tumor bearing an ALK rearrangement. This patient had debulking surgery after 40 weeks of treatment and has been treated with PF-02341066 for greater than 52 weeks.

Preliminary PK data are available for the first 56 patients enrolled in the ongoing Phase 1 trial. After oral administration of PF-02341066 on an empty stomach, peak plasma concentrations were reached at ~ 4 hours post dose and followed by a multi-exponential declining pattern with an average terminal half-life of 42 to 53 hours. Non-linearity of pharmacokinetics was observed at 50 and 100 mg QD doses as the AUC_{tau} and C_{max} increased more than proportionally with the dose. Patients receiving doses ranging from 100 mg QD to 300 mg BID generally demonstrated linear pharmacokinetics as evidenced by proportional increases in mean AUC_{tau} and C_{max} after single or multiple doses. The steady state condition appeared to be reached by Cycle 1 Day 15. The repeated administration at 250 mg BID for 15 days or longer produced a median trough plasma concentration of 249 ng/mL (44 nM, free drug), exceeding the target efficacious levels predicted for inhibition of ALK based on preclinical mouse tumor models.

PF-02341066 showed time-dependent inhibition of CYP3A isozymes in human liver microsomes with a k_{inact} of 0.11 min^{-1} and K_i of 3.0 μM. In order to assess the effect of PF-02341066 on CYP3A activity in the GI tract and the liver, the PK of midazolam (a CYP3A substrate probe) following a single oral 2 mg dose was evaluated before (Day -7) and after (Cycle 2 Day 1) repeated administration of PF-02341066 at 250 mg BID in 13 patients. A 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of PF-02341066 dosing at 250 mg BID, suggesting that PF-02341066 is a moderate inhibitor of CYP3A.

Results from a pilot food effect study suggested that co-administration with a standard high-fat meal appeared not to change the geometric mean of AUC_{24} and C_{max} of PF-02341066 following single 250-mg PF-02341066 doses in cancer patients.

As of 23 December 2011, there have been 5 patients (<1% of all patients treated with PF-02341006) with possible drug-induced severe hepatotoxicity, 2 of them with fatal outcome. Four of these patients had hepatic laboratory results meeting Hy's Law case criteria (ALT or AST >3 x ULN with concurrent total bilirubin >2 x ULN).

Additional information on PF-02341066 is available in the investigator's brochure and US package insert.

The level of activity with PF-02341066 in the enriched population in the Phase 1 trial suggests that NSCLC tumors containing a translocation or inversion event involving the ALK gene locus may be dependent on ALK signaling. Since the clinical activity of the agents available for second-line treatment in this subset of patients with ALK fusions is not known, it would be important to compare PF-02341066 to those agents as a therapeutic option for these patients.

Objectives:

Primary Objective:

- To demonstrate that PF-02341066 (Arm A) is superior to standard of care chemotherapy, pemetrexed or docetaxel (Arm B), in prolonging PFS in patients with advanced NSCLC whose tumors harbor a translocation or inversion event involving the ALK gene locus and who have received only one prior chemotherapy regimen for advanced NSCLC and this regimen must have been platinum-based.

Secondary Objectives:

- To compare secondary measures of clinical efficacy including overall survival (OS), objective response rate (ORR), and disease control rate (DCR) between the two treatment groups, and evaluate duration of response (DR) and time to tumor response (TTR).
- To assess the safety and tolerability of PF-02341066 compared to pemetrexed or docetaxel.
- To compare patient reported outcomes (PRO) of health-related quality of life (HRQoL), disease/treatment-related symptoms of lung cancer, and general health status in both treatment arms.
- To characterize the effects of PF-02341066 at therapeutic doses on QT interval in this patient population.
- To determine PK in this patient population using population PK (POPPK) methods and explore correlations between PK, response and/or safety findings.
- To explore the relationship of ALK gene fusion to the presence of ALK protein and fusion transcript.
- To correlate modulation of soluble biomarkers to PK and outcome measures.

Endpoints:

Primary Endpoint:

- PFS based on RECIST version 1.1 (confirmed by independent radiology review).

Secondary Endpoints:

- 6-month, and 1-year OS, OS, ORR (confirmed by independent radiology review), DCR at 6 and 12 weeks, DR and TTR.
- Type, incidence, severity, seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.
- Plasma concentrations of PF-02341066.
- QTc.
- Types of EML4-ALK fusion variants and ALK protein expression.
- Plasma concentrations of soluble c-Met ectodomain and HGF scatter proteins.
- Time to deterioration (TTD) in patient reported pain, dyspnea, and cough.
- HRQoL, lung cancer disease/treatment-related symptoms, and general health status.

Trial Design:

This is an open-label multi-center, randomized Phase 3 efficacy and safety study of PF-02341066 versus standard of care chemotherapy, pemetrexed or docetaxel, in patients with previously treated NSCLC whose tumors harbor ALK fusions.

A total of 318 patients will be randomized in a 1:1 ratio to receive PF-02341066 (Arm A) or pemetrexed or docetaxel (Arm B). For patients randomized to Arm B, the first choice will be pemetrexed. This is due to the docetaxel restrictive labeling for liver function test elevations and peripheral neuropathy. There are 2 exceptions: patients who have had pemetrexed as part of their prior chemotherapy regimen or patients who have received pemetrexed as maintenance therapy will receive docetaxel if randomized to Arm B. These patients will only be allowed to enter the study if they meet the liver function test and peripheral neuropathy eligibility criteria before being randomized. If they do not meet the docetaxel eligibility criteria, these patients will have the option to enroll in a single arm trial evaluating PF-02341066 (Protocol A8081005). Additionally, patients who have had docetaxel as part of their prior chemotherapy and have NSCLC that is predominantly squamous cell carcinoma will not be eligible for this trial but will have the option to enroll in Protocol A8081005.

The randomization will be stratified by ECOG performance status (0-1 vs 2), presence of brain metastases (presence vs absence) and previous treatment with an EGFR tyrosine kinase inhibitor (yes vs no). Each treatment cycle is defined as 21 days.

ALK break apart fluorescence in situ hybridization (FISH) assay will be used as the primary assay for detecting ALK fusion events in tumor samples for determining the eligibility of patients entering the trial. Clinical sites that have a local laboratory that can assess the ALK gene fusion by FISH may allow ALK fusion positive patients to initially enter the study

based on their results until the central laboratory, selected by the Sponsor, can accept samples for analysis. Clinical sites that do not have a local laboratory that can assess the ALK gene fusion by FISH may allow ALK fusion positive patients to initially enter the study based on the results from a secondary laboratory, selected by the Sponsor, until the central laboratory can accept samples for analysis. All positive samples, whether tested at the local or secondary laboratory, will still be sent to the central laboratory for analysis by FISH. Local and secondary laboratory test results will no longer be accepted once the central laboratory can accept samples for analysis.

The primary endpoint for this study was met in June 2012. Thus, upon approval of Amendment #13, patients in Arm A will no longer be required to have independent radiology review of images. In addition, a reduced schedule of assessments provided in Appendix 8 for patients in Arm A will now be used in place of Table 1.

Patients will continue with the assigned study treatment until RECIST-defined progression of disease as determined by independent radiology review, unacceptable toxicity or consent withdrawal. However, upon approval of Amendment #13, the requirement for independent radiology review will no longer be applicable for patients in Arm A. Patients may continue treatment as assigned beyond the time of RECIST-defined progression of disease, as determined by independent radiology review, at the discretion of the investigator if the patient is perceived to be experiencing clinical benefit. For these patients, tumor assessments will no longer be evaluated by an independent radiology laboratory. However, as noted above, upon approval of Amendment #13, the requirement for independent radiology review will no longer be applicable for patients in Arm A. In addition, patients in Arm B who have RECIST-defined progression of disease as determined by independent radiology review will have the option to enroll in Protocol A8081005.

Trial Treatments:

PF-02341066, 250 mg BID, will be administered orally at approximately the same time each day on a continuous daily dosing schedule, ie, no break in dosing. PF-02341066 can be dosed without regard to meals. Cycles are defined in 21-day periods to facilitate scheduling of visits and assessments.

Docetaxel, 75 mg/m^2, will be administered by intravenous infusion over 1 hour or according to institutional practices on Day 1 of a 21-day cycle. Patients will also be required to take dexamethasone, 8 mg orally, twice daily, the day before, the day of and the day after docetaxel dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethasone will be allowed per country regulations.

Pemetrexed, 500 mg/m^2, will be administered by intravenous infusion over 10 minutes or according to institutional practices on Day 1 of a 21-day cycle. Patients will also be required to take folic acid, 350-1000 μg orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. Vitamin B_{12}, 1000 μg, will be injected intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and will be repeated approximately every 9 weeks until

discontinuation. Patients will also be required to take dexamethasone, 4 mg orally, twice daily, the day before, the day of and the day after pemetrexed dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethsone will be allowed per country regulations.

Assessments:

See Table 1 for schedule of assessments. After approval of Amendment #13, refer to Appendix 8 for the reduced schedule of assessments for patients in Arm A. Patients in Arm B must continue to follow the schedule of assessments in Table 1.

Statistical Methods:

Sample Size Determination

The following assumptions are made: median PFS for Arm B is 4.5 months; accrual will be accomplished over a 20-month period and follow-up for PFS will continue for at least 4 months after the last patient is randomized. A total sample size of 288 patients (217 total PFS events) will provide 90% probability to demonstrate superiority of Arm A over Arm B, assuming a 1.56 fold improvement over Arm B in PFS based on a one-sided log- rank test at the 2.5% level of significance. To account for events being censored due to potential discordance between the investigators and independent radiology review, up to 30 extra patients will be enrolled for a total sample size of 318.

The median survival for Arm B is assumed to be 8 months.[11] With an overall one-sided α of 2.5% and one interim analysis (that was performed at the time of PFS analysis with all available OS events, corresponding to 40% of the required number of total OS events), the study will have 80% power to detect a 44% increase in OS when 238 deaths have occurred..

Statistical Analysis of Primary and Secondary Efficacy Endpoints

PFS will be summarized using the Kaplan-Meier method and displayed graphically. The median event time for each treatment arm and corresponding 2-sided 95% confidence interval (CI) for the median will be provided for PFS. A one-sided log-rank test stratified for baseline stratification factors will be used to compare PFS between the two treatment arms. The Cox regression model, stratified for baseline stratification factors, will be fitted, and the estimated hazard ratio and 2-sided 95% CI will be provided.

An unstratified log-rank test (one-sided, alpha = 0.025) and Cox regression model will also be used as secondary analyses for PFS. Additionally, a Cox regression model, stratified for baseline stratification factors, will be used to explore the potential influences of the other factors on the primary PFS endpoint.

Based on the full analysis population, the best response (CR, PR, SD or PD) per RECIST as determined by independent radiology review for each patient will be summarized by treatment arm. ORR will be calculated as the number of patients with a best response of CR or PR divided by the total number of randomized patients in each treatment group. The

corresponding exact 2-sided 95% confidence interval will be calculated using a method based on the F-distribution. DCR will be calculated as the number of patients with best response of CR, PR, or SD divided by the total number of randomized patients in each treatment group. Mantel Haenszel tests will be used to compare ORR and DCR between the treatment arms, using the randomization strata. The difference in ORR and DCR between the two treatment groups will be provided and the 95% confidence interval will be calculated based on the normal approximation.

OS will be analyzed similarly as described for PFS. A log-rank test, stratified by the randomization strata, will be used in analyzing OS, and RPSFTM (rank preserving structural failure time model[32]) may be used as a sensitivity analysis. For patients who enroll into A8081005 from Arm B after disease progression, their OS will be included in this analysis. DR will be calculated for the subgroup of patients with objective disease response and summarized using the Kaplan-Meier method. TTR will be calculated for the subgroup of patients with objective disease response and summarized using descriptive statistics.

The 6-month survival probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log [-log(6-months survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the 6-months survival probability itself. The 1-year survival probability will be estimated similarly.

The proportion of patients with each of the ALK fusion variants of the EML4-ALK fusion will be summarized, and their correlations with the clinical outcome will be evaluated. The relationship of EML4-ALK variants and ALK protein expression will be explored. The correlation between ALK protein expression and the clinical outcome will be evaluated.

TTD in patient reported pain, dyspnea, and cough will be defined as the time from randomization to the earliest time the patient's score shows a 10 point or higher increase after baseline. Patients will be censored at the last time when they completed an assessment for pain, dyspnea, and cough if they have not deteriorated. A 10 point or higher change in the score is perceived by patients as clinically significant. [23] TTD of the three pre-specified symptom (pain, dyspnea, and cough) scales will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will be provided for each symptom and the unstratified log-rank test will be the primary method to compare the time to first deterioration between the two treatment groups. The median time and 2-sided 95% CI for the median also will be provided based on the Brookmeyer Crowley method. The Hochberg procedure will be used to adjust for multiple comparisons.[24]

Patient-reported HRQoL, disease/treatment related symptoms of lung cancer, visual effects, and general health status will be assessed. Summary statistics (mean [and SE], median, range and 95% CI) of absolute scores will be reported for the items and scales of the European Organization for the Research and Treatment of Cancer (EORTC QLQ-C30) questionnaire, its lung cancer module (QLQ-LC13), EQ-5D VAS scale, and the newly developed visual symptom assessment questionnaire (VSAQ-ALK). The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Line charts depicting the

means and mean changes of subscales over time will be provided for each treatment arm. For the EQ-5D health state profiles, the proportions of patients reported having “no”, “some”, or “extreme” problems at each time point will be reported.

The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QOL, and single items of the EORTC QLQ-C30 and the LC-13 will be summarized in a table and compared between the two treatment arms. Additional analyses may be performed such as repeated measures mixed-effects modeling. Descriptive statistics will be reported by cycle for the items on the VSAQ-ALK.

Table 1. Schedule of Activities (Refer to Appendix 8 after IRB/IEC approval of Amendment #13 for patients in Arm A)

Protocol Activities	Screening	Study Treatment [1]			End of Treatment	
		Cycle 1		Cycles ≥ 2		
	≤ 28 Days Prior to Randomization	Day 1 (± 2)[2]	Day 15 (± 2)	Day 1 (± 2; except as noted below)	End of Txt / Withdrawal [3]	Post Txt Follow-up
Baseline Documentation						
Informed Consent [4]	X					
Medical/ Oncological History [5]	X					
Baseline Signs/Symptoms		X				
Mandatory Tumor Tissue for Molecular Profiling [6]	X					
Physical Examination [7]	X	(X)		X	X	
ECOG Performance Status	X	X		X	X	
Ophthalmologic Examination [8]	X			Cycle 5, then every 4 cycles (France only)		
Laboratory Studies						
Hematology [9]	X	(X)	X	X	X	
Blood Chemistry [9]	X	(X)	X	X	X	
Coagulation [9]	X					
Dipstick Urinalysis and Reflex Microscopy[10]	X (Korea only)	X (Korea only)		X (Korea only)	X (Korea only)	
12-lead ECG [11]	X	X		Cycle 2		
Pregnancy Test (as appropriate) [12]	X				X	
Disease Assessments						
Tumor Assessments (including scans) [13]	X			every 6 weeks (± 1 week)	X	X
Other Clinical Assessments						
Adverse Events and Hospitalizations [14]	X	X	X	X	X	X
Concomitant Medications/Treatments [15]	X	X	X	X	X	X
EORTC QLQ-C30, QLQ-LC13, EQ-5D and VSAQ-ALK [16]		X		X	X	

Protocol Activities	Screening	Study Treatment [1]			End of Treatment	
		Cycle 1		Cycles ≥ 2		
	≤ 28 Days Prior to Randomization	Day 1 (± 2)[2]	Day 15 (± 2)	Day 1 (± 2; except as noted below)	End of Txt / Withdrawal [3]	Post Txt Follow-up
Multiple Gate Acquisition (MUGA) Scan or Echocardiogram [17] (France, Ireland and any sub-study site)	X			Cycle 3, then every 4 cycles		
Survival Follow-up [18]						X
Study Treatment						
PF-02341066 (Arm A only)		Daily				
Pemetrexed or Docetaxel (Arm B only) [19]		X		X		
Special Laboratory Studies						
Optional Blood Sample for Biomarkers and Optional Tumor Tissue for Molecular Profiling (Arm A only) [20]		X		Cycle 2	X	
Pharmacokinetics (Arm A only) [21]		X		Cycles 2, 3, 5		

( ) – if not performed within 7 days of study treatment.

Footnotes for Schedule of Activities
1. Study Treatment: All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. All cycles are 21 days in duration. Once the primary endpoint for the study has been summarized and reported, ongoing patients in Arm A will only need to visit the clinic every other cycle for study assessments instead of every cycle. In addition, tumor assessments will no longer be required. Enough study medication for two cycles of treatment will be dispensed at each clinic visit. During the non-visit cycle, patients must telephone the clinical site to provide an update of adverse events and concomitant medications.
2. Cycle 1/Day 1: Blood chemistry, hematology, and physical examination not required if acceptable screening assessment is performed within 7 days prior to the start of study treatment.
3. End of Treatment/Withdrawal: Obtain these assessments if not completed during the previous 4 weeks on study (during the last 6 weeks for disease assessments).
4. Informed Consent: Must be obtained prior to undergoing any trial specific procedure.
5. Medical/Oncological History: To include information on prior regimens.

Footnotes for Schedule of Activities
6. Mandatory Tumor Tissue for Molecular Profiling: Paraffin block(s) of adequate size to allow if possible for at least 10 slides with cuts that are 5-microns thick. If no block is available, then the sites should try to obtain at least 10 slides with cuts that are 5-microns are acceptable. Archived or fresh tumor samples are acceptable. These samples will be used for the assessment of ALK gene fusion by FISH by the central laboratory. If samples are tested at the site local laboratory or secondary laboratory (at least four 5-micron thick slides are required), positive samples (blocks or slides enough if possible for 10 slides of 5-microns thick) must be sent to central laboratory for analysis of ALK fusion by FISH. Local and secondary laboratory test results will no longer be accepted once the central laboratory can accept samples for analysis.Tumor samples that are sent directly to the central laboratory for testing, may also be tested by FISH by a secondary laboratory for concordance. Tumor samples may also be used for analysis of the presence of ALK protein and ALK fusion transcripts. The mandatory tumor tissue can be evaluated outside the 28-day screening window.
7. Physical Examination: includes an examination of major body systems, height (at screening only); weight, blood pressure and pulse rate (at baseline and on Day 1 of each cycle).
8. Ophthalmologic Examination: includes visual acuity, fundoscopy, and slit lamp and should be performed by an ophthalmologist. The ophthalmologic examination should be repeated during the study when visual disturbances have been observed and when there is an increase in the grade for visual disturbances. For all patients enrolled in France, ophthalmology exams will be performed after the completion of every 4 cycles.
9. Hematology, Blood Chemistry and, Coagulation: Required tests are listed in Appendix 1 of protocol. For Arm A only: If ALT ≥ grade 3 and total bilirubin ≥ grade 2, then liver function tests need to be repeated every 48-72 hours until ALT ≤ grade 2. A 4 ml serum sample obtained just prior to the first dose of study medication will be stored frozen on-site through completion of the study for possible use as a baseline reference should additional laboratory tests be indicated, for example, additional testing to exclude other causes of liver injury (see Section 8.5.1).
10. Dipstick urinalysis and Reflex Microscopy: In Korea, repeat exams should be completed at Day 1 of every cycle and at the end of treatment; all other countries should repeat as clinically indicated (at the time of the initial diagnosis of a renal cyst). Reflex Microscopy required if urine dipstick is positive for blood or protein. See Section 5.4.1for further details.
11. 12-lead ECG: See Section 7.3.3 for further details.
12. Pregnancy Test: See Section 7.2.2 for further details.
13. Tumor Assessments: CT or MRI will include chest, brain, abdomen and pelvis at screening. A bone scan is also required at screening. All subsequent scans will be based on a calendar schedule beginning from the date of randomization. Scans performed 6 weeks after randomization have a + 1 week allowance; all subsequent scans will be performed at 6-week intervals (± 1 week). Tumor Assessments should continue every 6 weeks until RECIST-defined disease progression confirmed by an independent radiology laboratory. If study drug is discontinued in the absence of confirmed RECIST defined disease progression, patients should remain on study until confirmation is received by the independent radiology laboratory. Brain must be included in subsequent tumor assessments if a patient has brain metastases, otherwise brain will only be evaluated when clinically indicated. Repeat bone scans are required every 12 weeks only if bone metastases are present at baseline otherwise a repeat bone scan is required only if new bone metastases are suspected. A bone scan is also required at the time of determination of response for patients who have bone metastases. CT or MRI scan should also be performed whenever disease progression is suspected (eg, symptomatic deterioration). All scans will be sent to an independent radiology laboratory for a blinded RECIST review.

Footnotes for Schedule of Activities
14. Adverse Events and Hospitalizations: Subjects must be followed for adverse events from the time they signed the protocol-specific informed consent until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. Serious adverse events should be monitored and reported from the time that the subject provides informed consent as described in the protocol. Hospitalizations will be recorded from 28 days prior to the start of study treatment until the last day of study drug administration.
15. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.
16. EORTC QLQ-C30, QLQ-LC13 EQ-5D, and VSAQ-ALK: Patients will complete the EORTC QLQ-C30, the QLQ-LC13, the EQ-5D, and the VSAQ-ALK questionnaires at the clinic prior to any study or medical procedure. Patients with visual disturbances ongoing at the End of Treatment visit must also complete the VSAQ-ALK at the 28-day follow-up visit after last dose. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. The VSAQ-ALK has been translated into different languages However, if the VSAQ-ALK is not available in the patient's preferred language, the patient does not need to complete this assessment.
17. MUGA Scan or Echocardiogram: MUGA scans or echocardiograms will be required from selected sites for a total of 30 patients/treatment arm. However, for all patients enrolled in France or Ireland, a MUGA scan or echocardiogram will be obtained as indicated for patients enrolling in the MUGA/echocardiogram substudy.
18. Survival Follow-Up: After discontinuation of study treatment, post-study survival status will be collected every 2 months until death or until 12 months after the randomization of the last patient or until the required number of OS events have been reached, whichever is earlier. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.
19. Pemetrexed or Docetaxel (Arm B only): See Section 5.2.3 for additional concomitant medications that must be administered with pemetrexed or docetaxel.
20. Optional Blood Sample for Biomarkers and Optional Tumor Tissue for Molecular Profiling (Arm A only): An optional blood sample will be collected for soluble biomarkers including c-Met ectodomain and HGF scatter factors, prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1 (corresponding to the 2-6 hour post-dose PK sample) and end of treatment if a patient discontinues due to disease progression. An optional fresh tumor sample will be collected at the end of treatment if a patient discontinues due to disease progression.
21. Pharmacokinetics (Arm A only): See Section 7.4.2 for collection details.

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APPENDICES

1. INTRODUCTION

1.1. Indication

PF-02341066 is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of one prior chemotherapy regimen in patients with tumors harboring a translocation or inversion event involving the ALK gene locus.

1.2. Background

Non-small cell lung cancer (NSCLC) is the most commonly fatal malignancy in the United States accounting for nearly 30% of all cancer related deaths[1], and a frequent cause of mortality throughout the world. In 2007, there were 1.5 million new cases diagnosed worldwide, with broad regional distribution.[2]

Approximately 85% of lung cancer is histologically defined as non-small cell and the remaining 15% as small cell. The majority of patients with NSCLC present with inoperable locally advanced (Stage IIIB) or metastatic (Stage IV) disease for which no curative treatment is available. In newly diagnosed patients, with good performance status, platinum-based doublet-combination chemotherapies are associated with a median overall survival (OS) of 7.4 to 9.9 months.[3, 4, 5, 6, 7, 8] With the addition of bevacizumab to chemotherapy, the resultant median OS was 12.5 months.[9] Three drugs (docetaxel, pemetrexed and erlotinib) have been approved by the FDA for patients with NSCLC after previous treatment with at least one prior chemotherapy regimen. The median progression-free survival (PFS) for these drugs ranged from 2.2 months for erlotinib[10] to 2.9 months for docetaxel or pemetrexed.[11]

1.3. ALK Fusion in NSCLC

An inversion within chromosome 2p resulting in the formation of a fusion gene product comprising portions of the echinoderm microtubule associated protein-like 4 (EML4) gene and the ALK gene was discovered in 2007 in NSCLC cell lines and archived clinical specimens.[12] A subsequent series of published studies indicated that EML4-ALK fusion events included 7 fusion variants, each comprised of the same portion of the ALK C-terminal kinase domain and each resulting in expression of catalytically active kinase fusion protein variants.[13, 14, 15, 16, 17] EML4-ALK fusion variants were demonstrated to transform NIH-3T3 fibroblasts.[12] Expression of EML4-ALK specifically in lung alveolar epithelial cells in transgenic mice demonstrated numerous bilateral lung adenocarcinoma with 100% penetrance only a few weeks after birth, confirming the potent oncogenic activity of the fusion kinase.[18] Although EML4 is the predominant fusion partner, other less common partners as well as yet unknown partners have also been reported [[19, 20, 21] and J. Iafrate, personal communication].

Collectively, a series of studies utilizing archived NSCLC specimens across a broad set of ethnicities indicated that the incidence of EML4-ALK fusion events ranged from 2-7% (mean 3.5%).[12, 13, 14, 15, 16, 17] A detailed meta-analysis of these studies indicates that the prevalence of EML4-ALK fusion events in lung cancer is approximately 6,000 patients/year

in the U.S. and up to 40,000 patients/year world wide.[12, 13, 14, 15, 16, 17] However, there are limitations to this estimation such as a small dataset (1500 tumor samples) and the different methodologies used across studies.[12, 13, 14, 15, 16, 17] This collective group of studies also indicated that the vast majority of EML4-ALK fusion events were observed in lung adenocarcinoma specimens compared with squamous or small cell histologies.[12, 13, 14, 15, 16, 17] A subset of the studies also established a statistically significant correlation of EML4-ALK fusion events with never or light smoking status although some independent studies demonstrated inversion events were also observed in patients with a smoking history and/or reported that smoking status was not a statistically significant cofactor.[12, 13, 16, 22] In addition, EML4-ALK fusion is rarely coincident with EGFR, HER-2, or K-Ras mutations or amplifications, indicating it is a distinct disease subtype.[22]

1.4. Pemetrexed versus Docetaxel in Previously Treated NSCLC

One Phase 3 study (n = 571) compared the efficacy and safety of pemetrexed versus docetaxel in patients with advanced NSCLC previously treated with chemotherapy.[25] In this study, median PFS was 2.9 months for each arm whereas the median OS for pemetrexed and docetaxel arms was 8.3 months versus 7.9 months (p = not significant). Patients on docetaxel had statistically significant higher rates of neutropenia, febrile neutropenia and neutropenia with infection than patients on pemetrexed. There were no statistically significant differences in the rates of thrombocytopenia or anemia. The most common non-hematological toxicities following pemetrexed treatment included fatigue, nausea, vomiting, stomatitis, rash, diarrhea and increase in ALT. The most common non-hematological toxicities following docetaxel treatment included alopecia, fatigue, diarrhea, stomatitis, nausea, neurosensory abnormalities, vomiting, and edema. There was a statistically significant greater occurrence of alopecia for patients receiving docetaxel and a statistically significant greater occurrence of an increase in ALT for patients receiving pemetrexed.

1.5. PF-02341066

1.5.1. PF-02341066 Background

PF-02341066 is a small-molecule inhibitor of the c-Met/HGFR receptor and ALK tyrosine kinases. The rationale for use of this mechanism to treat cancer is supported by an emerging paradigm in oncology that robust clinical efficacy can be obtained with well-tolerated inhibitors directed toward oncogenic tyrosine kinases that are genetically altered through activating mutations, gene translocations, or gene amplification. Recent examples include imatinib mesylate in gastrointestinal stromal tumors with mutant c-Kit or chronic myelogenous leukemia with BCR-Abl gene translocations, erlotinib in non-small cell lung cancer with mutant EGFR, tratuzumab in breast cancers with amplified HER-2/neu, and sunitinib targeting the VHL-dependent VEGF pathway in renal cell carcinoma. PF-02341066 demonstrated potent activity against NPM-ALK, an oncogenic fusion protein variant of the ALK, which results from a chromosomal translocation which is implicated in the pathogenesis of human anaplastic large cell lymphoma.[18] Consistent with its predicted mechanism of action, PF-02341066 inhibited target-dependent tumor cell proliferation or

invasion, induced tumor cell apoptosis, and inhibited angiogenesis in nonclinical tumor models. Oral administration of PF-02341066 also demonstrated efficacy, including marked cytoreductive antitumor activity, in several tumor models that expressed activated c-Met/HGFR or NPM-ALK. The collective rationale for investigation of PF-02341066 in clinical studies is built on genetic alteration of its molecular targets, its predicted ability to target multiple processes that are common to cancer progression, and preclinical efficacy data.

1.5.2. PF-02341066 Clinical Data

An ongoing Phase 1 trial (A8081001) evaluating PF-02341066 as an oral single agent is being conducted to investigate safety, pharmacokinetics and pharmacodynamics in patients with advanced cancer (excluding leukemias). This trial includes a dose escalation component followed by a dose expansion component in a selected cohort of molecularly-defined patients referred to as the enriched population. During the dose escalation phase, PF-02341066 was administered under fasting conditions QD or BID on a continuous schedule. The objectives of the dose escalation component of the trial were to establish the MTD, DLTs, and PK of PF-02341066 in patients with advanced cancer. Enrollment for the dose escalation part of the trial is complete and 37 patients have been dosed. Three DLTs have been observed including Grade 3 ALT increase in 1 patient at 200 mg QD and Grade 3 fatigue in 2 patients at 300 mg BID. The MTD was determined to be 250 mg BID administered in a continuous daily dosing regimen. The most common treatment-related adverse events were nausea, emesis, diarrhea, and fatigue, which were primarily Grade 1-2 in severity. Nausea and emesis were independent of dose or duration of treatment and were effectively managed using I.V. or oral anti-emetics. Treatment-related sight disturbances were observed in 6 patients and occurred at doses of 200 mg BID or above. All of these visual events were Grade 1 in severity and were reversible upon discontinuation of PF-02341066.

As of 15 May 2009, there were 31 patients enrolled in the enriched population cohort of the ongoing Phase 1 trial examining patients with tumors harboring c-Met amplification/gene mutation or EML4-ALK fusion variants. There are 27 NSCLC patients enrolled in this trial, 25 in the enriched population cohort and 2 in the dose escalation portion. These patients had a median of 3 previous treatments (range 1-7) with the majority exhibiting a previous treatment best response of stable disease (SD) or progressive disease (PD). In the ongoing Phase 1 trial, 10 EML4-ALK patients have currently experienced a PR (including 3 unconfirmed at the time of data cut-off). All PRs had occurred at the time of their first or second post-dose scan. The duration of response has ranged from 2+ to 23+ weeks. One of the responding patients experienced progressive disease as of the data cut-off date. In addition, 5 patients have/had stable disease as their best response (duration 8+, 8+, 16, 20 and 40 weeks). Ten patients have not yet had a post-dose scan and 4 patients had a best response of PD. There has also been 1 confirmed PR in a patient with inflammatory myofibroblastic tumor bearing an ALK rearrangement. This patient had debulking surgery after 40 weeks of treatment and has been treated with PF-02341066 for greater than 52 weeks.

Preliminary PK data are available for the first 56 patients enrolled in the ongoing Phase 1 trial. After oral administration of PF-02341066 on an empty stomach, peak plasma concentrations were reached at ~ 4 hours post dose and followed by a multi-exponential declining pattern with an average terminal half-life of 42 to 53 hours. Non-linearity of pharmacokinetics was observed at 50 and 100 mg QD doses as the AUC_{tau} and C_{max} increased more than proportionally with the dose. Patients receiving doses ranging from 100 mg QD to 300 mg BID generally demonstrated linear pharmacokinetics as evidenced by proportional increases in mean AUC_{tau} and C_{max} after single or multiple doses. The steady state condition appeared to be reached by Cycle 1 Day 15. The repeated administration at 250 mg BID for 15 days or longer produced a median trough plasma concentration of 249 ng/mL (44 nM, free drug), exceeding the target efficacious levels predicted for inhibition of ALK based on preclinical mouse tumor models.

PF-02341066 showed time-dependent inhibition of CYP3A isozymes in human liver microsomes with a k_{inact} of 0.11 min^{-1} and K_i of 3.0 μM. In order to assess the effect of PF-02341066 on CYP3A activity in the GI tract and the liver, the PK of midazolam (a CYP3A substrate probe) following a single oral 2 mg dose was evaluated before (Day -7) and after (Cycle 2 Day 1) repeated administration of PF-02341066 at 250 mg BID in 13 patients. A 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of PF-02341066 dosing at 250 mg BID, suggesting that PF-02341066 is a moderate inhibitor of CYP3A.

Results from a pilot food effect study suggested that co-administration with a standard high-fat meal appeared not to change the geometric mean of AUC_{24} and C_{max} of PF-02341066 following single 250-mg PF-02341066 doses in cancer patients.

As of 23 December 2011, there have been 5 patients (<1% of all patients treated with PF-02341006) with possible drug-induced severe hepatotoxicity, 2 of them with fatal outcome. Four of these patients had hepatic laboratory results meeting Hy's Law case criteria (ALT or AST >3 x ULN with concurrent total bilirubin >2 x ULN).

1.5.3. PF-02341066 Additional Data

Additional information on PF-02341066 is available in the investigator's brochure and US package insert.

1.6. Study Rationale

There is very limited information on the efficacy of anti-cancer therapies in patients with NSCLC harboring EML4-ALK fusions. The only known evaluation is a retrospective analysis by A. Shaw and her colleagues that compared treatment outcomes for NSCLC patients with tumors harboring EML4-ALK inversions, EGFR mutations and patients whose tumors are wild type for both ALK and EGFR.[22] In this study, the response rate to first-line treatment with platinum-containing chemotherapy for EML4-ALK tumors was lower than for wild type tumors (25% vs 36%), although not statistically significant. There was no difference in time to progression on chemotherapy across the three groups. Patients with tumors harboring an EML4-ALK fusion responded poorly to EGFR inhibitors compared to

both the wild type group and the EGFR-mutated group (0% vs 13% vs 70%; p <0.001). These data support the EML4-ALK fusion bearing tumors as a distinctive subgroup of NSCLC. Since the clinical activity of the agents available for second-line treatment in this subset of patients with ALK fusions is not known, it would be important to compare PF-02341066 to these agents as a therapeutic option for these patients.

1.7. Rationale for Using FISH Assay for Detection of ALK Gene Fusion Events

The presence of an ALK fusion event in NSCLC patients will be required for eligibility, as these patients are the target population for the label indication. Thus, a diagnostic test for identification of EML4-ALK fusion will be developed in parallel with the clinical development of PF-02341066. The ALK and EML4 genes reside adjacent to each other in opposite orientation on chromosome 2p. The ALK break apart FISH assay is based on a dual color probe which is designed to distinguish the 5' region of the ALK gene locus (green) from the 3' region of the ALK gene locus (orange). The EML4-ALK fusion event (resulting from the inversion of the EML4 gene locus including 5' end of ALK gene) can be detected by the spatial separation of the 5' and 3' ALK probes. According to published reports, EML4 is the predominant fusion partner in NSCLC tumors.[26] In addition, two less common partners as well as yet unknown partners have also been reported [[19, 20, 21] and J. Iafrate, personal communication]. These fusions could be detected by the loss of 5' ALK probe in this assay. The ALK break apart FISH assay is the primary screening assay for Study A8081001. Among the tumors containing abnormalities of the ALK gene, the majority have exhibited a spatial separation of the 5' and 3' ALK probes and tumors from two patients have shown loss of 5' ALK probe. Therefore, the ALK break apart FISH assay will be used as the primary screening assay and eligibility to the current trial will be based on identifying either a spatial separation of the 5' and 3' probes or loss of detection of the 5' probe. If possible, it is planned to explore the concordance of FISH results with the presence of ALK protein as detected by Immunohistochemistry (IHC), to characterize the fusion transcripts by (Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and to assess their correlation to clinical benefit.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective:

- To demonstrate that PF-02341066 (Arm A) is superior to standard of care chemotherapy, pemetrexed or docetaxel (Arm B), in prolonging PFS in patients with advanced NSCLC whose tumors harbor a translocation or inversion event involving the ALK gene locus and who have received only one prior chemotherapy regimen for advanced NSCLC and this regimen must have been platinum-based.

Secondary Objectives:

- To compare secondary measures of clinical efficacy including overall survival (OS), objective response rate (ORR), and disease control rate (DCR) between the two treatment groups, and evaluate duration of response (DR) and time to tumor response (TTR).
- To assess the safety and tolerability of PF-02341066 compared to pemetrexed or docetaxel.
- To compare PRO of HRQoL, disease/treatment-related symptoms of lung cancer, and general health status in both treatment arms.
- To characterize the effects of PF-02341066 at therapeutic doses on QT interval in this patient population.
- To determine PK in this patient population using POPPK methods and explore correlations between PK, response and/or safety findings.
- To explore the relationship of ALK gene fusion to the presence of ALK protein and fusion transcript.
- To correlate modulation of soluble biomarkers to PK and outcome measures.

2.2. Endpoints

Primary Endpoint:

- PFS based on RECIST version 1.1 (confirmed by independent radiology review).

Secondary Endpoints:

- 6-months, and 1-year OS, OS, ORR (confirmed by independent radiology review), DCR at 6 and 12 weeks, DR and TTR.
- Type, incidence, severity, seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.
- Plasma concentrations of PF-02341066.
- QTc.
- Types of EML4-ALK fusion variants and ALK protein expression.
- Plasma concentrations of soluble c-Met ectodomain and HGF scatter proteins.
- TTD in patient reported pain, dyspnea, and cough.
- HRQoL, lung cancer disease/treatment-related symptoms, and general health status.

3. STUDY DESIGN

This is an open-label multi-center, randomized Phase 3 efficacy and safety study of PF-02341066 versus standard of care chemotherapy, pemetrexed or docetaxel, in patients with previously treated NSCLC whose tumors harbor ALK fusions.

A total of 318 patients will be randomized in a 1:1 ratio to receive PF-02341066 (Arm A) or pemetrexed or docetaxel (Arm B). Each treatment cycle is defined as 21 days.

ALK break apart fluorescence in situ hybridization (FISH) assay will be used as the primary assay for detecting ALK fusion events in tumor samples for determining the eligibility of patients entering the trial. Clinical sites that have a local laboratory that can assess the ALK gene fusion by FISH may allow ALK fusion positive patients to initially enter the study based on their results until the central laboratory, selected by the Sponsor, can accept samples for analysis. Clinical sites that do not have a local laboratory that can assess the ALK gene fusion by FISH may allow ALK fusion positive patients to initially enter the study based on the results from a secondary laboratory, selected by the Sponsor, until the central laboratory can accept samples for analysis. All positive samples, whether tested at the local or secondary laboratory, will still be sent to the central laboratory for analysis by FISH. Local and secondary laboratory test results will no longer be accepted once the central laboratory can accept samples for analysis.

The primary endpoint for this study was met in June 2012. Thus, upon approval of Amendment #13, patients in Arm A will no longer be required to have independent radiology review of images. In addition, a reduced schedule of assessments provided in Appendix 8 for patients in Arm A will now be used in place of Table 1.

Patients will continue with the assigned study treatment until RECIST-defined progression of disease as determined by independent radiology review, unacceptable toxicity or consent withdrawal. However, upon approval of Amendment #13, the requirement for independent radiology review will no longer be applicable for patients in Arm A. If a patient discontinues study treatment due to unacceptable toxicity, tumor assessments should continue on study until RECIST-defined progression of disease determined by independent radiology review. Patients may continue treatment as assigned beyond the time of RECIST-defined progression of disease, as determined by independent radiology review, at the discretion of the investigator if the patient is perceived to be experiencing clinical benefit. However, as noted above, upon approval of Amendment #13, the requirement for independent radiology review will no longer be applicable for patients in Arm A. For these patients, tumor assessments will no longer be evaluated by an independent radiology laboratory. In addition, patients in Arm B who have RECIST-defined progression of disease as determined by independent radiology review will have the option to enroll in a single arm trial evaluating PF-02341066 (Protocol A8081005).

The importance of timely and complete disease assessments in this study cannot be overstated. The need to truncate treatment cycles to manage toxicity may result in inconvenient scheduling of disease assessments. Disease assessments must be performed as

scheduled according to the calendar to prevent the introduction of bias into the assessment of efficacy based on toxicity. A series of incomplete disease assessments will result in censoring of the primary endpoint of progression-free survival back to the time of the last full assessment that did not show progression. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1. Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic.

2. Positive for translocation or inversion events involving the ALK gene locus (eg, resulting in EML4-ALK fusion) as determined by an ALK break apart FISH assay and defined by an increase in the distance of 5' and 3' ALK probes or the loss of the 5' probe.

3. Patients must have had progressive disease after only one prior chemotherapy regimen. This regimen must have been platinum-based and may have included maintenance therapy. Patients must be considered appropriate candidates for additional chemotherapy with either single-agent pemetrexed or single-agent docetaxel.

    - Includes patients who received one prior platinum-based chemotherapy for treatment of de novo Stage IIIB/IV NSCLC.

    - Includes patients who have received one prior platinum-based chemotherapy in the adjuvant setting following surgical resection for early disease and whose disease has recurred within 6 months of completion of prior chemotherapy

    - Includes patients who received one prior platinum-based chemotherapy in combination with radiation therapy for Stage III locoregional disease and whose disease has recurred within 6 months of completion of prior chemotherapy.

    - Includes patients who received 2 prior platinum-based chemotherapy regimens, if the first regimen was given as adjuvant therapy or was given in combination with radiation therapy for locally advanced disease.

- Includes patients who have received prior treatment with an EGFR tyrosine kinase inhibitor, such as erlotinib or gefitinib, providing these patients have also received only one prior platinum-based chemotherapy regimen as in one of the scenarios described above.

4. Patients with brain metastases are eligible if asymptomatic or if treated must be neurologically stable for at least 2 weeks and is not taking any medications contraindicated in Exclusion Criteria #12, 13, 14.

5. Any prior chemotherapy or major surgeries must have been completed at least 4 weeks prior to initiation of study medication. Any prior radiation (except for palliative) or minor surgeries/procedures must have been completed at least 2 weeks prior to the initiation of study medication. Palliative radiation (≤ 10 fractions) must have been completed 48 hours prior to the start of study treatment. Any acute toxicity must have recovered to ≤Grade 1 (except alopecia).

6. Tumors must have measurable disease as per RECIST (version 1.1); see Appendix 6.

7. Female or male, 18 years of age or older (for patients enrolled in Japan: consent from a legally acceptable representative is required for all patients who are under 20 years old).

8. ECOG performance status 0-2.

9. Adequate organ function as defined by the following criteria:

   - Hepatic function.

   - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy; however, for patients who if randomly assigned to Arm B must receive docetaxel, ALT and/or AST must not be >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN.

   - Total serum bilirubin ≤1.5 x ULN however for patients who if randomly assigned to Arm B must receive docetaxel, total serum bilirubin must be ≤1 x ULN.

Bone marrow function

- Absolute neutrophil count (ANC) ≥1500/μL.

- Platelets ≥100,000/μL.

- Hemoglobin ≥8.0 g/dL.

Renal function

- Creatinine clearance (based on modified Cockcroft-Gault formula) ≥45 ml/min.

10. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment.

11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures including completion of PRO measures.

12. For patients enrolled in Japan: agree to use effective contraception during the study period and for at least 90 days after completion of the study treatment (excludes surgically sterile male patients or surgically sterile or postmenopausal female patients).

4.2. Exclusion Criteria

Patients presenting with any of the following will not be randomized into the trial:

1. Current treatment on another therapeutic clinical trial.

2. Prior therapy specifically directed against ALK.

3. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function, carcinomatous meningitis, or leptomeningeal disease.

4. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischemic attack.

5. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc interval >470 msec.

6. Previous treatment with PF-02341066.

7. Patients who if randomly assigned to Arm B must receive pemetrexed and who have NSCLC with predominantly squamous cell carcinoma.

8. Patients who if randomly assigned to Arm B must receive docetaxel and who have peripheral neuropathy with Grade >2.

9. Patients who if randomly assigned to Arm B must receive docetaxel and who have had a hypersensitivity reaction to medications formulated with polysorbate 80.

10. [Deleted per Amendment #7].

11. Pregnancy or breastfeeding.

12. Use of drugs or foods that are known potent CYP3A4 inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice.

13. Use of drugs that are known potent CYP3A4 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.

14. Use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited, dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (* withdrawn from U.S. market).

15. Prior malignancy (other than current NSCLC): patients will not be eligible if they have evidence of active malignancy (other than non-melanoma skin cancer or localized cervical cancer, or localized and presumed cured prostate cancer) within the last 3 years.

16. For Japan only: patients who have following complications or symptoms:

    - Serious wound such as chronic wound, or grade≥3 gastrointestinal ulcer.

    - Serious gastrointestinal symptoms such as grade≥3 diarrhea.

17. Other severe acute or chronic medical or psychiatric conditions, or laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for entry into this study.

18. Patients with known interstitial fibrosis or interstitial lung disease.

4.3. Randomization Criteria

At the time of registration, the clinical site staff must provide site and subject identifiers and demographic information. Patients will be randomized in a 1:1 ratio based on a random permuted block design using a centralized Interactive Voice Response System (IVRS)/website to receive either PF-02341066 (Arm A) or pemetrexed or docetaxel (Arm B). The randomization will be stratified by ECOG performance status (0-1 vs 2)**,** brain metastases (presence vs absence) and previous treatment with an EGFR tyrosine kinase inhibitor (yes vs no).

4.4. Life Style Guidelines

4.4.1. Contraception

Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraceptive during the period of the trial and for at least 90 days after completion of treatment (180 days for pemetrexed). Male patients must be surgically sterile or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment (180 days for pemetrexed). The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

As of Amendment #13, all male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 90 days after the last dose of investigational product. The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, injected or implanted hormonal methods of contraception
2. Correctly placed intrauterine device (IUD) or intrauterine system (IUS).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy.

For patients enrolled in the United Kingdom, adequate contraception is defined as double barrier contraception, eg, condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device.

4.4.2. Sunlight Exposure

Patients treated with PF-02341066 should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study period.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

After a subject has provided written informed consent, completed the necessary screening assessments and is shown to have NSCLC positive for the ALK fusion gene (either by the local laboratory of the clinical site or secondary laboratory until the central laboratory can accept samples for analysis or by the central laboratory), the clinical site must contact IVRS to enroll the subject into study.

For patients randomized to Arm B, the first choice of treatment will be pemetrexed. This is due to the docetaxel restrictive labeling for liver function test elevations and peripheral neuropathy. There are 2 exceptions: patients who received pemetrexed as part of their prior chemotherapy regimen or patients who have received pemetrexed as maintenance therapy, will receive docetaxel if randomized to Arm B. These patients will only be allowed to enter the study if they meet the liver function test and peripheral neuropathy eligibility criteria before being randomized. If they do not meet the docetaxel eligibility criteria, these patients will have the option to enroll in a single arm trial evaluating PF-02341066 (Protocol A8081005). Additionally, patients who have had docetaxel as part of their prior chemotherapy and have NSCLC that is predominantly squamous cell carcinoma will not be eligible for this trial but will have the option to enroll in Protocol A8081005.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

5.2.1.1. PF-02341066

PF-02341066 will be provided as tablets containing 50 or 100 mg of study medication and will be packaged in HDPE bottles.

5.2.1.2. Pemetrexed

Commercially available pemetrexed (Alimta®) will be supplied by the study center or by the Sponsor as a single-use vials containing 500 mg of pemetrexed.

5.2.1.3. Docetaxel

Commercially available docetaxel (Taxotere®) concentrate will be supplied by the study center or by the Sponsor as single-use vials containing either 80 mg/2 mL or 20 mg/0.5 mL. The diluent for docetaxel (13% w/w ethanol in water for injection) is provided with the docetaxel concentrate in one carton.

5.2.2. Preparation and Dispensing

5.2.2.1. PF-02341066

PF-02341066 will be supplied as 50 and 100 mg tablets for oral administration. PF-02341066 will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

5.2.2.2. Pemetrexed

Pemetrexed should be reconstituted with 20 mL of 0.9% sodium chloride injection (preservative free) to give a solution containing 25 mg/mL of pemetrexed.[34] The appropriate volume of reconstituted pemetrexed should then be further diluted to 100 mL with 0.9% sodium chloride injection (preservation free). Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.2.2.3. Docetaxel

Docetaxel will be prepared and dispensed according to the product labeling[27] or equivalent documentation. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.2.3. Administration

5.2.3.1. PF-02341066

PF-02341066, 250 mg BID, will be administered orally at approximately the same time each day on a continuous daily dosing schedule, ie, no break in dosing. PF-02341066 can be dosed without regard to meals. Cycles are defined in 21-day periods to facilitate scheduling of visits and assessments.

Patients should be instructed that if they vomit anytime after taking a dose, then they must not “make it up” with an extra dose, but instead, resume subsequent doses as prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed.

Medication errors may result, in this study, from the administration or consumption of the wrong drug, at the wrong time, or at the wrong dosage strength, or with a wrong mean of administration or by the wrong subject. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRFs and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an adverse event, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s), is captured on an adverse event (AE) CRF page (refer to Adverse Event Reporting section for further details).

5.2.3.2. Pemetrexed

Pemetrexed, 500 mg/m^2, will be administered by intravenous infusion over 10 minutes or according to institutional practices on Day 1 of a 21-day cycle. In order to reduce treatment-related hematologic and GI toxicities, patients will also be required to take folic acid, 350-1000 µg orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. In addition, Vitamin B_{12}, 1000 µg, will be injected intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and will be repeated approximately every 9 weeks until discontinuation. In order to reduce cutaneous reactions, patients will also be required to take dexamethasone, 4 mg orally, twice daily, the day before, the day of and the day after pemetrexed dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethasone will be allowed per country regulations.

5.2.3.3. Docetaxel

Docetaxel, 75 mg/m^2, will be administered by intravenous infusion over 1 hour or according to institutional practices on Day 1 of a 21-day cycle. In order to reduce cutaneous reactions, patients will also be required to take dexamethasone, 8 mg orally, twice daily, the day before, the day of and the day after docetaxel dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethasone will be allowed per country regulations.

5.2.4. Compliance

Patients receiving PF-02341066 will be required to return all bottles of study medication at the beginning of each cycle. The number of tablets remaining will be documented and recorded.

5.3. Drug Storage and Drug Accountability

PF-02341066 should be stored at room temperature (15 to 30°C). Pemetrexed and docetaxel should be stored as directed in the product package insert (or equivalent documentation). Medication should be kept in a secured locked area at the study site in accordance with

applicable regulatory requirements. Returned medication for PF-02341066 should be stored separately from medication that needs to be dispensed.

Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products. Any temperature excursions should be reported immediately.

To ensure adequate records, all study drugs will be accounted for in the case report form (CRF) and drug accountability inventory forms as instructed by the sponsor. Unless otherwise authorized, at the end of the clinical trial, all PF-02341066 supplies unallocated or unused by the patients must be returned to the sponsor or its designee. Patients must return all containers to a designated study center participant.

5.4. Dose Modifications

5.4.1. PF-02341066

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Nausea and Emesis

For nausea and emesis, treat with standard anti-emetics such as prochlorperazine or ondansetron. Taking the medication with food may reduce nausea. The use of prophylactic antiemetics should be considered.

Diarrhea

For Grade 1 diarrhea, symptomatic care such as loperamide (Imodium) or no intervention at investigator judgment. For Grade 2 diarrhea, loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). No dose modification unless patient is intolerant or symptom is recurrent. For Grade ≥3 (despite use of loperamide), treatment should be withheld until recovery to Grade ≤1.

Bradycardia

For a heart rate <40 beats per minute, the patient should be evaluated fully including an assessment of concomitant medications. The dosage of any medication known to be associated with bradycardia, eg, beta-blockers, should be adjusted accordingly. If the bradycardia is symptomatic at any time or does not improve within 7 days of adjusting the concomitant medications, hold PF-02341066 dosing until recovery. Patient may continue treatment only with the agreement of both the sponsor and investigator.

Pneumonitis/Pneumonia

Investigators must evaluate thoroughly patients who demonstrate potential signs /symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug related lung injury the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria.
- Blood culture should be performed in febrile patients.
- Thoracentesis if pleural fluid is present (examined for same pathogens as sputum).
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture and cytology (same pathogens as above).
- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate.
- A plasma sample for BNP (B-type Natriuretic peptide) to evaluate for evidence of CHF.
- For Asian patients, a blood sample for β-D-glucan to evaluate for the presence of fungal pneumonia (eg, Pneumocystis *jirovecii*).

If clinically appropriate, high dose corticosteroid treatment should be initiated. Should the event be fatal an autopsy is highly recommended to confirm/exclude the diagnosis. For any case of suspected pneumonitis please contact the Sponsor. For appropriate dose modifications see Table 2.

Renal Cysts

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

Monitoring with appropriate imaging should be performed per protocol (eg, every 6 weeks with contrast-enhanced CT scanning or magnetic resonance imaging assuring full visualization of the kidneys). In addition, multitask dipstick urinalysis (should include test for protein and blood) should be performed at the time of the renal cysts diagnosis and on Day 1 of each cycle thereafter; in Korea, multitask dipstick urinalysis should be performed in all patients at screening and on Day 1 of each cycle thereafter and at the end of treatment; all

other countries should repeat as clinically indicated (at the time of the initial diagnosis of a renal cyst). Urine reflex microscopy is required whenever urine dipstick is positive for blood or protein.

5.4.2. PF-02341066 Dose Modifications for Treatment-Related Toxicity

Patients will be monitored closely for toxicity and the dose of PF-02341066 may be adjusted as indicated in Table 2. Intrapatient dose reduction by 1 and if needed, 2 dose level(s) will be allowed depending on the type and severity of toxicity encountered (Dose Level -1 is 200 mg BID; Dose Level -2 is 150 mg BID, however following IRB/IEC approval of Amendment #9, dose level -2 will be 250 mg QD). Patients requiring more than 2 dose reductions due to treatment-related toxicity will be discontinued from the study.

PF-02341066 treatment may be delayed for a maximum of 42 days to allow sufficient recovery from any toxicity, if in the judgment of the investigator, the patient is still deriving clinical benefit. However, if a patient has a significant toxicity from PF-02341066 treatment which fails to recover within 21 days and, in the opinion of the investigator, requires discontinuation of PF-02341066 treatment based on the severity of the adverse event, then this patient does not need to be further dosed with PF-02341066 and can remain in the trial with ongoing tumor assessments until RECIST-defined progression by the independent radiology review, if applicable. See Section 3.

Table 2. PF-02341066 Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic General (except as noted below), eg, neuropathy, edema (including peripheral edema and localized edema), fatigue, and skin rash (including erythematous, macular, papular, and pruritic rash).	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator*.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator*.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT elevation with total bilirubin < 2 X ULN (in the absence of cholestasis or hemolysis).	Continue at the same dose level.	Continue at the same dose level. Obtain repeat ALT and total bilirubin when symptomatic or within 7 days. For France only: Consult with Sponsor (according to letter provided under separate cover) to determine whether (1) to continue with same dose level; (2) withhold dose until toxicity is grade ≤1 or has returned to baseline, then resume treatment at the same dose level; or (3) withhold dose until toxicity is grade ≤1 or has returned to baseline, then reduce the dose by 1 level.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment by reducing the dose by one dose level. If grade 3 ALT elevation recurs reduce further (at most by 2 dose levels from initial dose level). If recurrence at dose level -2, discontinue permanently If grade 3 ALT elevation does not recur after at least 4 weeks, the dose may be escalated by single dose level increments up to the initial dose level. For France only: Discontinue treatment and do not retreat.	See grade. 3 For France only: Discontinue treatment and do not retreat.
ALT elevation concurrent with total bilirubin elevation ≥ 2 X ULN (in the absence of cholestasis or hemolysis).	Continue at the same dose level. Obtain repeat ALT and total bilirubin within 48 hours.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Left ventricular systolic dysfunction.	Continue at the same dose level.	Continue at the same dose level.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Prolonged QTc.	Continue at the same dose level.	Continue at the same dose level. Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities.	Interrupt PF-02341066 until recovery to baseline. Assess and correct electrolytes and concomitant medications. Resume treatment by reducing the dose by one dose level, unless an alternative cause for QTc prolongation is found and corrected, resume at the same dose level.	Discontinue treatment and do not retreat.
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect).	Withhold dose until toxicity is Grade 0, ie, has returned to baseline, then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs.	Withhold dose until toxicity is Grade 0, ie, has returned to baseline, then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Visual disturbance.	Continue at the same dose level. Repeat ophthalmologic examination+.	Continue at the same dose level. Repeat ophthalmologic examination+.	Interrupt PF-02341066 until recovery. Repeat ophthalmologic examination+. Resume treatment by reducing by one dose level.	Discontinue treatment and do not retreat. Repeat ophthalmologic examination+.
Hematologic (excluding lymphopenia**).	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at the same dose level or reduce by 1 level after discussion with the Sponsor **.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment**.

* Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.

** Patients who develop Grade 3 or 4 lymphopenia without other dose-limiting events (eg, opportunistic infection) may continue study treatment without interruption.

+ Ophthalmologic examination includes visual acuity, fundoscopy, and slit lamp and should be performed by an ophthalmologist.

5.4.3. Pemetrexed

Patients will be monitored closely for toxicity and the dose of pemetrexed may be adjusted as indicated in Table 3.

Table 3. Pemetrexed Dose Modifications for Treatment-Related Non-Hematological Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic *	Continue at the same dose level.	Including Grade 3 increases in transaminases, continue at the same dose level.	Excluding neurotoxicities, increases in transaminases, and muscositis, reduce to 75% of previous dose; mucositis, reduce dose to 50% of previous dose; neurotoxicities, discontinue treatment.	Excluding neurotoxicities and muscositis, reduce to 75% of previous dose; mucositis, reduce dose to 50% of previous dose; neurotoxicities, discontinue treatment.

* Hospitalizations for diarrhea (irrespective of grade), reduce to 75% of previous dose.

Hematologic Toxicity

- ANC <500/μL and platelets ≥50,000/μL: reduce to 75% of previous dose.
- Platelet <50,000/μL (regardless of ANC): reduce to 50% of previous dose.

5.4.4. Docetaxel

Patients will be monitored closely for toxicity and the dose of docetaxel may be adjusted as indicated in Table 4. Patients requiring more than 1 dose reduction due to treatment-related toxicity will be discontinued from the study.

Table 4. Docetaxel Dose Modifications for Treatment-Related Non-Hematological Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic *	Continue at the same dose level.	Continue at the same dose level.	Including severe or cumulative cutaneous reactions, withhold dose until toxicity has returned to ≤ baseline, then resume treatment at 55 mg/m^2; peripheral neuropathy, discontinue treatment.	Withhold dose until toxicity has returned to ≤ baseline, then resume treatment at 55 mg/m^2; peripheral neuropathy, discontinue treatment.

* Includes nausea only if despite maximal medical therapy and vomiting only if despite maximal antiemetic therapy.

Hematologic Toxicity

- ANC <500/μL for >1 week; withhold dose until toxicity has returned to ≤ baseline, then resume treatment at 55 mg/m$^{2.}$
- Febrile neutropenia (ANC <500/μL and fever >8°C with IV antibiotics and/or hospitalization); withhold dose until toxicity has returned to ≤ baseline, then resume treatment at 55 mg/m$^{2.}$

5.4.5. Re-treatment Criteria for Pemetrexed and Docetaxel

Patients should not begin a new cycle with treatment with pemetrexed or docetaxel unless:

- ANC is ≥1500/μL.
- Platelet count is ≥100,000/μL.
- Calculated creatinine clearance is ≥45 mL/min (pemetrexed only).
- Total bilirubin ≤1 x ULN (docetaxel only).
- ALT and/or AST must not be >1.5 x ULN when alkaline phosphatase is >2.5 x ULN (docetaxel only).

If these re-treatment criteria are not met (including the adverse events described in Table 3 and Table 4) on the day that a new treatment cycle is scheduled to start, pemetrexed or docetaxel may be delayed for a maximum of 42 days to allow sufficient time for recovery. However, if a patient has a significant toxicity from pemetrexed or docetaxel treatment which fails to recover within 21 days or, in the opinion of the investigator, requires discontinuation of the chemotherapy treatment based on the severity of the adverse event, then this patient does not need to be further dosed with chemotherapy and can remain in the trial with ongoing tumor assessments until RECIST-defined progression by the independent radiology review.

5.5. Concomitant Medication(s)

Anticancer therapy with agents other than PF-02341066, pemetrexed or docetaxel is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.5.1. PF-02341066

The metabolism of PF-02341066 is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of PF-02341066 in humans. The concurrent use of potent CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice,

are not allowed in the study. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in the study.

In vitro data indicate that the most pronounced inhibitory potential of PF-02341066 was observed toward CYP3A4 (testosterone)-mediated drug metabolism. PF-02341066 has minimal potential to inhibit other human CYP isoforms such as CYP1A2, 2C8, 2C9, 2C19 and 2D6. PF-02341066 also showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In cancer patients, a mean 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of PF-02341066 dosing at 250 mg BID, suggesting that PF-02341066 is a moderate inhibitor of CYP3A. In particular, co-administration of PF-02341066 with CYP3A4 substrates with narrow therapeutic indices (TI) associated with life-threatening arrhythmias including, but not limited to dihydroergotamine, ergotamine, pimozide, triazolam, astemizole*, cisapride*, and terfenadine* (* withdrawn from U.S. market) must be avoided from the time of the first dose of PF-02341066 until treatment discontinuation. In addition, caution must be exercised in subjects receiving PF-02341066 in combination with other CYP3A4 substrates, particularly those with narrow TIs, including but not limited to alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus.

Additionally, the concurrent use of non-prescription drugs (excluding vitamins) or herbal supplements is not recommended. Acetaminophen/ paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.Pemetrexed

Non-steroidal anti-inflammatory drugs (NSAID) with long half-lives, eg, >10 hours, should be discontinued at least 5 days before, the day of and 2 days following pemetrexed dosing. Patients who take NSAIDs concomitantly with pemetrexed should be monitored closely for toxicity, especially myelosuppression, renal and gastrointestinal toxicity.

5.5.2. Antiemetic and Antidiarrheal Therapy

Supportive care may include premedication with antiemetics to limit treatment-related nausea and vomiting. Patients may receive prophylaxis of treatment-induced diarrhea. Taking the medication with food may reduce nausea. Prophylactic use of antiemetics should be considered.

5.5.3. Hematopoietic Growth Factors

The use of hematopoietic growth factors is at the discretion of the treating physician. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician. However, in Japan, erythropoietin and darbepoietin will not be allowed to be used for chemotherapy-related anemia because these drugs have not been approved for this indication. Patients with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

5.5.4. Other Concomitant Medications

Anti-inflammatory (except as noted above for pemetrexed) or narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated.

Patients on this trial may be supported with appropriate hormone replacement therapy as clinically indicated in the absence of disease progression or unacceptable treatment-associated toxicity.

Bisphosphonate therapy for metastatic bone disease is permitted. Bisphosphonate therapy should be given as per local medical practice.

5.5.5. Concomitant Radiotherapy or Surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. PF-02341066 treatment should be interrupted during palliative radiotherapy – stopping 1 day before and resuming treatment 1 day after. Palliative radiotherapy should be performed at least 1 day before or 1 day after pemetrexed or docetaxel dosing.

The effect of PF-02341066 in wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds (potential antiangiogenic effect). In the event elective surgery is necessary during study participation, PF-02341066 dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery. A 48-hour window should also be used for patients receiving pemetrexed or docetaxel treatment.

6. STUDY PROCEDURES

Once Amendment #13 has been approved by the IRB/IEC, the reduced schedule of activities described in Appendix 8 should be followed for patients in Arm A.

6.1. Screening

For screening procedures, see Table 1.

6.2. Study Period

For procedures during the study period, see Table 1.

6.3. Follow-up Visit

For follow-up visit procedures, see Table 1.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons.

Reasons for trial treatment discontinuation include (further collection of data can still occur):

- Disease progression by RECIST as determined by independent radiology review unless the patient is considered to be deriving clinical benefit by the investigator.
- Unacceptable toxicity.
- Need for treatment delay for more than 6 weeks due to lack of toleration.
- Global deterioration of health-related symptoms.
- Protocol non-compliance.
- Pregnancy.

Reasons for trial discontinuations (no further collection of data) include:

- Withdraw of consent.
- Patient loss to follow-up.
- Death.
- Study termination by Sponsor.

If a patient does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.5. Schedule of Activities Following Completion of Primary Endpoint (Arm A only)

The following procedures will be followed for patients in Arm A once Amendment #13 has been approved by the IRB/IEC. Ongoing patients in Arm A will only need to visit the clinic every other cycle for study assessments instead of every cycle. Enough study medication

until the next clinic visit will be dispensed at each clinic visit. During the non-visit cycle, patients must telephone the clinical site to provide an update of adverse events and concomitant medications. The reduced schedule of assessments for patients in Arm A is described in Appendix 8.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

Assessment of efficacy, adverse events, laboratory safety assessment (hematology, coagulation, and chemistry), physical examination, ECG, MUGA scans, tumor measurements, PK sampling, tumor tissue for molecular profiling and plasma soluble biomarkers will be done according to time points specified in Table 1, then as described in Appendix 8 after IRB/IEC approval of Amendment #13 for patients in Arm A.

7.1. Efficacy Assessments

Disease assessments are to be performed as scheduled according to the calendar days regardless of treatment delays. On-study tumor assessments are to be performed every 6 weeks from the date of randomization (with the exception of bone scans that are to be performed, if required, every 12 weeks) until radiographic PD has been documented. The randomization date should always be used as the baseline when calculating when the next tumor assessment is due. CT or MRI scan should also be performed whenever disease progression is suspected (eg, symptomatic deterioration). The determination of anti-tumor efficacy will be based on objective tumor assessments made according to the RECIST system (Appendix 6). The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging modality should be used throughout the study to measure disease. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans. CT or MRI scans will include chest, brain, abdomen and pelvis at screening. Brain must be included in subsequent tumor assessments if a patient has brain metastases, otherwise brain will only be evaluated when clinically indicated. A bone scan is required at screening. Repeat bone scans are required every 12 weeks only if bone metastases are present at baseline otherwise a repeat bone scan is required only if new bone metastases are suspected. A bone scan is also required at the time of determination of response for patients who have bone metastases. All scans will be sent to an independent radiology laboratory for a blinded RECIST review. Tumor assessments should continue every 6 weeks until RECIST-defined disease progression confirmed by independent radiology laboratory. If study drug is discontinued in the absence of confirmed RECIST defined disease progression, patients should remain on study until confirmation is received by the independent radiology laboratory.

When new effusions or ascites are present and represent the only potential site of disease progression, cytologic analysis should be performed and the results, malignant or non-malignant, should be recorded on the CRF.

Measurable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

7.2. Safety Assessments

7.2.1. Adverse Events

Adverse Events will be classified by type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0), timing, seriousness, and relatedness.

Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

7.2.2. Pregnancy Testing

For female subjects of childbearing potential, pregnancy tests will be done at screening and also whenever one menstrual cycle is missed during the treatment period (or when potential pregnancy is otherwise suspected), and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

7.3. Laboratory Safety Assessments

For a listing of hematology, coagulation, blood chemistries, and urinalysis, see Appendix 1.

7.3.1. Physical Examination

A complete physical examination will include the assessment of all body systems, the measurement of body weight, height (screening only) and vital signs. Body surface area (BSA) should be determined for pemetrexed and docetaxel dosing. Blood pressure and pulse rate will be obtained in the sitting position. Blood pressure should be measured in the dominant arm, ie, writing arm, and recorded to the nearest mmHg. The same arm should be used throughout the study.

7.3.2. Performance Status

ECOG Performance Status scale will be used (Appendix 2).

7.3.3. ECG Measurements

A 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. Triplicate ECG measurements will be obtained at all time points except a single ECG measurement at screening. For triplicate measures, three consecutive 12-lead ECGS will be collected

approximately 2 minutes apart. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. ECG interval readings by the ECG recorder's algorithm will be used for safety evaluations in all patients. Blinded manual interval measurements at a core ECG laboratory will be used for primary statistical analysis of ECG data in a subgroup of patients in Arm A (as described below). ECG measurements will include PR interval, QT interval, RR interval and QRS complex. Additional ECGs will be performed as clinically indicated.

Arm A

ECGs should be performed immediately before PK blood draws at respective time points. If the QTc is prolonged (>500 msec), then the ECG should be read by a cardiologist at the site for confirmation.

Crizotinib should be withheld until the drug relationship of the event is determined (rule out electrolyte imbalance or influence of concomitant medication). Any manual overread done at the site must be entered into the eCRF as an unplanned ECG result. In case of a PF-02341066 treatment related QTc interval measurement higher than 500 msec (grade ≥3), dosing should be permanently discontinued for a Grade 4 QTc prolongation event and temporarily discontinued for Grade 3 QTC prolongation event and continuous electrocardiogram (ECG) monitoring will be done under hospital supervision until the QTc value becomes lower than 500 msec. ECG surveillance will again be performed when PF-02341066 is restarted on a reduced dose due to this grade 3 prolongation of the QTc as described in Table 2, ie, dose reduction by one dose level. This same procedure will also be performed if the dose is escalated up one dose level. This supervision of ECGs should be the same for the collection times indicated in this section.

Subgroup at selected sites (requires approximately 40 patients): ECGs should be obtained at 0 (pre-dose) 4 and 8 hours following morning PF-02341066 dosing on Day 1 of Cycle 1 and 0 (pre-dose), 2, 4, 6, and 8 hours following morning PF-02341066 dosing on Day 1 of Cycle 2. All ECGs should be obtained after a fast of at least 1 hour. All ECG tracings from this subgroup will be sent electronically to a core ECG laboratory for blinded manual interval measurements. Forty patients in the subgroup must complete the following ECG measurements: baseline (pre-dose on Day 1 of Cycle 1) and all five (5) time points on Day 1 of Cycle 2. Patients may also participate in this sub-study from Study A8081005.

All other patients: ECGs should be obtained at 0 hour (pre-dose) on Day 1 of Cycle 1 and 2-6 hours following morning PF-02341066 dosing on Day 1 of Cycles 1 and 2.

Arm B

A single ECG measurement will be obtained at screening.

7.3.4. MUGA Scans or Echocardiograms

MUGA scans or echocardiograms will be required from selected sites for a total of 30 patients per each treatment arm. However, for all patients enrolled in France or Ireland, MUGA scans or echocardiograms will be obtained as described in Table 1, then as described in Appendix 8 after IRB/IEC approval of Amendment #13 for patients in Arm A.

7.3.5. Ophthalmology Examinations

At screening, each patient will have an ophthalmologic exam including visual acuity, fundoscopy, and slit lamp**.** Additional eye examinations will be performed when visual disturbances have been observed and when there is an increase in grade for visual disturbance**s**. For all patients enrolled in France, ophthalmology exams will be obtained as described in Table 1, then as described in Appendix 8 after IRB/IEC approval of Amendment #13 for patients in Arm A.

Findings from the ophthalmology examinations should be reported as adverse events if a finding is considered to be an adverse event by the investigator or Sponsor.

7.4. Pharmacokinetics

7.4.1. Plasma Pharmacokinetic Assessment

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). During the trial, actual collection times may change but the number of samples will remain the same.

PK samples will be assayed for PF-02341066 (including its active moieties, if appropriate) using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the storage and shipping of plasma samples will be provided in the Study Manual.

As part of understanding the pharmacokinetics of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and /or evaluation of the bioanalytical methods for crizotinib and its metabolites (if possible) once Amendment #7 has been IRB approved. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

7.4.2. Plasma Pharmacokinetic Assessment for PF-02341066 (Arm A only)

For patients in the ECG subgroup, plasma PK samples for PF-02341066 (including its active moieties, if appropriate) will be obtained at the times indicated for ECGs in Section 7.3.3. Additional plasma PK samples will be collected prior to morning dosing and 2-6 hours following morning dosing on Day 1 of Cycles 3 and 5.

For all other patients in Arm A, plasma PK samples will be collected prior to morning dosing and 2-6 hours following morning dosing on Day 1 of Cycles 2, 3 and 5.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events

At each time point, blood samples (2 mL) for analysis of PF-02341066 concentrations will be collected into appropriately labeled collection tubes containing K2EDTA at protocol-specified times. Once collected, samples should be processed immediately and kept out of direct sunlight due to the light sensitive nature of PF-02341066. Blood samples will be placed immediately on ice-bath and centrifuged at approximately 1700 g for 10 minutes at 4ºC. Plasma samples (approximately 1 mL) will be stored in appropriately labeled tubes at approximately -20°C within 1 hour of collection. Details regarding the sample handling and shipping will be provided in the Lab Manual.

7.5. Optional Soluble Biomarker Analysis (Arm A only)

Blood samples (4 mL) for assaying plasma levels of HGF Scatter factor and soluble c-Met ectodomain will be collected in appropriately labeled collection tubes at the specific time points shown in Table 1, then as described in Appendix 8 after IRB/IEC approval of Amendment #13. Detailed sample collection procedures will be specified in the Lab Manual.

7.6. Tumor Tissue for Molecular Profiling

ALK break apart FISH assay will be used as the primary assay for detecting ALK fusion events in tumor samples for determining the eligibility of patients for entering the trial. Clinical sites that have a local laboratory that can assess the ALK gene fusion by FISH may allow ALK fusion positive patients to initially enter the study until the central laboratory can accept samples for analysis. Clinical sites that do not have a local laboratory that can assess the ALK gene fusion by FISH may allow ALK fusion positive patients to initially enter the study based on the results from a secondary laboratory, selected by the Sponsor, until the central laboratory can accept samples for analysis. All positive samples, whether tested at the local or secondary laboratory, will still be sent to the central laboratory for analysis by FISH. Local and secondary laboratory test results will no longer be accepted once the central laboratory can accept samples for analysis. Samples that are sent directly to the central laboratory for testing, may also be tested for FISH at a secondary laboratory for concordance. Tumor samples may also be used for investigating the presence of ALK protein and ALK fusion transcripts.

7.7. Optional Tumor Tissue for Biomarker Analysis (Arm A only)

An optional tumor sample will be collected at the end of treatment if a patient discontinues due to disease progression. The tumor tissue will be used to determine possible mechanisms for resistance to PF-02341066 treatment.

7.8. Patient Reported Outcomes

PROs of HRQoL, lung cancer specific disease/treatment related symptoms and general health status will be assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[28, 29], its corresponding module for lung cancer (QLQ-LC13)[30], the EuroQol 5D (EQ-5D)[31] questionnaire**,** and the newly developed visual symptom assessment questionnaire (VSAQ-ALK). Specifically, the VSAQ-ALK was developed to assess and better understand the visual symptoms patients have reported in the Phase 1 trial, A8081001.

Patients will complete the self-administered questionnaires as described in Table 1, then as described in Appendix 8 after IRB/IEC approval of Amendment #13 for patients in Arm A. The EORTC QLQ-C30, the QLQ-LC13, the EQ-5D, and VSAQ-ALK should be completed by patients prior to any testing, treatment, or discussion with the physician or clinic personnel.

7.8.1. EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ-C30 (Version 3.0) and the QLQ-LC13 module (Appendix 3 and Appendix 4 respectively) are both validated and reliable self-report measures.[28, 29, 30] The EORTC QLQ-C30 consists of 30 questions which are incorporated into five functional domains (physical, role, cognitive, emotional, and social domains); a global health status/ global quality of life scale; three symptom scales (fatigue, pain, nausea and vomiting scales); and six single items that assess the additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and the perceived financial burden of treatment.[28, 29] The QLQ-LC13 consists of one multi-item scale and nine single items that assess the specific symptoms (dyspnea, cough, hemoptysis, and site specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of lung cancer patients receiving chemotherapy.[30] The scales assessing pain, dyspnea, and cough, from the EORTC QLQ-C30 and the QLQ-LC13 will be used to evaluate the TTD of pain, dyspnea and cough symptoms. The EORTC QLQ-C30 and the QLQ-LC13 module require about 15 minutes to complete and are available in many languages.

7.8.2. EQ-5D

The EQ-5D is a validated and reliable self-report preference-based measure developed by the EuroQoL Group to assess health-related quality of life (Appendix 5). It consists of the EQ-system measures a patients' health state on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." The EQ VAS records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).[31] The EQ-5D takes less than 5 minutes to complete.

7.8.3. VSAQ-ALK

The VSAQ-ALK is a self report measure that was developed to assess and better understand the problems that some patients reported with their eyesight upon starting treatment in the ongoing A8081001 trial (Appendix 7). These problems are called visual disturbances and symptoms may include the appearance of overlapping shadows and after images; shimmering, flashing or trailing lights; strings, streamers, or floaters; as well as hazy or blurry vision. The VSAQ-ALK consists of seven items which assess the frequency, duration, bother, and impact of visual disturbances on activities daily living. The VSAQ-ALK has been translated into different languages. However, if the VSAQ-ALK is not available in the patient's preferred language, the patient does not need to complete this assessment. If the patient is unable to read or is illiterate, then the VSAQ-ALK does not need to be completed. The VSAQ-ALK should take less than 5 minutes to complete. The VSAQ-ALK will also be administered during the 28-Day Follow-up visit after last dose to patients with ongoing visual disturbances at the End of Treatment visit (see Table 1).

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be- required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Following the active safety reporting period, other SAEs of which the investigator becomes aware should be reported to Pfizer, unless the

SAE is attributed by the investigator to complications of either the underlying malignancy or any subsequent anti-cancer therapy or to the patient's participation in a subsequent clinical study.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

- If a subject begins a new anticancer therapy, the adverse event reporting period for non-SAEs ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;

- Medication error.

- Worsening of signs and symptoms of the malignancy under study should be reported as adverse events in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or

- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with CTC grade 5 (see Section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Potential Cases of Drug-Induced Liver Injury

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.

- For subjects with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

    Concurrent with

    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time ULN over baseline or ≥3 times ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and for oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time

(PT)/INR and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. Where further testing for acute hepatitis A, B, or C infection may be warranted, additional testing for acute hepatitis E infection should be considered. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);

- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

The investigator will use the following definitions of Severity in accordance with CTC Version 4.0 to describe the maximum intensity of the adverse event. If the event is serious, the CTC grade reported in the adverse event CRF must be consistent with the description of CTC grade included in the narrative section of the serious adverse event report.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero [EIU] occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product

2. A male has been exposed, (eg, due to treatment or environmental exposure), to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified

and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as serious adverse events follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg,. follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.

8.10. Withdrawal Due To Adverse Events (See Also Section 6.4 Patient Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to other causes, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event).

In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding- cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.12.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

In addition to recording observed or volunteered adverse events additional data will be solicited from the patients in the study to more fully characterize the clinical pharmacology of PF-02341066. These additional measurements are described Section 7.8.

The EORTC QLQ-C30, the QLQ-LC13, the EQ-5D and the VSAQ-ALK are collected and evaluated in a different manner than the observed or volunteered adverse events. Given these differences, no attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and the additional data collected with the patient reported questionnaires. Additional data collected with the EORTC QLQ-C30, the QLQ-LC13**,** the EQ-5D and the VSAQ-ALK will be presented in separate tables, figures, and data listings, and will be reviewed in the final study report. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded on the Adverse Event pages on the Case Report Form (CRF).

8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

A detailed methodology for summary and statistical analysis of the data collected in this trial will be documented in a Statistical Analysis Plan that will be dated and maintained by Pfizer. The document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Based on data collected from ongoing single-arm PF-02341066 studies in ALK-positive NSCLC patients that received prior second-line, single-agent pemetrexed or docetaxel a median time to tumor progression of 4.6 months (95% CI: 2.8, 6.6 months) was calculated and 4.5 months of median PFS was assumed as the estimate for the control arm in the present trial. Thus, a total sample size of 288 patients (217 total PFS events) will provide 90% probability to demonstrate superiority of Arm A over Arm B, assuming a 1.56 fold improvement over Arm B in PFS (4.5 months to 7 months) based on a one-sided log- rank test at the 2.5% level of significance. It is assumed that accrual will be accomplished over a 20 month period and follow-up for PFS will continue for at least 4 months after the last patient is randomized. To account for events being censored due to potential discordance between the investigators and independent radiology review, up to 30 extra patients will be enrolled for total sample size of 318.

The median survival for Arm B is assumed to be 8 months. With an overall one-sided α of 0.025 and one interim analysis (that was performed at the time of PFS analysis with all available OS events, corresponding to 40% of the required number of total OS events), the study will have 80% power to detect a 44% increase in OS when 238 deaths have occurred.

9.2. Definitions of Efficacy Assessments

9.2.1. Time to Event Endpoints

For the purposes of the definitions of efficacy endpoints, the term “on study” includes the period from randomization until PD or initiation of subsequent anti-tumor therapy in the absence of PD or death, whichever comes first.

PFS is defined as the time from randomization to first documentation of objective disease progression as determined by independent radiology review or to death on study due to any cause, whichever occurs first.

OS is defined as the time from randomization to the date of death due to any cause. For patients still alive at the time of analysis, the OS time will be censored on the last date the patients were known to be alive.

DR is defined as the time from the first documentation of objective tumor response (CR or PR) as determined by independent radiology review that is subsequently confirmed to the first documentation of objective disease progression or to death due to any cause, whichever occurs first. DR will only be calculated for the subgroup of patients with objective response.

TTR is defined as the time from randomization to first documentation of objective tumor response (CR or PR). For patients proceeding from PR to CR, the onset of PR is taken as the onset of response. TTR will only be calculated for the subgroup of patients with objective response.

PFS and DR will be censored on the date of the last evaluable on-study tumor assessment documenting absence of progressive disease for patients who are alive, on study and progression free at the time of the analysis, are given antitumor treatment other than study treatment or have documentation of PD or death after a long gap, eg, ≥14 weeks). Patients having no tumor assessments after screening will have time to event endpoints censored on the date of randomization. Other censoring situations will be described in detail in the statistical analysis plan (SAP), for each endpoint analyzed.

TTD is defined as the time from randomization to the earliest time the patient's score shows a 10 point or higher increase after baseline in patient reported pain, dyspnea, or cough symptoms. Patients will be censored at the last time when they completed an assessment for pain, dyspnea, and cough if they have not deteriorated. A 10 point or higher change in the score is perceived by patients as clinically significant. [23]

9.2.2. Response Rate Endpoints

ORR is defined as the percent of patients with CR or PR according to RECIST (as determined by independent radiology review), relative to the total population of randomized patients. Patients who do not have an on-study assessment will be included as non-responders. DCR at 6 and 12 weeks is defined as the percent of patients with a CR, PR or SD at 6 and 12 weeks, respectively, according to RECIST (as determined by the independent radiology review), relative to the total population of randomized patients. Designation of best response of SD requires the criteria to be met at least once after randomization, at a minimum interval of 6 weeks.

9.3. Analysis Populations

9.3.1. Full Analysis Population (FA)

The FA population will include all patients who are randomized with study drug assignment designated according to initial randomization. The full analysis population will be the primary population for evaluating time-to-event efficacy endpoints (ie, PFS and OS), ORR, DCR and patient characteristics.

9.3.2. Safety Analyses

The safety analyses population will include all patients who receive at least one dose of study medication, with treatment assignments designated according to actual study treatment received. The safety analyses population will be the primary population for evaluating treatment administration/compliance and safety in the study.

9.3.3. PRO Evaluable Population

The PRO evaluable population is defined as the patients from the safety analyses population who completed a baseline PRO assessment and at least one post-baseline PRO assessment. The PRO evaluable population will be the primary population for the analysis of change from baseline scores and the TTD in patient reported pain, dyspnea, and cough.

9.4. Efficacy Analyses

9.4.1. Analysis of Primary Endpoint

PFS will be summarized in the FA set based on the independent radiology review of tumor data using Kaplan-Meier method by treatment arms. PFS curves will also be displayed graphically. Differences in median PFS between treatment arms will be analyzed by the log rank test (1-sided, alpha = 0.025) stratified for baseline factors (listed in Section 4.3). The median event time (and other quartiles) and corresponding 2-sided 95% CI will be provided for each treatment arm. The Cox regression model, stratified for baseline stratification factors, will be fitted, and the estimated hazard ratio (Arm A/Arm B) and 2-sided 95% CI will be provided.

An unstratified log-rank test (1-sided, alpha = 0.025) and Cox regression model may be used as secondary analyses for PFS. Additionally, a Cox regression model, stratified for baseline stratification factors, will be used to explore the potential influences of the other factors on the primary PFS endpoint. Several planed sensitivity analyses on PFS will be described in the statistical analysis plan.

9.4.2. Analysis of Secondary Endpoints

Based on the full analysis population, the best response (CR, PR, SD or PD) per RECIST as determined by independent radiology review for each patient will be summarized by treatment arm. ORR will be calculated as the number of patients with a best response of CR or PR divided by the total number of randomized patients in each treatment group. The corresponding exact 2-sided 95% confidence interval will be calculated using a method based on the F-distribution. DCR will be calculated as the number of patients with best response of CR, PR, or SD divided by the total number of randomized patients in each treatment arm. Mantel Haenszel tests will be used to compare ORR and DCR between the treatment arms, using the randomization strata. The difference in ORR and DCR between the two treatment groups will be provided and the 95% confidence interval will be calculated based on the normal approximation.

As appropriate, the analysis described above for ORR and DCR may be repeated on the SA population as a sensitivity analysis.

OS will be analyzed similarly as described for PFS. A log-rank test will be used in the analysis of OS and RPSFTM[32] may be used as a sensitivity analysis. Survival times for patients who enroll into A8081005 from Arm B will be included in this analysis. .

The 6-month survival probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log [-log(6-months survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the 6-months survival probability itself. The 1-year survival probability will be estimated similarly.

DR will be calculated for the subgroup of patients with objective disease response and summarized using the Kaplan-Meier method. TTR will also be calculated for the subgroup of patients with objective disease response and summarized using descriptive statistics.

9.5. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, efficacy endpoints, safety parameters, patient reported outcomes, and cancer biomarkers. Data will also be displayed graphically, where appropriate. Relationships between baseline patient characteristics, and outcome variables will be explored using regression models or other appropriate techniques.

The proportion of patients with each of the ALK fusion variants of the EML4-ALK fusion will be summarized, and their correlations with the clinical outcome will be evaluated. The relationship of EML4-ALK variants and ALK protein expression will be explored. The correlation between ALK protein expression and the clinical outcome will be evaluated.

9.5.1. Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

9.5.2. Baseline Characteristics

Demographic characteristics such as patient age, gender, height, weight, ethnicity, prior anti-cancer therapy, medical history, extent of disease and ECOG performance status will be tabulated.

9.5.3. Treatment Administration/Compliance

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

9.5.4. ECG Analysis Plan

QT measurements corrected by heart rate (QTc) will be used for the data analysis and interpretation. In addition to commonly used techniques including Bazett's (QTcB) and Fridericia's (QTcF) methods, a study-specific correction method will be evaluated (QTcS) for the ECG sub-group of Arm A. QTcF will be used for the primary analysis.

9.5.4.1. ECG Subgroup of Arm A

9.5.4.1.1. Sample Size Determination

Based upon the standard deviation of change from baseline of QTc of 16 ms (Study A8081001), a total sample size of 40 patients from both Studies A8081007 (Arm A) and A8081005 should be sufficient for greater than 90% probability that all five boundaries of upper one-sided 95% confidence intervals for the change from baseline of QTc at all five QTc sampling time points on Cycle 2 Day 1 are under 20 ms, assuming the true change from baseline in QTc is 10 ms.

9.5.4.1.2. Statistical Analysis of QTc

The changes in QTc (QTcB, QTcF, and /or QTcS) from baseline will be summarized using descriptive statistics and categorical analysis by nominal time point.

A random effect model with the nominal time point as a fixed effect and the patients as a random effect will be used to estimate the mean change in QTc (QTcF, QTcS optional) from baseline at each post-baseline nominal time point. The 90% confidence intervals for the changes from baseline in QTc will be provided at each post-baseline nominal time point.

9.5.4.2. Summary and Categorical Analysis of ECG for Arm A – All Patients

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

For all patients in the safety analysis population, individual change in QTc (QTcB, QTcF) will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

For all patients in the safety analysis population, categorical analysis of the QTcF/QTcB data will be conducted and summarized as follows:

1. The number and percentage of subjects with maximum increase from baseline in QTcF/QTcB (<30, 30- 60, and ≥60 ms).

2. The number of and percentage subjects with maximum post-dose QTcF/QTcB (<450, 450-<480, 480- <500, and >500 ms).

3. PR changes from baseline ≥50% if absolute baseline value was <200 ms, and ≥25% if absolute baseline value was >200 ms.

4. QRS changes from baseline ≥50% if absolute baseline value was <100 ms, and ≥25% if absolute baseline value was >100 ms.

The analyses described above for all patients in Arm A will be repeated separately for the ECG sub-population in Arm A for QTcB/QTcF/QTcS.

9.5.5. Pharmacokinetic/Pharmacodynamic Analysis

Concentration data of PF-02341066 will be listed by patient and by actual collection time and day.

Concentration-QTc modeling analysis will be conducted using the ECG data from this study and/or combined data with other clinical studies of PF-02341066. A separate study specific QT correction factor will be estimated for the QT-RR measurements in each clinical study of PF-02341066. Linear, log-linear, and/or saturable models will be examined for the concentration-QTc relationship. Exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model. Diagnostic evaluation will be included to explore the adequacy of the model.

Population pharmacokinetic analysis of samples collected in this study will be performed in accordance with the FDA guidance on Population Pharmacokinetics (February 1999). All patients treated with PF-02341066 and for whom drug plasma concentration results (from at least 1 visit) are available will be included in the population analysis. The plasma concentration data set from this study will be pooled with data sets from additional PF-02341066 studies. Population pharmacokinetic analysis will involve mixed effects modeling performed using appropriate software (eg, NONMEM). The data from the analysis will describe the PK following multiple dose administration of PF-02341066 and describe covariates that are important determinants of PF-02341066 disposition.

In addition, population PK/PD analysis will be explored, as necessary, based on emerging safety/clinical response data.

The results of these modeling analyses may be reported separately from the clinical study report.

9.5.6. MUGA Scan or Echocardiogram Analysis

For the subgroup (30 patients in each treatment arm) with MUGA scans or echocardiograms, individual LVEF (left ventricular ejection fraction [%]) and its changes from baseline will be summarized by treatment and by time point. The number of patients and the percentage whose maximum relative decrease from baseline in LVEF is greater than 20% will be calculated by treatment arm. An analysis on LVEF will be performed for all patients with a post-dose MUGA scan or echocardiogram.

9.5.7. Patient Reported Outcomes Analyses

The scales assessing pain, dyspnea, and cough, from the EORTC QLQ-C30 and the QLQ-LC13 will be used to evaluate the TTD of pain, dyspnea and cough symptoms. TTD of the three pre-specified symptom (pain, dyspnea, and cough) scales will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will be provided for each symptom and the unstratified log-rank test will be the primary method to compare the time to first deterioration between the two treatment groups. The median time and 2-sided 95% CI for the median also will be provided based on the Brookmeyer Crowley method. The Hochberg procedure will be used to adjust for multiple comparisons.[24]

Rates of improvement over the first 21-day cycle in the pre-specified symptom (pain, dyspnea, cough) scales will be compared between the two treatment groups. Improvement is defined as a decrease of at least 10 points in the symptoms scales. The number and proportion of patients who reported “improved”, “stable”, or “deteriorated” pain, dyspnea and cough symptoms will be summarized and compared between treatment groups.

Summary statistics (mean [and SE], median, range and 95% CI) of absolute scores will be reported for the items and scales of the QLQ-C30, the QLQ-LC13, the EQ-5D VAS, and the VSAQ-ALK. The mean change of absolute scores from baseline (and 95% CI) will also be assessed and compared between treatment arms, controlling for baseline scores. Line charts depicting the means and mean changes of subscales over time will be provided for each treatment arm. For the EQ-5D health state profiles, the proportions of patients reported having “no”, “some”, or “extreme” problems at each time point will be reported.

The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QOL, and single items of the EORTC QLQ-C30 and the QLQ-LC-13 will be summarized[28, 29, 30] in a table and compared between the two treatment arms. Additional analyses may be performed such as repeated measures mixed-effects modeling. Descriptive statistics will be reported by cycle for the items on the VSAQ-ALK.

9.6. Safety Analysis

9.6.1. Adverse Events

All patients who receive any study medication will be included in the summaries and listings of safety data. Overall safety profile and tolerability of Arm A and Arm B will be characterized by type, frequency, severity, timing, duration and relationship of study therapy of adverse events and laboratory abnormalities.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.0.

In all summaries, emphasis will be placed on treatment emergent adverse events (TEAEs), namely, those with initial onset or that worsen in severity after the first dose of study medication. Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE (version 4.0) grade. Summaries will also be provided of treatment related TEAEs, namely, those judged by the investigator to be related or likely related to study medication.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE version 4.0 Grade 3 or higher, trial drug related events, and serious adverse events will be considered with special attention. Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9.6.2. Laboratory Tests

Hematology, blood chemistry and coagulation laboratory data will be summarized by treatment arm and by cycle. The hematologic and chemistry laboratory results will be graded according to the NCI CTCAE version 4.0 severity grade. For parameters for which an NCI CTCAE version 4.0 scale does not exist, the frequency of patients with a laboratory abnormality meeting pre-specified criteria for the local or central lab will be summarized by treatment..

9.6.3. Baseline Characteristics

Patient characteristics at trial entry will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables for FA (see Section 9.3 for definitions of trial populations). Imbalances in patient characteristics in the treated populations will be assessed.

9.6.4. Ophthalmologic Analysis

Visual Acuity Exam Results: The change from baseline in visual acuity will be summarized by treatment for all patients from the SA population with baseline and at least one post-baseline ophthalmologic assessment.

Biomicroscopy (Slit Lamp) and Fundoscopy Exam Results: For baseline results, percentage of patients falling into each category of the examination status (normal, mild, moderate or severe) will be summarized for each structure by treatment and by eye.

For post-baseline results, percentage of patients falling into each category of the examination status (new findings/worsening of finding, no change, improvement of finding etc) will be summarized for each eye structure by treatment and by eye.

9.7. Data Monitoring Committee (DMC)

This study will use an External Data Monitoring Committee (E-DMC).

An independent third-party E-DMC will monitor the safety of the patients on a periodic basis. The E-DMC will determine whether the trial may continue based on ongoing reviews of safety data. The E-DMC membership and governance is outlined in a separate charter.

The Sponsor will designate an external third-party biostatistician not affiliated with the project to prepare data for E-DMC review. Only if action or consultation with Health Authorities is required will other sponsor staff be involved. Clinical sites will be restricted from access to study results until the conclusion of the study.

In addition to the use of an E-DMC, the safety of the trial will also be monitored by the Internal Oncology Business Unit -Safety Data Monitoring Committee (IOBU-SDMC). The IOBU-SDMC is a single, BU-internal, project-independent advisory group established to enhance the early detection of potential safety signals in OBU-sponsored clinical trials. The activities of this committee are intended to be complementary and supplemental to existing Pfizer safety risk management processes.

The IOBU-SDMC will function in conjunction with the existing E-DMC. The scope of the IOBU-SDMC will be limited to safety data review, no efficacy data will be made available to the committee. Upon identification of a new potential safety concern, this committee will inform the E-DMCs in a manner that maintains study integrity. The safety data received by the committee for review will be kept confidential.

Detailed information about the IOBU-SDMC is available in the IOBU-SDMC charter maintained by the Sponsor.

9.8. Independent Radiology Review

The radiographic images will be evaluated by an independent radiology laboratory to assess tumor status and to determine response and progression of disease. The radiographic images documenting efficacy endpoints must be made available to allow the independent review. For patients who may have progressive disease, the radiographic images will be reviewed within 72 hours of receipt so that investigators will not make any treatment changes until they have received confirmation from the radiology laboratory. The radiology laboratory will work with each clinical site to institute an acquisition protocol and other processes that will allow electronic transfer, where possible, of appropriate imaging scans used for tumor assessments. The independent review will be blinded with regard to treatment assignments. Two independent reviewers will read scans. Differences between the two independent reviewers should be resolved by a third reviewer (adjudicator) for final determination. For primary statistical analysis of response data, the results of the independent review will be used.

In an effort to harmonize selection of target lesions at baseline between the Independent Central Review and the investigators' assessments, all sites will be required to complete a Baseline Clinical Subject Profile form to be sent with the baseline scans for the Independent Central Review. This form identifies any pre-existing (pre-baseline) radiographic findings that could mimic metastatic disease and any major anatomic alterations resulting from prior surgeries or interventional procedures. In addition, this form captures the anatomic field and the start and stop dates of radiation therapy, and whether the subject has progressed in the field since the last radiation therapy treatment. This process significantly increases the probability of comparable target lesion selection at baseline between the site and the Independent Radiographic Review.

As the primary endpoint of the study was met in June 2012, there is no longer a requirement to send tumor images for patients in Arm A to the independent radiology laboratory upon IRC/IEC approval of Amendment #13. For patients in Arm B, tumor images should continue to be sent to the independent radiology laboratory in order to permit patient crossover.

9.9. Central Laboratory for Assessment of ALK Gene Fusion by FISH

A central laboratory will be used as the final determination of patient eligibility utilizing the ALK break apart FISH assay. Samples provided to the central laboratory must either be paraffin block(s) of adequate size to allow if possible for at least 10 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 10 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.

9.10. Core ECG Laboratory

For the ECG sub-study (Arm A in selected sites), all post-screening ECGs will be read in a blinded fashion by a central reader. The ECG recordings will be transferred digitally to a central reader where they will be stripped of any information which could permit identification of the patient, site, date or time. The ECGs will be evaluated for interval assessments including PR, QT, RR and QRS.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms / Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

12.5. Reporting Of Safety Issues And Serious Breaches Of The Protocol Or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Study Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application [CTA]).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-02341066 at any time.

If this study is prematurely terminated or discontinued, Pfizer will promptly notify the investigators. After notification, the investigators must contact all participating subjects and the hospital pharmacy (if applicable) within a time period set by Pfizer. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1. Communication of Results by Pfizer:

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results:

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US).

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Required Laboratory Tests

	Conventional	Conversion	SI Units
Hematology			
Hemoglobin (Hgb)	g/dL	x 10	g/L
Platelet count (Plt)	$10^3/mm^3$	x 10^9	10^{12}/L
White blood count (WBC)	$10^3/mm^3$	x 10^6	10^9/L
White blood cell differential	%	x 0.01	fraction
Chemistry			
Total bilirubin	mg/dL	x 17.1	μmol/L
Alanine transaminase (ALT)	U/L	N/A	U/L
Aspartate transaminase (AST)	U/L	N/A	U/L
Alkaline phosphatase	U/L	N/A	U/L
Total protein	g/dL	x 10	g/L
Albumin	g/dL	x 10	g/L
Sodium	MEq/L	x 1.0	mmol/L
Potassium	MEq/L	x 1.0	mmol/L
Chloride	MEq/L	x 1.0	mmol/L
Total Calcium	mg/dL	x 0.25	mmol/L
Phosphorus	mg/dL	x 0.323	mmol/L
Blood urea nitrogen (BUN)	mg/dL	x 0.357	mmol/L
Creatinine	mg/dL	x 88.4	μmol/L
Uric acid	mg/dL	x 0.059	mmol/L
Magnesium	mg/dL	X 0.41	mmol/L
Glucose	mg/dL	x 0.055	mmol/L
LDH	U/L	N/A	U/L
Coagulation			
Protime INR	(unitless)	N/A	(unitless)

	Conventional	Conversion	SI Units
In cases of suspected Drug Induced Liver Injury (DILI) as described in Section 8.5.1- values to be reported on SAE form			
Creatine Kinase (CPK)	U/L	N/A	U/L
Indirect Bilirubin	mg/dL	x 17.1	□mol/L
Direct Bilirubin	mg/dL	x 17.1	□mol/L
Gamma-glutamyl transferase (GGT)	U/L	N/A	U/L
Urinalysis			
Dipstick and Reflex Microscopy	(unitless)	N/A	(unitless)

Appendix 2. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 3. EORTC QLQ-C30 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4. EORTC QLQ-LC13 Questionnaire

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

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

Appendix 5. EQ-5D Health Questionnaire

EQ-5D HEALTH QUESTIONNAIRE (Page 1 of 2)

By placing a check (X) in one box in each group below, please indicate which statements best describe your own health state 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 (eg 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 ☐

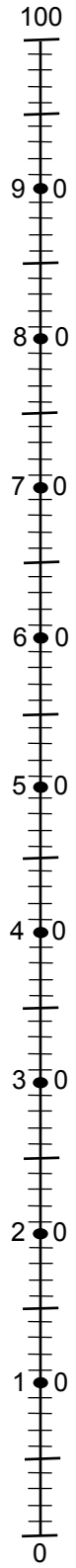
I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

To help people say how good or bad a health state 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 health state is today.

Your own health state today



Appendix 6. RECIST version 1.1 Tumor Assessment Criteria[33]

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

Measurable Lesions

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-measurable Lesions

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥ 10 but < 15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Special Considerations Regarding Specific Lesions

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of $\geq$ 15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The

baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR): at** least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

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 germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up

- No FDG-PET at baseline and a positive FDG-PET at follow- up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Confirmation of Tumor Response

Confirmation of response is required for non-randomized trials with primary endpoint of response, but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by the RECIST 1.1 Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted inTable 5.

Table 5. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = inevaluable.			

Best overall response

The best overall response is determined once all the data for the patient is known. Best response in trials in which confirmation of complete or partial response is not required (ie. randomized trails) is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later).

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'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

Appendix 7. Visual Symptom Assessment Questionnaire (VSAQ-ALK)

We would like to ask some questions about problems you may be experiencing with your eyesight. These problems are called visual disturbances and may include but are not limited to the appearance of the following: overlapping shadows or after images; shimmering, flashing or trailing lights; streamers, strings, or floaters in your peripheral vision; as well as hazy or blurry vision.

Please select the response that best applies to your experience of visual disturbances in the <u>past three weeks</u>.

1. **In the past three weeks, have you experienced any visual disturbances?**

   ☐ Yes If *yes* go to Question 2.

   ☐ No If *no*, thank you and please return the questionnaire.

2. **In the past three weeks, how often did you experience a visual disturbance?**

   ☐ One day a week or less often

   ☐ Two or three days a week

   ☐ Four to six days a week

   ☐ Seven days a week

3. **In the past three weeks, when did you experience a visual disturbance? (Check <u>all</u> that apply)**

   ☐ Morning

   ☐ Afternoon (from 12 PM -4 PM)

   ☐ Evening

4. **In the past three weeks, how long did each visual disturbance last on average? (Check only <u>one</u>)**

   ☐ 30 seconds or less

   ☐ More than 30 seconds but not longer than one minute

   ☐ More than one minute but not longer than five minutes

   ☐ More than five minutes but not longer than ten minutes

   ☐ More than ten minutes

   ☐ Don't remember

5. In the past three weeks, how often did you experience a visual disturbance when adjusting to changes in lighting (eg, coming indoors on a bright sunny day)?

☐ Never

☐ Rarely

☐ Sometimes

☐ Often

☐ Always

6. In the past three weeks, how much have you been bothered by. . . (Check <u>one</u> box on each line below):

	Did not experience	Not at all	A little	Moderately	Quite a bit	Extremely
a. Visual disturbances?	☐	☐	☐	☐	☐	☐
b. Appearance of overlapping shadows or after images?	☐	☐	☐	☐	☐	☐
c. Appearance of shimmering, flashing, or trailing lights?	☐	☐	☐	☐	☐	☐
d. Appearance of streamers, strings, or floaters?	☐	☐	☐	☐	☐	☐
e. Difficulty seeing at night?	☐	☐	☐	☐	☐	☐
f. Hazy or blurry vision?	☐	☐	☐	☐	☐	☐
g. Difficulty adapting to bright lights (e.g., going out on a bright day)?	☐	☐	☐	☐	☐	☐
h. Difficulty adapting to dim light (e.g., entering a darkened room)?	☐	☐	☐	☐	☐	☐

7. During the past three weeks, how much did visual disturbances affect your ability to do your regular daily activities?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If visual disturbances affected your activities only a little, choose a low number. Choose a high number if visual disturbances affected your activities a great deal.

Consider only how much visual disturbances affected your ability to do your regular daily activities

Visual disturbances had no effect on my daily activities											Visual disturbances completely prevented me from doing my daily activities
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	

CIRCLE A NUMBER

Appendix 8. Reduced Schedule of Assessments for patients in Arm A

Table 6. Schedule of Activities

Protocol Activities	Study Treatment/Each Cycle[1]		
	Day 1 (±2; except as noted below)	End of Treatment/ Withdrawal[2]	Post Treatment Follow-up
Baseline Documentation			
Physical Examination[3]	X	X	
ECOG Performance Status	X	X	
Ophthalmologic Examination[4]	Cycle 5, then every 4 cycles (France only)		
Laboratory Studies			
Hematology[5]	X	X	
Blood Chemistry[5]	X	X	
Dipstick Urinalysis and Reflex Microscopy[6]	X (Korea only)	X (Korea only)	
12-lead ECG[7]	Cycles 1 and 2 only		
Pregnancy Test (as appropriate)[8]	(X)	X	
Disease Assessments			
Tumor Assessments (including scans)[9]	Standard of Care	X	X
Other Clinical Assessments			
Adverse Events and Hospitalizations[10]	X	X	X
Concomitant Medications/Treatments[11]	X	X	X
EORTC QLQ-C30, QLQ-LC13, EQ-5D and VSAQ-ALK[12]	X	X	
Multiple Gate Acquisition (MUGA) Scan or Echocardiogram[13] (France, Ireland and any sub-study site)	Cycle 3, then every 4 cycles		
Survival Follow-up[14]			X
Study Treatment			
PF-02341066	X		
Special Laboratory Studies			
Optional Blood Sample for Biomarkers and Optional Tumor Tissue for Molecular Profiling[15]	Cycle 2 (if applicable)	X	
Pharmacokinetics[16]	Cycles 2, 3, 5 (If applicable)		

( ) – if applicable.

Footnotes for Schedule of Activities
1. Study Treatment: All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. All cycles are 21 days in duration. Ongoing patients in Arm A will only need to visit the clinic every other cycle for full study assessments. Enough study medication for two cycles of treatment will be dispensed at each clinic visit. During the non-visit cycle, patients must telephone the clinical site to provide an update of adverse events and concomitant medications. Patients in Arm B must continue to follow the schedule of assessments in Table 1.
2. End of Treatment/Withdrawal: Obtain these assessments if not completed during the previous 4 weeks on study.
3. Physical Examination: includes an examination of major body systems, weight, blood pressure and pulse rate (at each cycle visit, ie, Day 1 of that cycle).
4. Ophthalmologic Examination: includes visual acuity, fundoscopy, and slit lamp and should be performed by an ophthalmologist. The ophthalmologic examination should be repeated during the study when visual disturbances have been observed and when there is an increase in the grade for visual disturbances. For all patients enrolled in France, ophthalmology exams will be performed after the completion of every 4 cycles.
5. Hematology and Blood Chemistry: Required tests are listed in Appendix 1 of protocol. For Arm A only: If ALT ≥ grade 3 and total bilirubin ≥ grade 2, then liver function tests need to be repeated every 48-72 hours until ALT ≤ grade 2.
6. Dipstick urinalysis and Reflex Microscopy: In Korea, repeat exams should be completed at Day 1 of each cycle visit, ie, Day 1 for that cycle and at the end of treatment; all other countries should repeat as clinically indicated (at the time of the initial diagnosis of a renal cyst). Reflex Microscopy required if urine dipstick is positive for blood or protein. See Section 5.4.1 for further details.
7. 12-lead ECG: See Section 7.3.3 for further details.
8. Pregnancy Test: See Section 7.2.2 for further details.
9. Tumor Assessments: The timing for tumor imaging may be completed per standard of care while receiving study treatment. Scans no longer need to be sent to the independent radiology laboratory for review. Note: For patients in Arm B, continue to follow the schedule of assessments in Table 1.
10. Adverse Events and Hospitalizations: Subjects must be followed for adverse events from the time they signed the protocol-specific informed consent until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. Serious adverse events should be monitored and reported from the time that the subject provides informed consent as described in protocol Section 8.2. Hospitalizations will be recorded from 28 days prior to the start of study treatment until the last day of study drug administration.
11. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment.
12. EORTC QLQ-C30, QLQ-LC13 EQ-5D, and VSAQ-ALK: Patients will complete the EORTC QLQ-C30, the QLQ-LC13, the EQ-5D**,** and the VSAQ-ALK questionnaires at the clinic prior to any study or medical procedure. Patients with visual disturbances ongoing at the End of Treatment visit must also complete the VSAQ-ALK at the 28-day follow-up visit after last dose. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. The VSAQ-ALK has been translated into different languages However, if the VSAQ-ALK is not available in the patient's preferred language, the patient does not need to complete this assessment.
13. MUGA Scan or Echocardiogram: MUGA scans or echocardiograms will be required from selected sites for a total of 30 patients/treatment arm. However, for all patients enrolled in France or Ireland, a MUGA scan or echocardiogram will be obtained as indicated for patients enrolling in the MUGA/echocardiogram substudy.

Footnotes for Schedule of Activities
14. Survival Follow-Up: After discontinuation of study treatment, post-study survival status will be collected every 2 months until death or until 12 months after the randomization of the last patient or until the required number of OS events have been reached, whichever is earlier. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.
15. Pharmacokinetics (Arm A only): See Section 7.4.2 for collection details.

Prescribing Information as of April 2003

℞ only

TAXOTERE® (docetaxel) Injection Concentrate

WARNING

TAXOTERE® (docetaxel) Injection Concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with TAXOTERE therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive TAXOTERE as a single agent at a dose of 100 mg/m^2 (see **WARNINGS**).

TAXOTERE should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with SGOT and/or SGPT >1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of TAXOTERE therapy and reviewed by the treating physician.

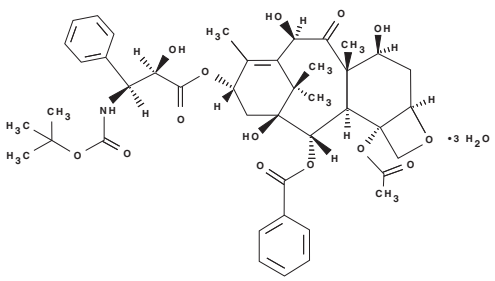
TAXOTERE therapy should not be given to patients with neutrophil counts of < 1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXOTERE.

Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% (2/92) of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the TAXOTERE infusion were reported in five patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy. TAXOTERE must not be given to patients who have a history of severe hypersensitivity reactions to TAXOTERE or to other drugs formulated with polysorbate 80 (see **WARNINGS**).

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) (see **PRECAUTIONS**).

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}\bullet\ 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. TAXOTERE (docetaxel) Injection Concentrate is a clear yellow to brownish-yellow viscous solution. TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2.0 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

TAXOTERE Injection Concentrate requires dilution prior to use. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials.

CLINICAL PHARMACOLOGY

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

HUMAN PHARMACOKINETICS

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase I studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow

recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with TAXOTERE.

Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding (see **PRECAUTIONS**).

CLINICAL STUDIES

Breast Cancer: The efficacy and safety of TAXOTERE have been evaluated in locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or anthracycline-containing regimens), primarily at a dose of 100 mg/m^2 given as a 1-hour infusion every 3 weeks, but with some experience at 60 mg/m^2, in two large randomized trials and a number of smaller single arm studies.

Randomized Trials: In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with TAXOTERE or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). 203 patients were randomized to TAXOTERE and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the TAXOTERE arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results:

Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously Treated with an Anthracycline-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	Docetaxel (n=203)	Mitomycin/ Vinblastine (n=189)	p-value
Median Survival	11.4 months	8.7 months	
Risk Ratio*, Mortality (Docetaxel: Control)	0.73		p=0.01 Log Rank
95% CI (Risk Ratio)	0.58-0.93		
Median Time to Progression	4.3 months	2.5 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.75		p=0.01 Log Rank
95% CI (Risk Ratio)	0.61-0.94		
Overall Response Rate	28.1%	9.5%	p<0.0001
Complete Response Rate	3.4%	1.6%	Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with TAXOTERE or doxorubicin (75 mg/m^2 every 3 weeks). 161 patients were randomized to TAXOTERE and 165 patients to doxorubicin. Approximately one-half of patients had received prior chemotherapy for metastatic disease, and one-half entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The study results are summarized below:

Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously Treated with an Alkylating-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	Docetaxel (n=161)	Doxorubicin (n=165)	p-value
Median Survival	14.7 months	14.3 months	
Risk Ratio*, Mortality (Docetaxel: Control)	0.89		p=0.39 Log Rank
95% CI (Risk Ratio)	0.68-1.16		
Median Time to Progression	6.5 months	5.3 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.93		p=0.45 Log Rank
95% CI (Risk Ratio)	0.71-1.16		
Overall Response Rate	45.3%	29.7%	p=0.004
Complete Response Rate	6.8%	4.2%	Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

Single Arm Studies: TAXOTERE at a dose of 100 mg/m^2 was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall response rate was 37.9% (72/190; 95% C.I.: 31.0-44.8) and the complete response rate was 2.1%.

TAXOTERE was also studied in three single arm Japanese studies at a dose of 60 mg/m^2, in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast cancer. Among 26 patients whose best response to an anthracycline had been progression, the response rate was 34.6% (95% C.I.: 17.2-55.7), similar to the response rate in single arm studies of 100 mg/m^2.

Hematologic and Other Toxicity: Relation to dose and baseline liver chemistry abnormalities. Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given TAXOTERE at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN); and 174 patients in Japanese studies given TAXOTERE at 60 mg/m^2 who had normal LFTs.

Hematologic Adverse Events in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m² with Normal or Elevated Liver Function Tests or 60 mg/m² with Normal Liver Function Tests

Adverse Event	TAXOTERE 100 mg/m² Normal LFTs* n=730 %	TAXOTERE 100 mg/m² Elevated LFTs** n=18 %	TAXOTERE 60 mg/m² Normal LFTs* n=174 %
Neutropenia			
Any <2000 cells/mm³	98.4	100	95.4
Grade 4 <500 cells/mm³	84.4	93.8	74.9
Thrombocytopenia			
Any <100,000 cells/mm³	10.8	44.4	14.4
Grade 4 <20,000 cells/mm³	0.6	16.7	1.1
Anemia <11 g/dL	94.6	94.4	64.9
Infection* **			
Any	22.5	38.9	1.1
Grade 3 and 4	7.1	33.3	0
Febrile Neutropenia**			
By Patient	11.8	33.3	0
By Course	2.4	8.6	0
Septic Death	1.5	5.6	1.1
Non-Septic Death	1.1	11.1	0

***Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN**
****Elevated Baseline LFTs: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN**
*****Incidence of infection requiring hospitalization and/or intravenous antibiotics was 8.5% (n=62) among the 730 patients with normal LFTs at baseline; 7 patients had concurrent grade 3 neutropenia, and 46 patients had grade 4 neutropenia.**
******Febrile Neutropenia: For 100 mg/m², ANC grade 4 and fever > 38°C with IV antibiotics and/or hospitalization; for 60 mg/m², ANC grade 3/4 and fever > 38.1°C**

Non-Hematologic Adverse Events in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m² with Normal or Elevated Liver Function Tests or 60 mg/m² with Normal Liver Function Tests

Adverse Event	TAXOTERE 100 mg/m² Normal LFTs* n=730 %	TAXOTERE 100 mg/m² Elevated LFTs** n=18 %	TAXOTERE 60 mg/m² Normal LFTs* n=174 %
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13.0	5.6	0.6
Severe	1.2	0	0
Fluid Retention* ** **Regardless of Premedication**			
Any	56.2	61.1	12.6
Severe	7.9	16.7	0
Neurosensory			
Any	56.8	50	19.5
Severe	5.8	0	0
Myalgia	22.7	33.3	3.4
Cutaneous			
Any	44.8	61.1	30.5
Severe	4.8	16.7	0
Asthenia			
Any	65.2	44.4	65.5
Severe	16.6	22.2	0
Diarrhea			
Any	42.2	27.8	NA
Severe	6.3	11.1	
Stomatitis			
Any	53.3	66.7	19.0
Severe	7.8	38.9	0.6

***Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN**
**** Elevated Baseline Liver Function: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN**
*****Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given with the 60 mg/m² dose**
NA = not available

Non-Small Cell Lung Cancer (NSCLC): The efficacy and safety of TAXOTERE has been evaluated in patients with unresectable, locally advanced or metastatic non-small cell lung cancer whose disease has failed prior platinum-based chemotherapy or in patients who are chemotherapy-naïve.

Monotherapy with TAXOTERE for NSCLC Previously Treated with Platinum-Based Chemotherapy

Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m² was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). TAXOTERE at a dose of 100 mg/m², however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used (see **BOXED WARNING, WARNINGS,** and **DOSAGE AND ADMINISTRATION** sections).

One trial (TAX317), randomized patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, no history of taxane exposure, and an ECOG performance status ≤2 to TAXOTERE or best supportive care. The primary endpoint of the study was survival. Patients were initially randomized to TAXOTERE 100 mg/m² or best supportive care, but early toxic deaths at this dose led to a dose reduction to TAXOTERE 75 mg/m². A total of 104 patients were randomized in this amended study to either TAXOTERE 75 mg/m² or best supportive care.

In a second randomized trial (TAX320), 373 patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, and an ECOG performance status ≤2 were randomized to TAXOTERE 75 mg/m², TAXOTERE 100 mg/m² and a treatment in which the investigator chose either vinorelbine 30 mg/m² days 1, 8, and 15 repeated every 3 weeks **or** ifosfamide 2 g/m² days 1-3 repeated every 3 weeks. Forty percent of the patients in this study had a history of prior paclitaxel exposure. The primary endpoint was survival in both trials. The efficacy data for the TAXOTERE 75 mg/m² arm and the comparator arms are summarized in the table below and in figures 1 and 2 showing the survival curves for the two studies.

Efficacy of TAXOTERE in the Treatment of Non-Small Cell Lung Cancer Patients Previously Treated with a Platinum-Based Chemotherapy Regimen (Intent-to-Treat Analysis)

	TAX317		TAX320	
	Docetaxel 75 mg/m² n=55	Best Supportive Care/75 n=49	Docetaxel 75 mg/m² n=125	Control (V/I) n=123
Overall Survival Log-rank Test	p=0.01		p=0.13	
Risk Ratio††, Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.56 (0.35, 0.88)		0.82 (0.63, 1.06)	
Median Survival 95% CI	7.5 months* (5.5, 12.8)	4.6 months (3.7, 6.1)	5.7 months (5.1, 7.1)	5.6 months (4.4, 7.9)
% 1-year Survival 95% CI	37%*† (24, 50)	12% (2, 23)	30%*† (22, 39)	20% (13, 27)
Time to Progression 95% CI	12.3 weeks* (9.0, 18.3)	7.0 weeks (6.0, 9.3)	8.3 weeks (7.0, 11.7)	7.6 weeks (6.7, 10.1)
Response Rate 95% CI	5.5% (1.1, 15.1)	Not Applicable	5.7% (2.3, 11.3)	0.8% (0.0, 4.5)

* p≤0.05; † uncorrected for multiple comparisons; †† a value less than 1.00 favors docetaxel.

Only one of the two trials (TAX317) showed a clear effect on survival, the primary endpoint; that trial also showed an increased rate of survival to one year. In the second study (TAX320) the rate of survival at one year favored TAXOTERE 75 mg/m^2.

Figure 1: TAX317 Survival K-M Curves - TAXOTERE 75 mg/m^2 vs. Best Supportive Care

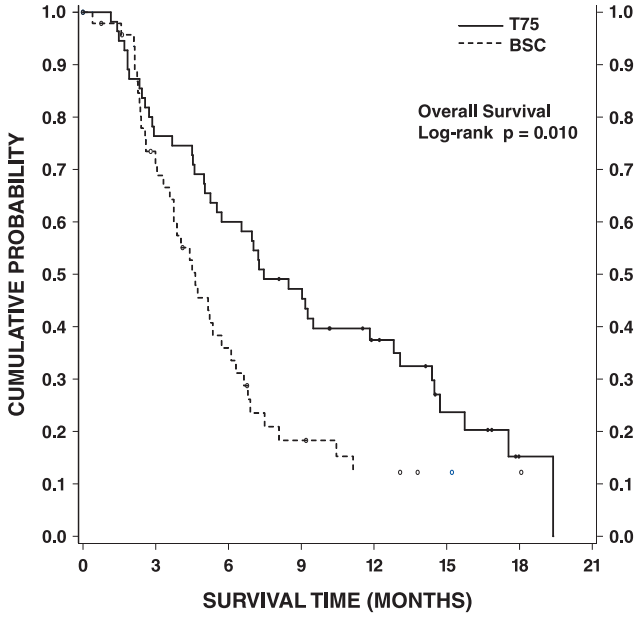
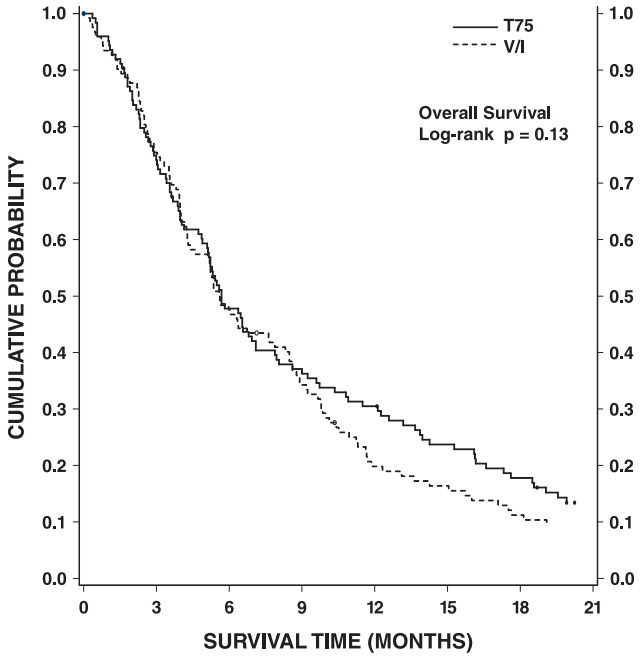


Figure 2: TAX320 Survival K-M Curves - TAXOTERE 75 mg/m^2 vs. Vinorelbine or Ifosfamide Control



Patients treated with TAXOTERE at a dose of 75 mg/m^2 experienced no deterioration in performance status and body weight relative to the comparator arms used in these trials.

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

In a randomized controlled trial (TAX326), 1218 patients with unresectable stage IIIB or IV NSCLC and no prior chemotherapy were randomized to receive one of three treatments: TAXOTERE 75 mg/m^2 as a 1 hour infusion immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks; vinorelbine 25 mg/m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m^2 administered on day 1 of cycles repeated every 4 weeks; or a combination of TAXOTERE and carboplatin.

The primary efficacy endpoint was overall survival. Treatment with TAXOTERE+cisplatin did not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and multiple comparisons) shows that the addition of TAXOTERE to cisplatin results in an outcome ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained. The efficacy data for the TAXOTERE+cisplatin arm and the comparator arm are summarized in the table below.

Survival Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC

Comparison	Taxotere+Cisplatin n=408	Vinorelbine+Cisplatin n=405
Kaplan-Meier Estimate of Median Survival	10.9 months	10.0 months
p-value[a]	0.122	
Estimated Hazard Ratio[b]	0.88	
Adjusted 95% CI[c]	(0.74, 1.06)	

[a]From the superiority test (stratified log rank) comparing TAXOTERE+cisplatin to vinorelbine+cisplatin

[b]Hazard ratio of TAXOTERE+cisplatin vs. vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that TAXOTERE+cisplatin is associated with a longer survival.

[c]Adjusted for interim analysis and multiple comparisons.

The second comparison in the study, vinorelbine+cisplatin versus TAXOTERE+carboplatin, did not demonstrate superior survival associated with the TAXOTERE arm (Kaplan-Meier estimate of median survival was 9.1 months for TAXOTERE+carboplatin compared to 10.0 months on the vinorelbine+cisplatin arm) and the TAXOTERE+carboplatin arm did not demonstrate preservation of at least 50% of the survival effect of vinorelbine added to cisplatin. Secondary endpoints evaluated in the trial included objective response and time to progression. There was no statistically significant difference between TAXOTERE+cisplatin and vinorelbine+cisplatin with respect to objective response and time to progression (see table below).

Response and TTP Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC

Endpoint	TAXOTERE+Cisplatin	Vinorelbine+Cisplatin	p-value
Objective Response Rate (95% CI)[a]	31.6% (26.5%, 36.8%)	24.4% (19.8%, 29.2%)	Not Significant
Median Time to Progression[b] (95% CI)[a]	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

[a]Adjusted for multiple comparisons.

[b]Kaplan-Meier estimates.

INDICATIONS AND USAGE

Breast Cancer: TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Non-Small Cell Lung Cancer: TAXOTERE as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

TAXOTERE in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

CONTRAINDICATIONS

TAXOTERE is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

TAXOTERE should not be used in patients with neutrophil counts of <1500 cells/mm^3.

WARNINGS

TAXOTERE should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Toxic Deaths

Breast Cancer: TAXOTERE administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (SGOT and/or SGPT > 1.5 times ULN together with AP > 2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer: TAXOTERE administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had a PS of 2 at study entry (see **BOXED WARNING, CLINICAL STUDIES**, and **DOSAGE AND ADMINISTRATION** sections).

Premedication Regimen: All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to TAXOTERE to reduce the severity of fluid retention and hypersensitivity reactions (see **DOSAGE AND ADMINISTRATION** section). This regimen was evaluated in 92 patients with metastatic breast cancer previously treated with chemotherapy given TAXOTERE at a dose of 100 mg/m^2 every 3 weeks.

Hypersensitivity Reactions: Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% of the 92 patients premedicated with 3-day corticosteroids. Hypersensitivity reactions requiring discontinuation of the TAXOTERE infusion were reported in 5 out of 1260 patients with various tumor types who did not receive premedication, but in 0/92 patients premedicated with 3-day corticosteroids. Patients with a history of severe hypersensitivity reactions should not be rechallenged with TAXOTERE.

Hematologic Effects: Neutropenia (< 2000 neutrophils/mm^3) occurs in virtually all patients given 60-100 mg/m^2 of TAXOTERE and grade 4 neutropenia (< 500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. TAXOTERE should not be administered to patients with neutrophils < 1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related and are described in **CLINICAL STUDIES**.

Three breast cancer patients with severe liver impairment (bilirubin > 1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia.

Hepatic Impairment: (see **BOXED WARNING**).

Fluid Retention: (see **BOXED WARNING**).

Pregnancy: TAXOTERE can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses ≥ 0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that TAXOTERE is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

There are no adequate and well-controlled studies in pregnant women using TAXOTERE. If TAXOTERE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE.

PRECAUTIONS

General: Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

Hematologic Effects: In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOTERE. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.

A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle (see **DOSAGE AND ADMINISTRATION** section).

Hypersensitivity Reactions: Hypersensitivity reactions may occur within a few minutes following initiation of a TAXOTERE infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. More severe reactions, however, require the immediate discontinuation of TAXOTERE and aggressive therapy. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of TAXOTERE (see **BOXED WARNING** and **WARNINGS**: **Premedication Regimen**).

Cutaneous: Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended (see **DOSAGE AND ADMINISTRATION** section). The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued TAXOTERE due to skin toxicity.

Fluid Retention: Severe fluid retention has been reported following TAXOTERE therapy (see **BOXED WARNING** and **WARNINGS**: **Premedication Regimen**). Patients should be premedicated with oral corticosteroids prior to each TAXOTERE administration to reduce the incidence and severity of fluid retention (see **DOSAGE AND ADMINISTRATION** section). Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. 9.8% (9/92) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the

last infusion of TAXOTERE to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

Neurologic: Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued (see **DOSAGE AND ADMINISTRATION** section). Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

Asthenia: Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Information for Patients: For additional information, see the accompanying Patient Information Leaflet.

Drug Interactions: There have been no formal clinical studies to evaluate the drug interactions of TAXOTERE with other medications. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving TAXOTERE as there is a potential for a significant interaction.

Carcinogenicity, Mutagenicity, Impairment of Fertility: No studies have been conducted to assess the carcinogenic potential of TAXOTERE. TAXOTERE has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in the mouse, but it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. TAXOTERE produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3 mg/kg (about 1/50 the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at IV doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3 and 1/15 the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Pregnancy: Pregnancy Category D (see **WARNINGS** section).

Nursing Mothers: It is not known whether TAXOTERE is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from TAXOTERE, mothers should discontinue nursing prior to taking the drug.

Pediatric Use: The safety and effectiveness of TAXOTERE in pediatric patients have not been established.

Geriatric Use: In a study conducted in chemotherapy-naïve patients with NSCLC (TAX326), 148 patients (36%) in the TAXOTERE+cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the TAXOTERE+cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI : 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI : 9.3 months, 14 months). In patients 65 years of age or greater treated with TAXOTERE+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with TAXOTERE+cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

When TAXOTERE was combined with carboplatin for the treatment of chemotherapy-naïve, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared to similar patients treated with TAXOTERE+cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

ADVERSE REACTIONS

The adverse reactions are described separately for TAXOTERE 100 mg/m^2, the maximum dose approved for breast cancer, and 75 mg/m^2, the dose approved for advanced non-small cell lung carcinoma after prior platinum-based chemotherapy and in combination with cisplatin for treatment of patients with non-small cell lung carcinoma who have not previously received chemotherapy for this condition.

TAXOTERE 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received TAXOTERE administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to TAXOTERE. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving TAXOTERE for the treatment of breast cancer and in patients with other tumor types.

Summary of Adverse Events in Patients Receiving TAXOTERE at 100 mg/m^2

Adverse Event	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Hematologic			
Neutropenia			
<2000 cells/mm^3	95.5	96.4	98.5
<500 cells/mm^3	75.4	87.5	85.9
Leukopenia			
<4000 cells/mm^3	95.6	98.3	98.6
<1000 cells/mm^3	31.6	46.6	43.7
Thrombocytopenia			
<100,000 cells/mm^3	8.0	24.6	9.2
Anemia			
<11 g/dL	90.4	91.8	93.6
<8 g/dL	8.8	31.1	7.7
Febrile Neutropenia***	11.0	26.2	12.3
Septic Death	1.6	4.9	1.4
Non-Septic Death	0.6	6.6	0.6
Infections			
Any	21.6	32.8	22.2
Severe	6.1	16.4	6.4
Fever in Absence of Infection			
Any	31.2	41.0	35.1
Severe	2.1	8.2	2.2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21.0	19.7	17.6
Severe	4.2	9.8	2.6
With 3-day Premedication	n=92	n=3	n=92
Any	15.2	33.3	15.2
Severe	2.2	0	2.2
Fluid Retention			
Regardless of Premedication			
Any	47.0	39.3	59.7
Severe	6.9	8.2	8.9
With 3-day Premedication	n=92	n=3	n=92
Any	64.1	66.7	64.1
Severe	6.5	33.3	6.5

Neurosensory			
Any	49.3	34.4	58.3
Severe	4.3	0	5.5
Cutaneous			
Any	47.6	54.1	47.0
Severe	4.8	9.8	5.2
Nail Changes			
Any	30.6	23.0	40.5
Severe	2.5	4.9	3.7
Gastrointestinal			
Nausea	38.8	37.7	42.1
Vomiting	22.3	23.0	23.4
Diarrhea	38.7	32.8	42.6
Severe	4.7	4.9	5.5
Stomatitis			
Any	41.7	49.2	51.7
Severe	5.5	13.0	7.4
Alopecia	75.8	62.3	74.2
Asthenia			
Any	61.8	52.5	66.3
Severe	12.8	24.6	14.9
Myalgia			
Any	18.9	16.4	21.1
Severe	1.5	1.6	1.8
Arthralgia	9.2	6.6	8.2
Infusion Site Reactions	4.4	3.3	4.0

***Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN**

****Elevated Baseline LFTs: SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN**

*****Febrile Neutropenia: ANC grade 4 with fever > 38°C with IV antibiotics and/or hospitalization**

Hematologic: (see **WARNINGS)**. Reversible marrow suppression was the major dose-limiting toxicity of TAXOTERE. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cells/mm^3 with fever > 38°C with IV antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions: Severe hypersensitivity reactions are discussed in the **BOXED WARNING, WARNINGS,** and **PRECAUTIONS** sections. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and appropriate therapy.

Fluid Retention: (see **BOXED WARNING**, **WARNINGS: Premedication Regimen**, and **PRECAUTIONS** sections**)**.

Cutaneous: Severe skin toxicity is discussed in **PRECAUTIONS**. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after TAXOTERE infusion, recovered before the next infusion, and were not disabling.

Severe nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

Neurologic: **(**see **PRECAUTIONS)**.

Gastrointestinal: Gastrointestinal reactions (nausea and/or vomiting and/or diarrhea) were generally mild to moderate. Severe reactions occurred in 3-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

Cardiovascular: Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. 8.1% (7/86) of metastatic breast cancer patients receiving TAXOTERE 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥ 10% associated with a drop below the institutional lower limit of normal.

Infusion Site Reactions: Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

Hepatic: In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in SGOT or SGPT > 1.5 times the ULN, or alkaline phosphatase > 2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on TAXOTERE, increases in SGOT and/or SGPT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. (Whether these changes were related to the drug or underlying disease has not been established.)

Monotherapy with TAXOTERE for Unresectable, Locally Advanced or Metastatic NSCLC Previously Treated with Platinum-Based Chemotherapy

TAXOTERE 75 mg/m^2: Treatment emergent adverse drug reactions are shown below. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or otherwise noted.

Treatment Emergent Adverse Events Regardless of Relationship to Treatment in Patients Receiving TAXOTERE as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy*

Adverse Event	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Neutropenia			
Any	84.1	14.3	83.2
Grade 3/4	65.3	12.2	57.1
Leukopenia			
Any	83.5	6.1	89.1
Grade 3/4	49.4	0	42.9
Thrombocytopenia			
Any	8.0	0	7.6
Grade 3/4	2.8	0	1.7
Anemia			
Any	91.0	55.1	90.8
Grade 3/4	9.1	12.2	14.3
Febrile Neutropenia**	6.3	NA†	0.8
Infection			
Any	33.5	28.6	30.3
Grade 3/4	10.2	6.1	9.2
Treatment Related Mortality	2.8	NA†	3.4
Hypersensitivity Reactions			
Any	5.7	0	0.8
Grade 3/4	2.8	0	0
Fluid Retention			
Any	33.5	ND††	22.7
Severe	2.8		3.4
Neurosensory			
Any	23.3	14.3	28.6
Grade 3/4	1.7	6.1	5.0

Neuromotor			
Any	15.9	8.2	10.1
Grade 3/4	4.5	6.1	3.4
Skin			
Any	19.9	6.1	16.8
Grade 3/4	0.6	2.0	0.8
Gastrointestinal			
Nausea			
Any	33.5	30.6	31.1
Grade 3/4	5.1	4.1	7.6
Vomiting			
Any	21.6	26.5	21.8
Grade 3/4	2.8	2.0	5.9
Diarrhea			
Any	22.7	6.1	11.8
Grade 3/4	2.8	0	4.2
Alopecia	56.3	34.7	49.6
Asthenia			
Any	52.8	57.1	53.8
Severe***	18.2	38.8	22.7
Stomatitis			
Any	26.1	6.1	7.6
Grade 3/4	1.7	0	0.8
Pulmonary			
Any	40.9	49.0	45.4
Grade 3/4	21.0	28.6	18.5
Nail Disorder			
Any	11.4	0	1.7
Severe***	1.1	0	0
Myalgia			
Any	6.3	0	2.5
Severe***	0	0	0
Arthralgia			
Any	3.4	2.0	1.7
Severe***	0	0	0.8
Taste Perversion			
Any	5.7	0	0
Severe***	0.6	0	0

***Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN**
****Febrile Neutropenia: ANC grade 4 with fever > 38°C with IV antibiotics and/or hospitalization**
*****COSTART term and grading system**
† Not Applicable; †† Not Done

Combination Therapy with TAXOTERE in Chemotherapy-Naïve Advanced Unresectable or Metastatic NSCLC

The table below presents safety data from two arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Adverse Events Regardless of Relationship to Treatment in Chemotherapy-Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving TAXOTERE in Combination with Cisplatin

Adverse Event	TAXOTERE 75 mg/m² + Cisplatin 75 mg/m² n=406 %	Vinorelbine 25 mg/m² + Cisplatin 100 mg/m² n=396 %
Neutropenia		
Any	91	90
Grade 3/4	74	78
Febrile Neutropenia	5	5
Thrombocytopenia		
Any	15	15
Grade 3/4	3	4
Anemia		
Any	89	94
Grade 3/4	7	25
Infection		
Any	35	37
Grade 3/4	8	8
Fever in absence of infection		
Any	33	29
Grade 3/4	< 1	1
Hypersensitivity Reaction*		
Any	12	4
Grade 3/4	3	< 1
Fluid Retention**		
Any	54	42
All severe or life-threatening events	2	2
Pleural effusion		
Any	23	22
All severe or life-threatening events	2	2
Peripheral edema		
Any	34	18
All severe or life-threatening events	<1	<1
Weight gain		
Any	15	9
All severe or life-threatening events	<1	<1
Neurosensory		
Any	47	42
Grade 3/4	4	4
Neuromotor		
Any	19	17
Grade 3/4	3	6
Skin		
Any	16	14
Grade 3/4	<1	1
Nausea		
Any	72	76
Grade 3/4	10	17
Vomiting		
Any	55	61
Grade 3/4	8	16
Diarrhea		
Any	47	25
Grade 3/4	7	3
Anorexia**		
Any	42	40
All severe or life threatening events	5	5
Stomatitis		
Any	24	21
Grade 3/4	2	1
Alopecia		
Any	75	42
Grade 3	< 1	0
Asthenia**		
Any	74	75
All severe or life threatening events	12	14
Nail Disorder**		
Any	14	< 1
All severe events	< 1	0
Myalgia**		
Any	18	12
All severe events	< 1	< 1

*** Replaces NCI term "Allergy"**
**** COSTART term and grading system**

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel+cisplatin arm and 8 patients (2.0%) in the vinorelbine+ cisplatin arm.

The second comparison in the study, vinorelbine+cisplatin versus TAXOTERE+carboplatin (which did not demonstrate a superior survival associated with TAXOTERE, see **CLINICAL STUDIES** section) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia and nail changes on the TAXOTERE+carboplatin arm, while a higher incidence of anemia, neurosensory toxicity, nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

Post-marketing Experiences

The following adverse events have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction

Cutaneous: rare cases of bullous eruption such as erythema multiforme or Stevens-Johnson syndrome. Multiple factors may have contributed to the development of these effects.

Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.

Hematologic: bleeding episodes

Hepatic: rare cases of hepatitis have been reported.

Neurologic: confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported.

Urogenital: renal insufficiency

OVERDOSAGE

There is no known antidote for TAXOTERE overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

In mice, lethality was observed following single IV doses that were ≥154 mg/kg (about 4.5 times the recommended human dose on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the recommended human dose on a mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the recommended human dose on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

DOSAGE AND ADMINISTRATION

Breast Cancer: The recommended dose of TAXOTERE is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.

Non-Small Cell Lung Cancer: For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials (see **BOXED WARNING, WARNINGS** and **CLINICAL STUDIES** sections).

For chemotherapy-naïve patients, TAXOTERE was evaluated in combination with cisplatin. The recommended dose of TAXOTERE is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.

Premedication Regimen: All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to TAXOTERE administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **BOXED WARNING**, **WARNINGS,** and **PRECAUTIONS** sections).

Dosage Adjustments During Treatment

Breast Cancer: Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during TAXOTERE therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during TAXOTERE therapy may tolerate higher doses. Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Non-Small Cell Lung Cancer:

Monotherapy with TAXOTERE for NSCLC Treatment After Failure of Prior Platinum-Based Chemotherapy

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during TAXOTERE treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

For patients who are dosed initially at TAXOTERE 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the TAXOTERE dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Special Populations:

Hepatic Impairment: Patients with bilirubin > ULN should generally not receive TAXOTERE. Also, patients with SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN should generally not receive TAXOTERE.

Children: The safety and effectiveness of docetaxel in pediatric patients below the age of 16 years have not been established.

Elderly: See **Precautions, Geriatric Use.** In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

PREPARATION AND ADMINISTRATION

Administration Precautions

TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOTERE Injection Concentrate requires <u>two</u> dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the TAXOTERE Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **<u>entire</u>** contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL docetaxel. The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for TAXOTERE 20 mg and TAXOTERE 80 mg.

Product	Diluent 13% (w/w) ethanol in water for injection Fill Range (mL)	Approximate extractable volume of diluent when entire contents are withdrawn (mL)	Concentration of the initial diluted solution (mg/mL docetaxel)
Taxotere® 20 mg/0.5 mL	1.88 – 2.08 mL	1.8 mL	10 mg/mL
Taxotere® 80 mg/2 mL	6.96 - 7.70 mL	7.1 mL	10 mg/mL

Preparation and Administration

A. Initial Diluted Solution

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the **entire** contents of the appropriate diluent vial (approximately 1.8 mL for TAXOTERE 20 mg and approximately 7.1 mL for TAXOTERE 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of TAXOTERE Injection Concentrate. **<u>If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.</u>**
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

   The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

   If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Stability: TAXOTERE infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).

HOW SUPPLIED

TAXOTERE Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE 80 MG/2 ML (NDC 0075-8001-80)

TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for TAXOTERE 80 mg. (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

TAXOTERE 20 MG/0.5 ML (NDC 0075-8001-20)

TAXOTERE (docetaxel) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg. (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

Storage: Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. OSHA Work-Practice Guidelines for Controlling Occupational Exposure to Hazardous Drugs. *Am J Health-Syst Pharm*. 1996; 53: 1669-1685.
2. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*. 1990; 47(95): 1033-1049.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985; 253(11): 1590-1592.
4. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
5. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffry, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
6. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Austr*. 1983; 426-428.
7. Jones, RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mt. Sinai Medical Center. *CA-A Cancer Journal for Clinicians*. 1983; Sept/Oct: 258-263.

Prescribing Information as of April 2003

Manufactured by Aventis Pharma Ltd.
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United Kingdom

Manufactured for
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Bridgewater, NJ 08807 USA
www.aventis-us.com

TAX-APR03-F-A

Patient Information Leaflet
Detach and give to Patient

Rev. April 2003

Patient Information Leaflet

Questions and Answers About Taxotere® Injection Concentrate
(generic name = docetaxel)
(pronounced as TAX-O-TEER)

What is Taxotere?

Taxotere is a medication to treat breast cancer and non-small cell lung cancer. It has severe side effects in some patients. This leaflet is designed to help you understand how to use Taxotere and avoid its side effects to the fullest extent possible. The more you understand your treatment, the better you will be able to participate in your care. If you have questions or concerns, be sure to ask your doctor or nurse. They are always your best source of information about your condition and treatment.

What is the most important information about Taxotere?

- Since this drug, like many other cancer drugs, affects your blood cells, your doctor will ask for routine blood tests. These will include regular checks of your white blood cell counts. People with low blood counts can develop life-threatening infections. The earliest sign of infection may be fever, so if you experience a fever, tell your doctor right away.
- Occasionally, serious allergic reactions have occurred with this medicine. If you have any allergies, tell your doctor before receiving this medicine.
- A small number of people who take Taxotere have severe fluid retention, which can be life-threatening. To help avoid this problem, you must take another medication called dexamethasone (DECKS-A-METH-A-SONE) prior to each Taxotere treatment. You must follow the schedule and take the exact dose of dexamethasone prescribed (see schedule at end of brochure). If you forget to take a dose or do not take it on schedule you must tell the doctor or nurse prior to your Taxotere treatment.
- If you are using any other medicines, tell your doctor before receiving your infusions of Taxotere.

How does Taxotere work?

Taxotere works by attacking cancer cells in your body. Different cancer medications attack cancer cells in different ways.

Here's how Taxotere works: Every cell in your body contains a supporting structure (like a skeleton). Damage to this "skeleton" can stop cell growth or reproduction. Taxotere makes the "skeleton" in some cancer cells very stiff, so that the cells can no longer grow.

How will I receive Taxotere?

Taxotere is given by an infusion directly into your vein. Your treatment will take about 1 hour. Generally, people receive Taxotere every 3 weeks. The amount of Taxotere and the frequency of your infusions will be determined by your doctor.

As part of your treatment, to reduce side effects your doctor will prescribe another medicine called dexamethasone. Your doctor will tell you how and when to take this medicine. It is important that you take the dexamethasone on the schedule set by your doctor. If you forget to take your medication, or do not take it on schedule, make sure to tell your doctor or nurse **BEFORE** you receive your Taxotere treatment. **Included with this information leaflet is a chart to help you remember when to take your dexamethasone.**

What should be avoided while receiving Taxotere?

Taxotere can interact with other medicines. Use only medicines that are prescribed for you by your doctor and **be sure** to tell your doctor all the medicines that you use, including nonprescription drugs.

What are the possible side effects of Taxotere?

Low Blood Cell Count – Many cancer medications, including Taxotere, cause a temporary drop in the number of white blood cells. These cells help protect your body from infection. Your doctor will routinely check your blood count and tell you if it is too low. Although most people receiving Taxotere do not have an infection even if they have a low white blood cell count, the risk of infection is increased.

Fever is often one of the most common and earliest signs of infection. Your doctor will recommend that you take your temperature frequently, especially during the days after treatment with Taxotere. If you have a fever, tell your doctor or nurse immediately.

Allergic Reactions – This type of reaction, which occurs during the infusion of Taxotere, is infrequent. If you feel a warm sensation, a tightness in your chest, or itching during or shortly after your treatment, tell your doctor or nurse immediately.

Fluid Retention – This means that your body is holding extra water. If this fluid retention is in the chest or around the heart it can be life-threatening. If you notice swelling in the feet and legs or a slight weight gain, this may be the first warning sign. Fluid retention usually does not start immediately; but, if it occurs, it may start around your 5th treatment. Generally, fluid retention will go away within weeks or months after your treatments are completed.

Dexamethasone tablets may protect patients from significant fluid retention. It is important that you take this medicine on schedule. If you have not taken dexamethasone on schedule, you must tell your doctor or nurse before receiving your next Taxotere treatment.

Gastrointestinal – Diarrhea has been associated with TAXOTERE use and can be severe in some patients. Nausea and/or vomiting are common in patients receiving TAXOTERE. Severe inflammation of the bowel can also occur in some patients and may be life threatening.

Hair Loss – Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows, and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back.

Your doctor or nurse can refer you to a store that carries wigs, hairpieces, and turbans for patients with cancer.

Fatigue – A number of patients (about 10%) receiving Taxotere feel very tired following their treatments. If you feel tired or weak, allow yourself extra rest before your next treatment. If it is bothersome or lasts for longer than 1 week, inform your doctor or nurse.

Muscle Pain – This happens about 20% of the time, but is rarely severe. You may feel pain in your muscles or joints. Tell your doctor or nurse if this happens. They may suggest ways to make you more comfortable.

Rash – This side effect occurs commonly but is severe in about 5%. You may develop a rash that looks like a blotchy, hive-like reaction. This usually occurs on the hands and feet but may also appear on the arms, face, or body. Generally, it will appear between treatments and will go away before the next treatment. Inform your doctor or nurse if you experience a rash. They can help you avoid discomfort.

Odd Sensations – About half of patients getting Taxotere will feel numbness, tingling, or burning sensations in their hands and feet. If you do experience this, tell your doctor or nurse. Generally, these go away within a few weeks or months after your treatments are completed. About 14% of patients may also develop weakness in their hands and feet.

Nail Changes – Color changes to your fingernails or toenails may occur while taking Taxotere. In extreme, but rare, cases nails may fall off. After you have finished Taxotere treatments, your nails will generally grow back.

Eye Changes – Excessive tearing, which can be related to conjunctivitis or blockage of the tear ducts, may occur.

If you are interested in learning more about this drug, ask your doctor for a copy of the package insert.

Aventis Pharmaceuticals Inc.
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Date _____

Day 1

Start
Dexamethasone tablets
2 times per day
AM
PM

Date _____

Day 2

Taxotere
Treatment Day

Take
Dexamethasone tablets
2 times per day
AM
PM

Date _____

Day 3

Take
Dexamethasone tablets
2 times per day
AM
PM

OTHER MEDICATIONS TAKEN

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09-6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

FOR OFFICE USE	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	
Study Staff Signature: _____	

Study Participant Self-Administration Study Drug Diary

Dana-Farber/Harvard Cancer Center

Participant Identifier: _____
Protocol # 09-302
Your MD_____ Phone_____
Your RN_____ Phone_____

STUDY DRUG INSTRUCTIONS

Study Drug: PF-02341066.
How Much: Your dose is 250 mg dose of PF-02341066.
How Often: You will take each dose twice a day.
When: You should take your dose every morning and every evening. The morning and evening doses should be approximately 12 hours apart. Dosing will be daily with no break.

SPECIAL INSTRUCTIONS

- If you vomit after taking PF-02341066, do not re-take the dose, but rather wait until the next scheduled dose.
- If you remember to take a missed dose within 6 hours of the scheduled time, then take that dose and go back on schedule for the next dose. If you do not remember within 6 hours of the scheduled time, do not make up the dose, and just take the next dose at the scheduled time.
- You must avoid sunbathing, prolong unprotected sun exposure, or tanning for the duration of the study.
- There are certain drugs (including over-the-counter medications and herbal supplements) or foods (such as grapefruit and grapefruit juice) that may interfere with the study treatment. You must tell your doctor of all medications, including herbal and nonprescription medicines you are taking before starting the study and while you are on study. Once you have been assigned to your study treatment, your doctor will let you know if your medications are safe to take while you are on the study.
- PF-02341066 must be handled and taken with care. PF-02341066 will be given to you at the beginning of each treatment cycle. PF-02341066 will be provided as tablets containing either 50 or 100 mg of study medication. Take care to keep your study medication in the bottles provided and do not transfer it to any other container. PF-02341066 should be stored at room temperature (59°F/ 15°C to

86°F/ 30°C).

- PF-02341066 will be provided in a childproof package. If you feel that this will be hard for you to open and close, please tell the study doctor and other arrangements will be made. Please make sure that no one else uses your study drug. Please keep it away from your other drugs. Keep study drug out of reach of children.
- You will be required to return all bottles of study medication at the beginning of each cycle. The number of tablets remaining will be documented and recorded.

DOSING LOG

CYCLE 1

PF-02341066
For each dose take: 2- 100mg tablets and 1- 50mg tablet, for a total of 3 tablets.

Please indicate the date, time, amount taken and any comments.

	Date	Amount Taken		Comments
		AM dose	PM dose	
Ex:	6/1/09	8am - 1	7:30pm - 1	Vomited PM dose
Day 1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

Symptom	Start Date	End Date	Severity

Patient Emergency Card

Protocol Number: A8081007

Patient Study Number: _____

This card is issued to a patient participating in a Pfizer Study investigating PF-02341066. In the event of a medical emergency, medical attendants can obtain additional information by telephone. *Please see back of card for details.*

Please remember to carry this card with you at all times. If you are in need of medical attention, this card should be shown to medical staff.

Patient Emergency Card

Primary Contact Information

Principal Investigator (PI): _____

Telephone number/s: _____

Emergency Contact Information

In case of Emergency and the doctor conducting the study is unavailable, medical staff can obtain further information by contacting:

Toll free Number: (*) 1-877-433-2619

* If required non-US callers add Access Country Code number, available at: www.business.att.com/bt/dial_guide.jsp

207757 Patient ID Card v1.0 US (English) 19.Oct.12