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CHILDREN'S ONCOLOGY GROUP
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A PHASE 1/2 STUDY OF PF-02341066, AN ORAL SMALL MOLECULE INHIBITOR OF ANAPLASTIC LYMPHOMA KINASE (ALK) AND C-MET, IN CHILDREN WITH RELAPSED/REFRACTORY SOLID TUMORS AND ANAPLASTIC LARGE CELL LYMPHOMA

Participation Limited to member COG Phase 1 Consortium Institutions and the following non-member collaborator (NMC) institutions:

<u>CTEP ID/Participating Institution</u> [redacted]
MA036/ Dana-Farber Cancer Institute
OH006/ Nationwide Children's Hospital
CO011/ Children's Hospital Colorado
TX011/ UT Southwestern/Simmons Cancer Center-Dallas
TN008/ Vanderbilt University/Ingram Cancer Center

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AGENT NSC# and IND#'s
PF-02341066-004, PF-02341066
(NSC# 749005, IND # 105573)

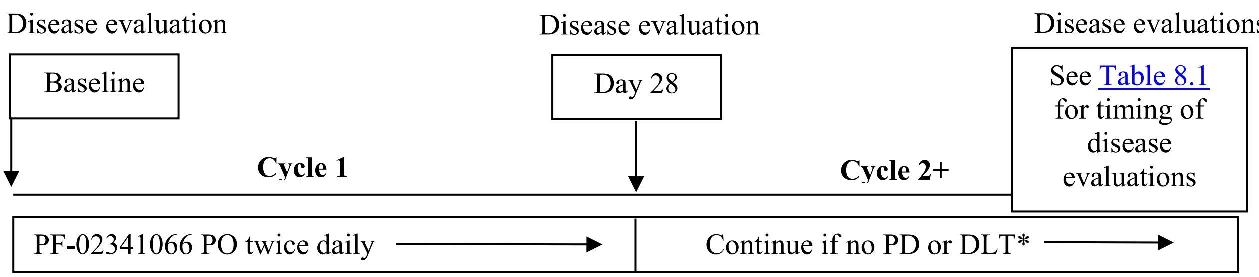
SEE APPENDICES V-A, VI, VIII, IX AND X FOR SPECIMEN SHIPPING ADDRESSES
SEE APPENDIX XVI FOR NON-MEMBER COLLABORATOR (NMC) PARTICIPATION

ABSTRACT

There is an emerging paradigm in oncology that clinical efficacy can be obtained with inhibitors directed toward oncogenic receptor tyrosine kinases (RTKs) that are mutated or otherwise dysregulated in certain tumor types. Examples of such successful intervention include imatinib in GIST with mutant c-Kit, erlotinib in NSCLC with mutant and/or amplified EGFR, trastuzumab in breast cancers with amplified HER-2, and sunitinib targeting the VHL-dependent VEGF pathway in RCC. The c-Met RTK is frequently altered or dysregulated in advanced cancers and has been implicated in tumor progression,[1] and therefore represents an attractive novel therapeutic target. It has been shown that the Met receptor has a role in PAX3-FKHR-mediated transformation in rhabdomyosarcomas, and that MET can serve as a therapeutic target in this disease.[2] The anaplastic lymphoma kinase gene (*ALK*), which has significant homology to the Met oncogene, plays a role in the pathogenesis of anaplastic large-cell lymphomas (ALCL), due to a chromosomal translocation that results in expression of an oncogenic kinase fusion protein known as NPM-*ALK*. *ALK* is an orphan tyrosine kinase transmembrane receptor with homology to neurotrophin receptors and the *MET* oncogene. Expression is restricted to the developing nervous system with a postulated role in the regulation of neuronal differentiation.[3] It has recently become clear that many human cancers activate *ALK* signaling by creating unique oncogenic fusions of the *ALK* gene at 2p23 with a variety of partners through chromosomal translocation events,[4] resulting in the generation of oncogenic *ALK* fusion genes and their encoded proteins. Recently, the interest in *ALK* biology has increased considerably, following the discovery of *ALK* translocations in a fraction of non-small-cell lung cancers[5] and in other solid tumors.[4] It is now clear that many human cancers activate *ALK* signaling by creating unique oncogenic fusions of *ALK* with a variety of partners through chromosomal translocation events. Previous work had shown that a substantial percentage of human-derived neuroblastoma cell lines express *ALK* transcripts and *ALK* protein, but no definitive role for this oncogene had been proven. We have recently discovered that activating mutations in the tyrosine kinase domain of the anaplastic lymphoma kinase (*ALK*) oncogene are the cause of hereditary neuroblastoma, and that these mutations can also be somatically acquired.[6] *ALK* was also recently identified as a molecular target in neuroblastoma by a screen of human cancer cell lines with pharmacologic antagonists of the *ALK* kinase domain.[7] We hypothesize that *ALK* is a critical neuroblastoma oncogene and that activation of this cell surface kinase is a tractable therapeutic target.

PF-02341066 is an orally bioavailable small molecule inhibitor of the catalytic activity of c-Met kinase and the NPM-ALK fusion protein. In biochemical and cellular screens, PF-02341066 was shown to be selective for c-Met and ALK at pharmacologically relevant concentrations across a panel of >120 diverse kinases.[8,9] PF-02341066 potently inhibited cell proliferation, which was associated with G_1S-phase cell cycle arrest and induction of apoptosis in ALK-positive ALCL cells but not ALK-negative lymphoma cells. In addition, inhibition of key NPM-ALK signaling mediators was observed at concentrations that required for inhibition of NPM-ALK phosphorylation and function. More recently, the *in vitro* activity of PF-02341066 was examined in a panel of ALCL and neuroblastoma cell lines. PF-02341066 was able to inhibit proliferation and *ALK*-mediated signaling in these cell lines at clinically achievable doses, with potent suppression of downstream effectors seen in the neuroblastoma cells.[7]

EXPERIMENTAL DESIGN SCHEMA



*Twice daily treatment with PF-02341066 will be discontinued if there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from therapy. Patients with stable disease or better who are having clinical benefit from PF-02341066 may continue receiving protocol therapy provided that the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and recommend a Phase 2 dose of PF-02341066 administered orally twice daily to children with relapsed/refractory solid tumors and anaplastic large cell lymphoma (ALCL).

1.1.2 To define and describe the toxicities of PF-02341066 administered on this schedule.

1.1.3 To characterize the pharmacokinetics of PF-02341066 in children with refractory cancer.

1.2 Secondary Aims

1.2.1 To preliminarily define the anti-tumor activity of PF-02341066 within the confines of a Phase 1 study.

1.2.2 To obtain initial Phase 2 data on the anti-tumor activity of PF-02341066 in children with relapsed/refractory neuroblastoma and ALCL.

1.2.3 To preliminarily examine the relationship between ALK status (e.g, the presence of a mutation, duplication, amplification, and/or translocation) in patients with NB or ALCL and response to PF-02341066.

1.2.4 To preliminarily examine the relationship between MRD status and clinical response to PF-02341066 in patients with ALCL.

1.2.5 To use a questionnaire to gather preliminary information on the palatability of the oral solution formulation of PF-02341066.

1.2.6 To evaluate for potential alterations in bone growth in pediatric patients.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

PF-02341066 is a small-molecule inhibitor of the c-Met/HGFR and ALK receptor tyrosine kinase. 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 Gleevec® in gastrointestinal stromal tumors with mutant c-Kit or chronic myelogenous leukemia with BCR-Abl gene translocations, Tarceva® in non-small cell lung cancer with mutant EGFR, Herceptin® in breast cancers with amplified HER-2/neu, and SU11248 targeting the VHL-dependent VEGF pathway in renal cell carcinoma. An extensive body of literature indicates that c-Met/HGFR is one of the most frequently mutated or otherwise abnormally activated RTKs in various human cancers.[1] The c-Met/Hepatocyte growth factor receptor (HGFR) has been well characterized for its role in regulation of cell growth, migration, and invasion of both tumor cells and endothelial cells.[1] An extensive body of literature indicates that c-Met/HGFR is one of the receptor tyrosine kinases (RTKs) most frequently mutated or otherwise abnormally activated in late-stage human cancer. When activated, c-Met/HGFR plays a critical role in regulation of tumor oncogenic processes such as mitogenesis, survival, invasive growth, metastasis and tumor angiogenesis. Activating mutations in c-Met/HGFR have been identified in multiple adult solid tumors.[1] Recent data shows that ALK is overexpressed in glioblastoma compared to normal brain, and that ribozyme-mediated targeting of ALK leads to reduced tumor growth of glioblastoma xenografts and increased apoptosis in the tumors.[10]

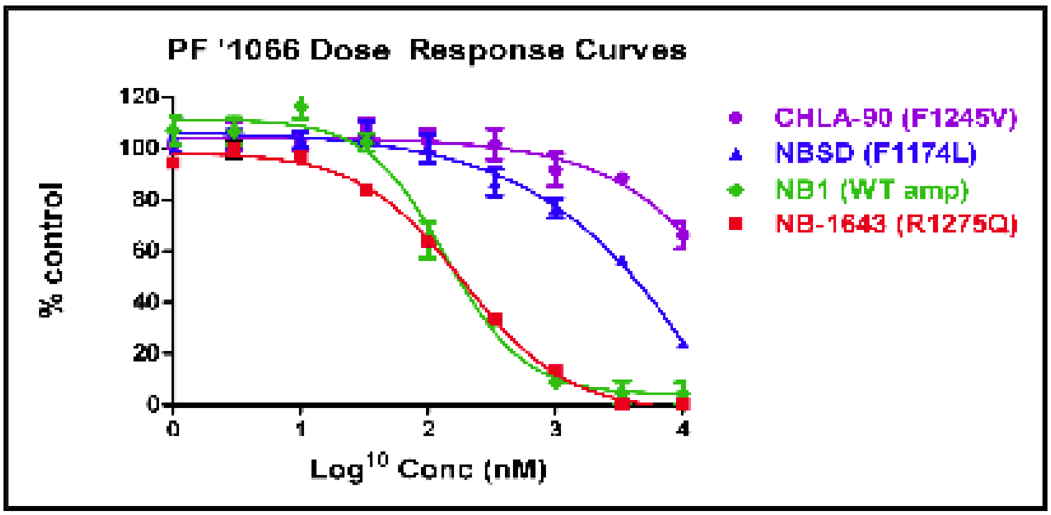
ALK was first described in anaplastic large cell lymphoma,[11] where a chromosomal translocation leads to production of an oncogenic fusion protein with the ALK intracellular region fused to the nucleophosmin (NPM) N-terminus. Similarly, ALK fusion transcripts, most commonly with EML4, are potent oncogenic drivers in a subset of non-small cell lung cancers (NSCLC),[5] and additional ALK fusions drive inflammatory myofibroblastic tumors (IMTs) and other cancers.[12] Among selective kinase inhibitors tested in a panel of 602 cell lines derived from a variety of human cancers, it was found that a selective inhibitor of ALK potently suppressed growth of lines derived from anaplastic large cell lymphomas and neuroblastomas.[7] Anaplastic lymphoma kinase (ALK) and its mutant translocation with the nucleophosmin gene (NPM-ALK) results in a constitutively active ALK receptor tyrosine kinase expressed in the majority (~80%) of anaplastic large cell lymphomas (ALCL).[13] 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.[13] In addition, recent data indicates that mutations in ALK are responsible for the majority of heritable neuroblastoma cases, and also are present in a substantial subset of high-risk neuroblastomas due to somatic mutation.[6,14] Preclinical data in neuroblastoma confirm the oncogenic potential of mutated ALK, and RNA inhibition of ALK message validates the feasibility of a targeted approach in this tumor type.[6] 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.

PF-02341066 is an orally bioavailable, selective c-Met/HGFR aminopyridine tyrosine kinase inhibitor and a potent ATP-competitive inhibitor of recombinant, human c-Met/HGFR kinase activity with a mean Ki of 4 nM. In preliminary biochemical screens, PF-02341066 inhibited HGF-stimulated or constitutive total tyrosine phosphorylation of wild type c-Met/HGFR with a mean IC_{50} value of 11 nM across a panel of human tumor cell lines. In addition, PF-02341066 demonstrated potent activity against NPM-ALK in a human lymphoma cell line (IC_{50} ~ 24 nM). PF-02341066 has also shown potent activity in preclinical *in vivo* xenograft models of GTL-16 gastric carcinoma (mean 60% regression) and the NCI-H441 non-small cell lung carcinoma (mean 48% regression) models. PF-02341066 also demonstrated near complete tumor growth inhibition in both the U87MG glioblastoma (97% growth inhibition) and PC-3 prostate carcinoma models (87% growth inhibition) at 50 mg/kg/day. In the Karpas 299 NPM-ALK positive human ALCL lymphoma tumor model, administration of PF-02341066 at 100 mg/kg/day resulted in complete regression of tumors of all mice in this dosing cohort within 15 days of the initial compound administration. After 17 days, PF-02341066 treatment was stopped, resulting in tumor regrowth. When tumors grew to a larger size (>600 mm^3), PF-02341066 treatment was reinitiated for an additional 13 days and complete regression of tumors was once again demonstrated. PF-02341066 exhibits convincing antitumor activity in several xenograft models. Importantly, it delivers antitumor efficacy in xenograft models with a large safety window, providing increased confidence that mechanism-based toxicity will not be limiting in the clinic.

These data, coupled with preclinical *in vitro* data in high-risk neuroblastoma, provide a compelling rationale for investigating PF-02341066 in pediatric solid tumors, including CNS tumors, neuroblastoma and ALCL.

There is robust preclinical rationale to maximize the recommended phase 2 dose based upon laboratory data that mutated ALK is more difficult to inhibit relative to translocated ALK (as seen in ALCL and lung cancer), and the fact that certain mutations (F1174L) are hyperactivated and thus are relatively resistant to ALK inhibition (Figure 1), but this resistance can be overcome in a dose-dependent manner.

Figure 1. Dose-response curves *in vitro* to PF-02341066 in 4 NB cell lines harboring different ALK mutations showing differential sensitivity.



2.2 Preclinical Studies

2.2.1 Antitumor Activity

Preclinical *in vitro* and *in vivo* data demonstrated that PF-02341066 is a potent and selective inhibitor of the c-Met/HGFR and ALK receptor tyrosine kinases, as well as several of their oncogenic variants (ATP binding site mutations in c-Met and the NPM-ALK fusion protein). In a series of cell-based functional assays, PF-02341066 potently inhibited human GTL-16 gastric carcinoma cell growth, HGF-stimulated human NCI-H441 lung carcinoma cell migration and invasion through a matrigel matrix and HGF-stimulated MDCK cell motility/scattering, with IC50 values ranging from 6.1 to 16 nM. Additionally, PF-02341066 inhibited proliferation of Karpas 299 ALCL cells that express an NPM-ALK fusion protein due to a t(2;5) chromosomal translocation (IC50 = 60 nM). Growth inhibition by PF-02341066 in these NPM-ALK positive lymphoma cells was associated with G0/G1 cell cycle arrest and induction of apoptosis. When investigated for potential antiangiogenic activity, PF-02341066 inhibited HGF-mediated HUVEC endothelial cell survival (IC50 = 11 nM) and matrigel invasion (IC50 = 35 nM) as well as HMVEC endothelial cell tubulogenesis in fibrin gels, with IC_{50}'s of 11 nM to approximately 80 nM. These studies suggest that PF-02341066 is active against tumors of diverse tissue types, and may also harbor anti-angiogenic effects.

The antitumor activity of PF-02341066 has also been evaluated in a variety of human tumor xenograft models representative of cancer indications in which dysregulation of c-Met/HGFR is implicated. PF-02341066 demonstrated potent cytoreductive activity in both the GTL-16 gastric carcinoma (mean 60% regression) and the NCI-H441 non-small cell lung carcinoma (mean 48% regression) models, suggesting the potential to monitor patient objective response as a means of assessing clinical efficacy. PF-02341066 also demonstrated near complete tumor growth inhibition in both the U87MG glioblastoma (97% growth inhibition) and PC-3 prostate carcinoma models (87% growth inhibition) at 50 mg/kg/day. In models in which multiple dose levels were evaluated (GTL-16, U87MG, and NCI-H441), dose-dependent inhibition of tumor growth correlated with inhibition of c-Met/HGFR phosphorylation. In these studies it was observed that complete inhibition of c-Met/HGFR was achieved for the full dosing interval at 50 mg/kg/day. In the Karpas 299 NPM-ALK positive human ALCL lymphoma tumor model, administration of PF-02341066 at 100 mg/kg/day resulted in complete regression of tumors of all mice in this dosing cohort within 15 days of the initial compound administration. After 17 days, PF-02341066 treatment was stopped, resulting in tumor regrowth. When tumors grew to a larger size (>600 mm^3), PF-02341066 treatment was reinitiated for an additional 13 days and complete regression of tumors was once again demonstrated.

2.2.2 Preliminary Activity of PF-02341066 in Neuroblastoma

Mutations in the *ALK* proto-oncogene are the major cause of hereditary neuroblastoma (NB)[6] and are somatically acquired in sporadic primary tumors.[14-16] We resequenced the *ALK* tyrosine kinase domain in 449 primary NB DNAs, and stained a tissue microarray (TMA) of 160 NBs with anti-*ALK* and anti-p*ALK* antibodies. We evaluated the anti-tumor activity of PF-02341066, an orally bioavailable small molecule inhibitor of *ALK*, against a panel of patient derived cell lines *in vitro* and *in vivo.* Mutations were discovered in at least 15% of NBs, and across the spectrum of NB phenotypes. R1275Q substitutions were most common (45%), followed by F1174L (15%), both located in key regulatory regions of the receptor's tyrosine kinase domain. Evaluation of matched constitutional DNAs demonstrated 10% of mutations were occult germline mutations. *ALK* was highly expressed in 50 % of TMA cores and p*ALK* in 30%. Integration of primary tumor microarrays showed a correlation between *ALK* copy number and mRNA expression. PF-02341066 showed differential sensitivity dependent on *ALK* status in a panel of 18 neuroblastoma cell lines *in vitro.* A wild type (WT) amplified line and 2 lines harboring the R1275Q mutation were sensitive with IC_{50}s in the 145 – 301 nM range, while four cell lines with the F1174Lwere more resistant (IC_{50}s >950 nM). Cell lines with normal copy number WT *ALK* were also more resistant. Inhibition of proliferation was correlated with abolishing phosphorylation of *ALK*, *STAT3* and *AKT*. These *in vitro* observations were recapitulated in xenograft studies of PF-02341066 sensitivity. PF-02341066 caused complete regression of R1275Q xenografts, but caused only minimal growth delay in F1174L and WT xenografts (N=10/arm). PF-02341066 is a potent inhibitor of the most common *ALK* mutation in neuroblastoma.

The pharmacokinetics of a single oral dose of PF-02341066 was studied in mice at the dose that produced the optimal therapeutic effect in neuroblastoma xenografts (200 mg/kg ≈ 80 mg/m^2). A one-compartment model was fit to the plasma concentration-time data (sampled over 28 h) and the parameters are shown below:

Parameter	Value	Units
Absorption rate constant (k_a)	2.2	h^{-1}
Apparent volume of distribution (V_d/F)	10	L/m^2
Elimination rate constant (k_{el})	0.056	h^{-1}
$AUC_{0\text{-}28h}$	116	mcg•h/mL
$AUC_{0\text{-}\infty}$	147	mcg•h/mL
Steady state trough concentration (C_{12h})	8.8	mcg/mL
Half-life ($t_{1/2}$)	12	h

Biochemical analyses linked the reduced susceptibility of F1174L-mutated ALK to PF-02341066 inhibition (compared with R1275Q) to increased ATP-binding affinity, as seen with development of resistance to EGFR inhibitors in non-small cell lung cancer (NSCLC). The activating R1275Q ALK mutation increases K_m for ATP, mirroring the common L858R EGFR mutation. By contrast, the activating F1174L ALK mutation slightly reduces K_m for ATP, so that its kinetic parameters resemble those of the gefitinib/erlotinib-resistant L858R/T790M EGFR mutant in NSCLC. Despite the resistance seen in the studies described here, our results indicate that patients harboring the F1174L mutation may benefit from treatment with ATP-competitive ALK inhibitors in some circumstances. Our biochemical results indicate that the reduced sensitivity of F1174L-expressing cell lines can be explained, at least in part, by an increased ATP-binding affinity compared with R1275Q – as manifest by $K_{m,\,ATP}$ values – which reduces the potency of ATP-competitive inhibitors (Table 1). For PF-02341066 itself, an increase in dosage to overcome the relative difference in $K_{m,\,ATP}$ compared with R1275Q-mutated ALK may be possible (Table 2, manuscript submitted).

Table 1. Kinetic parameters of ALK-TKD. Data are shown as mean ± SEM of at least 3 independent experiments.

kinase	k_{cat} (min^{-1})	$K_{m,\,peptide}$ (mM)	$k_{cat}/K_{m,\,peptide}$ ($min^{-1}\cdot mM^{-1}$)	$K_{m,\,ATP}$* (mM)	$k_{cat}/K_{m,\,ATP}$ ($min^{-1}\cdot mM^{-1}$)
Wild-type	9.32 ± 0.85	2.88 ± 0.42	3.41 ± 0.44	0.134 ± 0.007	69.7
R1275Q	119 ± 13	2.56 ± 0.32	46.8 ± 1.9	0.326 ± 0.033	364
F1174L	365 ± 61	9.18 ± 1.43	39.7 ± 2.8	0.127 ± 0.011	2870
pWild-type	424 ± 63	1.80 ± 0.17	237 ± 35	0.159 ± 0.012	2660
pR1275Q	347 ± 15	1.39 ± 0.10	252 ± 24	0.248 ± 0.015	1400
pF1174L	436 ± 51	1.25 ± 0.20	357 ± 25	0.109 ± 0.001	3980

* Determined at 1 mM peptide.

Table 2. ALK-TKD inhibition by PF-02341066 *in vitro* at two different ATP concentrations. Data are shown as mean ± SEM for at least 3 independent experiments.

kinase	*IC_{50}, 2 mM ATP (nM)*	*IC_{50}, 0.2 mM ATP (nM)*
Wild-type	147 ± 6	--
R1275Q	84.6 ± 8.0	80.4 ± 4.8
F1174L	130 ± 10	88.5 ± 6.4

2.2.3 Animal Toxicology

The primary PF-02341066 toxicities in nonclinical studies were observed in the gastrointestinal tract (rat, dog, monkey), hematopoietic system (rat, dog, monkey), kidneys (rat), reproductive organs (rat), and actively growing long bones (rat). Emesis and diarrhea were dose-limiting toxicities observed during the single-dose escalation range-finding study in dogs. Microscopic evidence of minimal to mild renal cortical tubule vacuolation was observed following 28 days of dosing in male rats treated with ≥50 mg/kg/day. Bone marrow hypocellularity was observed in toxicity studies in rats and monkeys treated for 28 days at doses of 150 mg/kg/day (rats, males only) and 50 mg/kg/day (monkeys). Bone marrow hypocellularity was not observed in dogs; however, a decrease in white blood cells was identified following 3 single doses up to 40 mg/kg and 7 days of PF-02341066 at 20 mg/kg/day. Repeated administration of PF-02341066 for 28 days caused minimally decreased bone formation at the primary spongiosa of growing long bones at a dose of 150 mg/kg/day in male rats. PF-02341066 administration was associated with decreased heart rate, increased LVEDP, and decreased myocardial contractility. Increases in sPR interval, QRS, and QT interval were believed to be secondary to the reduction in heart rate. Additional effects related to PF-02341066 administration involved genetic toxicity findings, and other findings of uncertain risk to humans including decreased cellularity in lymphoid organs, elevated liver enzymes, potential for phototoxicity, and effects on the salivary glands.

2.2.4 Non-clinical Pharmacokinetic Studies

Single-dose pharmacokinetics of PF-02341066 in the male Sprague-Dawley rat, Beagle dog, and cynomolgus monkey following intravenous administration demonstrated moderate systemic plasma clearance in all preclinical species (9 to 47 mL/min/kg). Volume of distribution at steady state ranged from 2.9 to 24 L/kg in the rat, 11 to 13 L/kg in the dog, and 13 L/kg in the monkey, which all greatly exceeded the volume of total body water and indicated extensive distribution of PF-02341066 into body tissues. The terminal half-life ranged from 2.3 to 17 hours. Linear pharmacokinetics were observed in all preclinical species at doses of 1 and 5 mg/kg. Oral bioavailability from the solution and suspension formulations at 12.5 to 50 mg/kg in rats ranged from 26% to 63%, and in dogs and monkeys ranged from 38% to 66%.

In vitro studies with pooled human liver microsomes and specific CYP probe substrates indicated the highest potency for crizotinib-mediated CYP inhibition was for CYP3A, with IC50 values of 8.2 μM and 7.3 μM for felodipine oxidase and testosterone 6β-hydroxylase activities, respectively. The inhibitor potency of crizotinib was less for CYP2B6 and CYP2C9, with IC50 values of 22 μM and 23 μM, respectively. Low inhibitor potency was observed for CYP1A2, CYP2C8, CYP2C19, and CYP2D6 (IC50 values >30 μM). Clinical interactions with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 are unlikely. Crizotinib demonstrated time-dependent inhibition of CYP3A in human liver microsomes with a k_{inact} of 0.11 min-1 and K_I of 3.0 μM (midazolam as the substrate). Crizotinib caused marked induction of CYP3A4 based on mRNA levels in human cryopreserved hepatocytes at concentrations up to 7 μM; however, a corresponding induction of CYP3A4 enzyme activity was not observed. This finding is likely due to the crizotinib-mediated time-dependent inhibition of CYP3A4.

The potential of crizotinib to inhibit P-gp was evaluated in an *in vitro* study in Caco-2 cells. Crizotinib demonstrated a concentration-dependent inhibitory effect on P-gp-mediated digoxin efflux, with an IC50 value of 5.8 μM. Therefore, coadministration of crizotinib could potentially increase the plasma concentration of P-gp substrates such as digoxin *in vivo* via inhibition of intestinal P-gp-mediated efflux.

Pfizer has developed PF-02341066, as an oral solution, for patients who are unable to swallow capsules. Based on the physiochemical properties of this agent, the bioavailability of the oral suspension (PIB - powder in bottle) should be comparable to the powder-in-capsule (PIC). *In vitro* dissolution tests showed that the dissolution rate was fast, dose-independent and formulation-independent when pH=1.0 (fasted state) or pH=4.5 (fed state). The only exception was that the 100-mg PIC had slightly slower dissolution rate than 50-mg PIC and an immediate release tablet (IRT) when pH=4.5 (fed state) with Paddle motion. Moreover, results from a recent bioavailability study in normal healthy subjects demonstrated bioequivalence between PIC and IRT in term of AUC and Cmax, suggesting that dissolution may not be a limiting step of absorption. The oral clearance (CL/F) of PF-02341066 was observed to be 80-100 L/hr administered as the PIC in adult patients (Study A8081001), indicating PF-02341066 is a drug with either high clearance (CL), low bioavailability (F), or both. The likely low bioavailability may be due to low permeability and/or extensive GI/hepatic metabolism rather than poor dissolution of the PIC formulation. Therefore, it is believed that the oral suspension (PIB) will have a similar bioavailability compared to the PIC, which is currently used in adult patient trials.

Pfizer has more recently developed PF-02341066 as an oral solution (OS), which along with their Formulated Capsule (FC), is moving forward for commercial development. The OS is a sweetened and flavored aqueous solution, containing PF-02341066 (25 mg/mL) and excipients. PF-02341066 is 100% dissolved in the OS. Results from study A8081019 demonstrated that OS of PF-02341066 was bioequivalent to the FC. *In vitro* dissolution tests showed that the dissolution rates of the solid formulations were fast and similar, suggesting that dissolution may be not limiting in PF-02341066 absorption. Based on these data, the OS is considered to be bioequivalent to the PIC formulation currently used in this trial.

2.3 Adult Studies

2.3.1 Phase 1 Studies

An ongoing Phase 1 trial (A8081001) evaluating PF-02341066 as an oral single agent is being conducted to investigate the safety, pharmacokinetics and pharmacodynamics of PF-02341066 in adult 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 MTD for QD administration is currently being determined.

ALK gene rearrangement-positive patients were identified for the expansion cohort of the ongoing Phase 1 trial using a diagnostic test with a break apart ALK FISH probe. One hundred and thirteen ALK+ NSCLC patients have entered the enriched population cohort as of 7 August 2010. Clinical activity data is reported for these 113 patients as of data cut-off date. Over 50% of the patients had at least 3 prior treatments for NSCLC and 15 patients had an ECOG performance status of 2 at baseline for this study.

The objective response rate (ORR) was: 56% (95%CI: 46%, 66%). The median duration of response for those patients who responded was 6.0 months. The median Progression Free Survival (PFS) was 9.2 months (95% CI: 7.6, 10.3 months).

The most common treatment-related adverse events in the evaluable subset is gastrointestinal toxicity consisting of nausea, diarrhea and vomiting. These adverse events 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. Diarrhea can be effectively controlled by anti-diarrheals. The percentage of patients having visual changes which consisted mainly of seeing shadows or streaks during changes in light has occurred in ~45% of patients. All of these visual events were Grade 1 in severity. These adverse events did not affect patient management as no patients temporarily stopped treatment, had their dose reduced or were permanently discontinued from treatment. Five patients have experienced Grade 3 (n=4) or Grade 4 (n=1) increases in ALT. These events occurred within the first cycle treatment, i.e. first 28 days of treatment. Patients were asymptomatic and the ALT increases were reversible upon discontinuation of study medication. Only one patient discontinued treatment due to an increase in ALT levels.

In a recent review of safety for PF-02341066, Pfizer has determined that there are 4 potential cases of pneumonitis in patients with non-small cell lung cancer (NSCLC), which may be related to PF-02341066. One additional case was a radiation recall pneumonitis. Based on the 4 cases that were not linked to radiation treatment and relative to all enrolled adult patients (N=255) who have been treated with PF-02341066, as of September 15, 2010, the current frequency of non-radiation recall pneumonitis is 1.6%. One of the 4 cases was fatal. The 3 other patients were permanently discontinued from the study and recovered from the event. The one patient who experienced radiation recall pneumonitis, was appropriately treated and was able to restart PF-02341066. Interpretation of the 4 non-radiation recall cases was complicated by the underlying non-small cell lung cancer for which the patients were being treated. In addition these 3 cases were complicated by the co-administration of other drugs known to potentially cause pneumonitis and/or other pulmonary complications.

2.3.2 Phase 2 Studies

There have been no Phase 2 studies in adults.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Preliminary pharmacokinetic (PK) data are available for the first 145 patients enrolled in the adult Phase 1 trial [17]. 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 43 to 51 hours. Following multiple oral dosing for 15 days or longer, crizotinib AUCtau increased with median accumulation ratios ranging from 1.7 to 3.4 after QD dosing and from 4.0 to 5.9 after BID dosing, respectively. No evidence of nonlinearity in PK was observed at doses ranging from 100 mg to 200 mg QD and 200 mg to 300 mg BID, as evidenced by generally proportional increases in mean AUC_{tau} and C_{max} after single or multiple doses. There was moderate variability in AUC_{tau} (coefficient of variation [CV], 12–60%) and C_{max} (CV, 21–71%) across all doses studied. Crizotinib concentrations reached steady state within 15 days after repeated administration at 250 mg BID. Median trough plasma concentration at steady state (274 ng/mL total or 57 nM free drug) exceeded the target efficacious levels predicted for inhibition of c-MET (13 nM) and ALK (~26 nM) based on preclinical mouse tumor models. Co-administration with a standard high-fat meal did not appear to change the geometric mean of AUC_{24} and C_{max} of crizotinib following single 250-mg crizotinib doses in cancer patients.

PF-02341066 showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In order to assess the effect of PF-02341066 on CYP3A activity in the GI tract and the liver, 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.[17] 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.

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There have been no previous clinical trials of PF-02341066 in children.

2.5 Overview of Proposed Pediatric Study

This will be a Phase 1 dose-finding study of PF-02341066 to determine the maximum dose that is safe and tolerable. Children with relapsed or refractory solid tumors and children with relapsed/refractory ALCL will be treated with PF-02341066 orally, on a continuous schedule. The starting dose will be 100 mg/m^2 (70% of the adult MTD of 250 mg twice daily or approximately 140 mg/m^2) administered orally twice daily continuously. Eligibility will include all relapsed/refractory solid tumors and patients with ALCL for the Phase 1 portion of this study (Part A1). Patients with recurrent/refractory malignancies that have confirmed ALK fusion proteins, ALK mutations or evidence for MET mutation or amplification, will be able to enroll at any time during the phase 1 portion of the protocol (Part A2). Except for the initial dose level, their accrual will lag one dose level behind the phase 1 trial. Patients with recurrent/refractory neuroblastoma not eligible for Part A1 will also be able to enroll on a separate stratum (Part A3) at one dose level below the dose level at which patients on Part A1 are actively enrolling. Due to the prevalence of *ALK* translocations in systemic ALCL, and with promising preclinical data on the activity of PF-02341066 in neuroblastoma, this study includes a Phase 2 expansion at the maximum tolerated dose in two separate parts of the study, to obtain preliminary efficacy data in patients with ALK+ relapsed/refractory neuroblastoma or ALCL (Part B or Part C), as well as patients with any ALK or MET activated tumor (Part A2).

To assess biological correlates of efficacy, we will access (when available) banked tumor DNA as well as tissue blocks from diagnosis or relapse in participating subjects with neuroblastoma and ALCL, for correlative biology studies. We will also obtain bone marrow prior to and while on treatment from patients with neuroblastoma, as well as bone marrow and peripheral blood from patients with ALCL. The study will include pharmacokinetic as well as correlative studies. A multi-strata Phase 2 study will open group-wide, and stage 1 data from the neuroblastoma and ALCL cohorts, as well as data for subjects enrolled at the MTD in this study, will be utilized as part of the COG-wide Phase 2 trial.

2.6 Preliminary Results of the Current Pediatric Study (May 2011)

A total of 39 subjects have been enrolled on the pediatric phase 1 study of PF-02341066. Twenty-five subjects were enrolled on Part A1, 9 subjects on Part A2, and 5 subjects on Part A3. On Part A1, no hematologic DLTs were observed during the first cycle; at dose level 4 (215 mg/m^2/dose BID), 1 subject experienced grade 3 dizziness, probably related to study drug, and 1 subject experienced grade 5 intra-tumoral hemorrhage, possibly related to study drug. One subject at dose level 2 (130 mg/m^2/dose BID) experienced a grade 4 intra-tumoral hemorrhage, with an attribution of unlikely related to study drug in Cycle 2 of therapy. There are no laboratory data or data from the adult trial with PF-02341066 to suggest that this drug leads to intra-tumoral hemorrhage. In >300 adult patients, including patients with NSCLC and brain metastases, there has not been any intra-tumoral hemorrhage observed. On Part A2, 1 subject experienced a grade 4 hematologic DLT (grade 4 neutropenia) at dose level 3 (165 mg/m^2/dose BID). On Part A3, no DLTs were seen. Therefore, dose level 4 will be expanded to enroll one additional non-CNS patient in Part A1 according to the rolling-six design and dose-escalation will proceed if criteria for DLT are not met. The current amendment will exclude potential participants with known primary and/or metastatic CNS involvement due to the occurrence of 2 CNS adverse events reported to date on this trial.

Nineteen children enrolled on the pediatric phase 1 trial had adequate pharmacokinetic sampling completed after the first dose of PF-02341066. The disposition of PF-02341066 in children was highly variable (apparent clearance [CL/F] ranged from 9 to 276 L/m^2/h). The relationship between dose and AUC of PF-02341066 was difficult to assess because of the variability (the $AUC_{0-\infty}$ at the 130 mg/m^2 dose level ranged from 1.2 to 14 mcg•h/mL). The $AUC_{0-\infty}$ at the 215 mg/m^2 dose level was 2.6 and 7.4 mcg•h/mL in 2 patients. The mean $t_{1/2}$ was 6.7 h, but it ranged from 2.9 to 21 h. The half-life was considerably shorter in children than adults, but may be underestimated because of sampling period after the first dose was 22-24 h. Therefore the $AUC_{0-\infty}$ may also be underestimated. Mean steady state trough concentrations were 112, 224, 286 and 441 at the 100, 130, 165 and 215 mg/m^2 dose levels, respectively. As a result of this artificially short half-life, it is likely that the AUC extrapolated to infinity is substantially underestimated and the AUC_{inf} of a single dose may not be equal to the AUC_{tau} at steady state. In addition, auto-induction of metabolism may also impact the steady-state AUC. To address this, we will perform steady state PK, which can be compared to the exposures in preclinical models. Given the importance placed on the PK in children on this trial as a way to relate to the preclinical studies and the primary driver for deciding to dose-escalate, PKs will be required for patients on Part A, Part B or Part C.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://members.childrensoncologygroup.org.
2. From the menu bar, click **eRDES**. *The eRDES sub-menu appears.*
3. Click **Reservation**. *The Studies requiring Reservations page appears.*

3.2 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
Emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions, call the CTSU General Helpdesk at: 1-888-823-5923.

3.3 Patient Registration

Prior to enrollment on study, all patients must have been registered via the RDE system into the COG Cancer Registry (Diagnosis/Registry). The patient registration application is available 24 hours a day, 7 days a week. The assigned COG patient identification number will be used to identify the patient in all future interactions with the COG. If you have problems with registration, please refer to the online help in the eRDE area of the COG website.

3.4 Reservation and Contact Requirements

Before enrolling a patient on study, a reservation must be made at the Statistics & Data Center and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient identification number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the COG website. Please refer to the Reservation System eRDES User Guide that can be downloaded at:
https://members.childrensoncologygroup.org/_files/Help/UserGuides/eRDES_ReservationSystem_UserGuide.pdf

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through one of the following mechanisms: a) the COG screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be faxed immediately following enrollment, using eRDES Document Imaging Program, to the Operations Center at (626) 447-2204. For more information on eRDES Document Imaging, please refer to the eRDES Document Imaging User Guide – Institutional, which can be downloaded at:
https://members.childrensoncologygroup.org/_files/Help/UserGuides/eRDES_DocumentImaging_UserGuide_Institutional.pdf

3.8 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be faxed, with the corresponding shuttle sheet, to the Operations Center at (626) 447-2204. The fax must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission to COG.

3.9 **Study Enrollment**

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.10 **Dose Assignment**

The dose level will be assigned via RDE at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. If more than 7 calendar days elapse between the date eligibility studies outlined in Section 4.1.7 were obtained and the start date of treatment, then the following studies must be repeated prior to treatment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory studies are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is off protocol therapy. Imaging studies, bone marrow aspirates and biopsies are required within 14 days prior to start of protocol therapy. If more than 14 days have elapsed between the date imaging studies to determine eligibility were obtained (i.e., for patients with neuroblastoma on Part A or Part B per Section 4.1.4.2) and the start date of treatment, then repeat imaging studies must be obtained prior to initiating protocol therapy.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

4.1 **Inclusion Criteria**

4.1.1 Age: Patients must be > than 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 BSA (Phase 2): Patients receiving the formulated capsules must have a BSA ≥ 0.63 m^2 at the time of study enrollment.

4.1.3 Diagnosis: Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4.1.3.1 a. Phase 1 (Part A1) - **COMPLETE**: *Patients with relapsed or refractory solid tumors or anaplastic large cell lymphoma (excluding patients with primary or metastatic CNS tumors or patients with primary cutaneous ALCL).*

b. Phase 1 (Part A2) - **COMPLETE**: Patients with confirmed ALK fusion proteins, ALK mutations, ALK amplification (defined as greater than 4-fold increase in the *ALK* signal number as compared to reference signal number on chromosome 2q arm) or MET mutation or amplification. Testing to confirm the presence of ALK fusion proteins, ALK mutations, ALK amplification or evidence of MET mutation or amplification for eligibility purposes must be performed as a CLIA-certified assay. ALK immunohistochemistry can be used as a surrogate for FISH for patients with IMT or ALCL.

Note: Evidence for MET mutation or amplification is defined as:
- positive for c-Met amplification by FISH; or
- positive for known c-Met kinase domain activating mutations including V1110L, H1112L, H1112Y, H1124D, M1149T, T1191I, V1206L, L1213V, V1238I, M1268T, P1009S, T1010I, R988C, V941L, but excluding Y1248C, Y1248H, Y1248D, and Y1253D; or
- Chromosomal translocations that lead to altered transcriptional regulation of c-Met and/or HGF including metastatic alveolar soft part sarcoma, clear cell sarcoma, rhabdomyosarcoma, or translocation associated renal cell carcinoma).

c. Phase 1 (Part A3)- **COMPLETE**: *Patients with relapsed or refractory neuroblastoma, with or without bone marrow involvement, who are not eligible for Part A1 or A2 or cannot enroll on Part A1 because of stratum suspension or lack of available slots. (These patients will be enrolled at one dose level below the dose level at which patients on Part A1 are actively enrolling.)*

4.1.3.2 Phase 2 (Part B): Patients with ALK+ relapsed or refractory neuroblastoma.

4.1.3.3 Phase 2 (Part C): Patients with ALK+ relapsed or refractory anaplastic large cell lymphoma (excluding patients with primary cutaneous ALCL).

4.1.3.4 Phase 2 (Part A2): Patients **with diagnoses other than neuroblastoma or ALCL with** confirmed ALK fusion proteins, ALK mutations, ALK amplification (defined as greater than 4-fold increase in the *ALK* signal number as compared to reference signal number on chromosome 2q arm) or MET mutation or amplification. Testing to confirm the presence of ALK fusion proteins, ALK mutations, ALK amplification or evidence of MET mutation or amplification for eligibility purposes must be performed as a CLIA-certified assay. ALK immunohistochemistry can be used as a surrogate for FISH for patients with IMT.

Note: Evidence for MET mutation or amplification is defined as:

- Positive for c-Met amplification by FISH; or
- Positive for known c-Met kinase domain activating mutations including V1110L, H1112L, H1112Y, H1124D, M1149T, T1191I, V1206L, L1213V, V1238I, M1268T, P1009S, T1010I, R988C, V941L, but excluding Y1248C, Y1248H, Y1248D, and Y1253D; or
- Chromosomal translocations that lead to altered transcriptional regulation of c-Met and/or HGF including metastatic alveolar soft part sarcoma, clear cell sarcoma, rhabdomyosarcoma, or translocation associated renal cell carcinoma).

4.1.4 Disease Status:

4.1.4.1 Phase 1 (Part A)
Patients must have either measurable and/or evaluable disease (see Sections 12.3, 12.4, 12.5, 12.6, and 12.7 for definitions).

4.1.4.2 Phase 2 (Part B)
Patients with neuroblastoma must have proven ALK+ disease with either measurable and/or evaluable disease as indicated below:

B1. Measurable tumor on MRI, CT scan or X-ray obtained within 2 weeks prior to study enrollment (see Section 12.3.1)

B2. Evaluable tumor by MIBG scan (See Section 12.5.1) and/or bone marrow involvement with tumor cells seen on routine morphology (see Section 12.6.1).

4.1.4.3 Phase 2 (Part C)
Patients must have proven ALK+ disease with either measurable or evaluable disease (see Sections 12.3.1, 12.4.1, and 12.7).

4.1.5 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥50 for patients ≤ 16 years of age (See Appendix I). Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.6 Prior Therapy

4.1.6.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy.

a. Myelosuppressive chemotherapy:

- Solid Tumors: Patients with solid tumors must not have received within 3 weeks of enrollment onto this study (6 weeks if prior nitrosourea).
- Lymphoma: Patients with lymphoma who relapse during standard maintenance therapy are eligible at time of relapse. For patients with ALCL who relapse while they are receiving cytotoxic therapy, at least 14 days must have elapsed since the completion of cytotoxic therapy. Note: Cytoreduction with hydroxyurea can be initiated and

continued for up to 24 hours prior to the start of PF-02341066.

b. Hematopoietic growth factors: At least 7 days since the completion of therapy with a growth factor.

c. Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the Study Chair.

d. Monoclonal antibodies: At least 7 days or 3 half-lives, whichever is longer, must have elapsed since prior treatment with a monoclonal antibody.

e. XRT: ≥ 2 wks for local palliative XRT (small port); ≥ 6 weeks must have elapsed since treatment with therapeutic doses of MIBG; ≥ 6 months must have elapsed if prior TBI, craniospinal XRT or ≥ 50% radiation of pelvis; ≥ 6 wks must have elapsed if other substantial BM radiation.

f. Bone Marrow/Stem Cell Transplant or Infusion without TBI:
   i. (Part A1 or Part C): No evidence of active graft vs. host disease and ≥ 3 months must have elapsed since stem cell transplant or infusion.

   ii. (Part A2, Part A3, or Part B): No evidence of active graft vs. host disease and ≥ 6 weeks must have elapsed since stem cell transplant or infusion.

g. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.

4.1.6.2 Patients must not have received prior therapy with PF-02341066.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

Patients on Part A1 or Part C of the study:

a. For patients with solid tumors or ALCL without bone marrow involvement:
   - Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
   - Platelet count ≥ 75,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)
   - Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

b. Patients with known bone marrow metastatic disease:

- Peripheral absolute neutrophil count (ANC) ≥ 750/mm^3
- Platelet count ≥ 25,000/mm^3 (may receive platelet transfusions)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)
- Not known to be refractory to red cell or platelet transfusions

Transfusions are permitted to meet both the platelet and hemoglobin criteria. Note: Patients with known bone marrow metastatic disease are not evaluable for hematological toxicity for the purposes of dose escalation.

Patients on Part A2, Part A3 or Part B of the study:
Patients eligible for Part A2, Part A3, or Part B of the study must meet the hematologic criteria below for enrollment:

- Peripheral absolute neutrophil count (ANC) ≥ 750/mm^3
- Platelet count ≥ 25,000/mm^3 (may receive platelet transfusions)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)
- Not known to be refractory to red cell or platelet transfusions

Transfusions are permitted to meet both the platelet and hemoglobin criteria.

4.1.7.2 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	**Female**
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[18] utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

4.1.7.4 Adequate Cardiac Function defined as:

- QTc ≤ 480 msec

4.1.8 Informed Consent: All patients and/or their parents or legal guardians must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.1.9 Drug Administration: Patients taking the capsule formulation must be able to swallow capsules. Feeding tube administration is allowed for patients receiving the oral solution (OS).

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding
Pregnant or breast-feeding women will not be entered on this study, as there is no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for the prior 7 days are not eligible.

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents, with the exception of hydroxyurea for patients with ALCL, are not eligible.

4.2.2.4 CYP3A4 Substrates with Narrow Therapeutic Indices: As PF-02341066 is an inhibitor of CYP3A4, patients chronically receiving medications known to be metabolized by CYP3A4 and with narrow therapeutic indices including pimozide, aripiprazole, triazolam, ergotamine and halofantrine are not eligible. The topical use of these medications (if applicable) is allowed. See Appendix II.

4.2.2.5 CYP3A4 Inhibitors: Patients chronically receiving drugs that are known potent CYP3A4 inhibitors within 7 days prior to study enrollment, including but not limited to ketoconazole, itraconazole, miconazole, clarithromycin, erythromycin, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, delavirdine, nefazodone, diltiazem, verapamil, and grapefruit juice are not eligible. The topical use of these medications (if applicable), *e.g.* 2% ketoconazole cream, is allowed. See Appendix II.

4.2.2.6 CYP3A4 Inducers: Patients chronically receiving drugs that are known potent CYP3A4 inducers within 12 days prior to study enrollment, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, tipranavir, ritonavir, and St. John's wort are not eligible. The topical use of these medications (if applicable) is allowed. See Appendix II.

4.2.3 Patients with known interstitial fibrosis or interstitial lung disease are not eligible.

4.2.4 Patients with a known history of myocardial infarction or cerebrovascular accident are not eligible.

4.2.5 Patients with CNS tumors or known CNS metastases are not eligible. Patients with a history of CNS metastases that have been surgically resected are eligible only if the baseline evaluation (see Section 8.1 footnote 18) shows no evidence of current CNS metastases. Patients with any evidence of CNS metastases on baseline evaluation are not eligible, regardless of whether the lesions have been previously treated and/or appear stable.

4.2.6 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.7 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PROGRAM

5.1 Treatment Overview

5.1.1 Drug Administration

Treatment Schedule Table	
Days 1-28	PF-02341066 orally twice daily
Day 28	End of Cycle

For patients receiving PF-02341066 capsule formulation, the capsules must be swallowed whole. For patients receiving PF-02341066 oral solution (OS), see the guidelines for preparation and administration in Appendix XIV. Feeding tube administration is allowed for patients receiving the OS. If a patient vomits after a dose of PF-02341066 (capsule or OS), it will not be repeated. See also Section 9.1.7 regarding administration instructions. Refer to the dosing nomogram in Appendix IIIB for the formulated capsules (FC) and see the formula and calculation in Appendix IV for the OS. After Cycle 1, patients may, for convenience, change formulations from FC to OS or vice versa.

Patients that enrolled on Parts A1, A2 & A3 prior to Amendment#6 must continue to receive their current formulation PIC or OS. Refer to the dosing nomogram Appendix IIIA for the PIC formulation and Appendix IV for the formula and calculation for the OS. Newly enrolled patients on Parts A2, B & C should receive therapy with either the FC or the OS.

A cycle of therapy is considered to be 28 days.

Drug doses should be adjusted based on the BSA determined **based on height and weight obtained within one week** prior to the beginning of each cycle.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease, an ANC ≥ 250/mm^3 (for patients with known bone marrow involvement) or ≥ 500/mm^3 (for patients without known bone marrow involvement), and has again met other laboratory parameters for hematologic, renal, and liver function as defined in the eligibility section (Sections

4.1.7.1, 4.1.7.2, and 4.1.7.3). Patients with stable disease or better who are having clinical benefit from PF-02341066 may continue receiving protocol therapy provided that the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

5.3 Dose Escalation Schema

5.3.1 Inter-Patient Escalation [Phase 1 (Part A) only] - **COMPLETE**

The starting dose will be 100 mg/m²/dose BID with dose levels for subsequent groups of patients as follows:

Dose Level	***Dose (mg/m²/dose BID)***
0	*70*
1	*100*
2	*130*
3	*165*
4	*215*
5	*280*
6	*365*

5.3.2 Patients with recurrent/refractory malignancies that have confirmed ALK fusion proteins, ALK mutations or ALK amplification (defined as greater than 4-fold increase in the *ALK* signal number as compared to reference signal number on chromosome 2q arm) or evidence for MET mutation or amplification who have exhausted all standard treatment options can be accrued to a separate stratum (Part A2) if they are not eligible for enrollment on the phase 1 dose escalation component of the trial (Part A1). These patients will be enrolled at one dose level below that of patients in part A1, or at the starting dose level (dose level 1) if dose escalation has not yet occurred. For patients enrolled with a confirmed ALK or MET aberration (Part A1 or A2), intra-patient dose escalation will be permitted for up to one dose level in cycles of therapy subsequent to cycle 1 if the patient is tolerating the dose at which they began therapy and if the next higher dose level has been established as tolerable. Part A2 will remain open during the Phase 2 portion of the study.

Patients with recurrent/refractory neuroblastoma, with or without bone marrow involvement, who are not eligible for Part A1 or A2 or cannot enroll on Part A1 because of stratum suspension or lack of available slots, can be accrued to a separate stratum (Part A3). These patients will be enrolled at one dose level below the dose level at which patients on Part A1 are actively enrolling. For these patients, intra-patient dose escalation will be permitted for up to one dose level if the patient is tolerating the dose at which they began therapy and if the next higher dose level has been established as tolerable.

5.3.3 **Dosing for the Phase 2 expansion, Part A2 (patients with ALK or MET+ tumors), Part B (patients with ALK+ neuroblastoma) and Part C (patients with ALK+ ALCL):** Patients in the initial Phase 2 expansion will be treated at the recommended dose from the Phase 1 component of this trial, which is 280 mg/m²/dose BID.

5.3.4 Intra-Patient Escalation

Intra-patient dose escalation is not allowed with the exception of dosing for patients in Part A1 (patients with ALK or MET+ tumors), A2 or Part A3 of the study, in cycles of therapy subsequent to cycle 1 (See Section 5.3.2). Sites will be notified by the COG Phase I Operations office if their patient may proceed with an intrapatient dose escalation following the completion of Cycle 1 or subsequent cycles.

5.4 Grading of Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning October 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.5 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to PF-02341066. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.5.1 Non-hematological dose-limiting toxicity:

- Any Grade 4 non-hematological toxicity
- Any Grade 3 non-hematological toxicity with the specific exclusion of:
  - Grade 3 nausea and vomiting of less < 3 days duration
  - Grade 3 ALT/AST that return to levels that meet initial eligibility criteria within 7 days of study drug interruption and that do not recur upon study drug re-challenge. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
  - Grade 3 fever or infection < 5 days duration.
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
- Grade 2 allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Any adverse event requiring interruption of study drug for ≥ 7 days or which recurs upon drug challenge.

5.5.2 Hematological dose limiting toxicity

For patients evaluable for hematological toxicity (See Section 4.1.7.1), DLT will be defined as:

- Grade 4 thrombocytopenia or Grade 4 neutropenia (see also Section 6.1)

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of Filgrastim.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 If a patient on Part A1 or without known bone marrow involvement on part A2, A3, B or C experiences Grade 4 neutropenia or thrombocytopenia, the treatment will be withheld. If a patient with known bone marrow involvement on part A2, A3, B or C experiences an ANC < $250/mm^3$, the treatment will be withheld. Counts should be checked every other day during Cycle 1 or twice weekly if during Cycle 2 or subsequent cycles until Grade 3 or less.

6.1.1.1 If the toxicity resolves to meet on study parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.1.1.2 If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.1.2 If hematological dose-limiting toxicity recurs in a patient who has resumed treatment at a dose level that is one below that assigned at study enrollment, the patient must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.5.1, the treatment will be withheld.

6.2.1.1 When the toxicity resolves to meet on study parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.2.1.2 If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.2.2 If non-hematological dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose level, at a dose level that is one below that assigned at study enrollment, the patient must be removed from protocol therapy.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

7.1.1 Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug with the exceptions noted below. If these treatments are administered the patient will be removed from protocol therapy.

7.1.2 Part C: Patients with ALCL who benefit from treatment (SD, PR or CR) with PF-02341066 during Cycle 1 may at the treating investigator's discretion receive intrathecal methotrexate in subsequent cycles of therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary (see Section 6.0).

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered in accordance with Section 6.1 or for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications

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 chronic concurrent use of potent CYP3A inhibitors and potent CYP3A inducers must be avoided from 7 days and 12 days, respectively, prior to the first dose of PF-02341066 until treatment discontinuation (See Sections 4.2.2.5 and 4.2.2.6). The list of potent CYP3A4 inhibitors and inducers in Sections 4.2.2.5 and 4.2.2.6 are also not permitted while the patient is on study therapy. The topical use of these medications (if applicable) is allowed. CYP3A4 inhibitors/inducers NOT listed in Sections 4.2.2.5 and 4.2.2.6 should be avoided whenever possible, and therapeutic alternatives to these agents are recommended. However, if no therapeutic alternatives are available, patients may continue to receive PF-02341066. Please see Appendix II for a list of common substrates, inhibitors, and inducers of CYP3A4.

PF-02341066 showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In the adult Phase 1 trial, the oral midazolam AUC was increased by 3.6-fold (90% CI: 2.7-4.9, n=13) after 28-day PF-02341066 administration at 250 mg BID, suggesting that PF-02341066 is a moderate inhibitor of CYP3A. Therefore, caution must be exercised in subjects receiving PF-02341066 in combination with drugs that are predominantly metabolized by CYP3A. In particular, chronic coadministration of PF-02341066 with CYP3A4 substrates with narrow therapeutic indices must be avoided from the time of the first dose of PF-02341066 until treatment discontinuation. See Section 4.2.2.5 for the list of CYP3A4 substrates with narrow therapeutic indices. PF-02341066 has minimal potential to inhibit other human CYP isoforms such as CYP1A2, 2C8, 2C9, 2C19 and 2D6.

Additionally, the concurrent use of non-prescription drugs (excluding vitamins) or herbal supplements is not recommended.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All enrollment/eligibility studies must be performed within 1 week prior to study enrollment (unless otherwise specified). If more than 7 calendar days elapse between the date eligibility studies outlined in Section 4.1.7 were obtained and the start date of treatment, then the following studies must be repeated prior to treatment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory studies are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is off protocol therapy. Imaging studies, bone marrow aspirates and biopsies are required within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Subsequent Cycles^
History	X	X	X
Physical Exam with vital signs	X	Weekly	X
Height, weight, BSA	X		X
Performance Status	X		X
CBC, differential, platelets	X	Weekly[1]	Weekly in Cycle 2 and then once every cycle thereafter[2]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, AST, bilirubin	X	Weekly	X
Total protein/albumin	X		X
Tumor Disease Evaluation (Phase 1: Parts A1, A2 & A3)[4, 15]	X[3]	End of Cycle 1	End of Cycles 3, 5, 7 and then every 3 cycles[21]
Tumor Disease Evaluation (Phase 2: Part A2)[4]	X	End of Cycle 1	End of Cycles 3, 5, 7 and then every 3 cycles[21]
Tumor Disease Evaluation Part B[4, 15]	X	End of Cycle 1	End of Cycles 3, 5, 7, and then every 3 cycles
Tumor Disease Evaluation Part C[4]	X[3]	End of Cycle 1	End of Cycle 3, 7, 11, 17, 23, and then yearly thereafter
PET scan [5]	X	End of Cycle 1	With Tumor Disease Evaluation
Bone marrow evaluation (Phase 1: Parts A1, A2 & A3)[6, 7, 16]	X	End of Cycle 1	End of Cycles 3, 5, 7 and then every 3 cycles[21]
Bone marrow evaluation (Phase 2: Part A2) [16]	X	End of Cycle 1	End of Cycles 3, 5, 7 and then every 3 cycles[21]
Bone marrow evaluation Parts B [6, 16]	X	End of Cycle 1	End of Cycles 3, 5, 7 and then every 3 cycles
Bone Marrow Evaluation Part C [7. 16]	X	End of Cycle 1	End of Cycle 3, 7, 11, 17, 23, and then yearly thereafter
CSF cytology[8. 17]	X	End of Cycle 1	As clinically indicated
Urinary HVA/VMA[9]	X		X
Pregnancy test[10]	X		
Snellen Eye chart[11]	X	End of Cycle 1	End of Cycles 3, 5, 7 and then every 3 cycles
Patient diary[12]		X	X
Pharmacokinetics[13]		X	
Correlative biology studies[14]	X	X	X
EKG	X		

CNS Imaging (CT or MRI) [18]	X		
Taste Questionnaire[19]		Weekly	X
Plain radiograph tibial growth plates[20]	X		See Section 8.5.1

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

1 If patients develop Grade 4 neutropenia or thrombocytopenia to < 20,000/mm^3 then CBCs should be checked at least every other day until recovery to Grade 3 (See also Section 6.0).

2 If patients develop Grade 4 neutropenia or thrombocytopenia to < 20,000/mm^3 then CBCs should be checked twice weekly until recovery to Grade 3 (See also Section 6.0).

3 Patients with ALCL must have CT neck/chest/abdomen/pelvis at study enrollment.

4 Tumor Disease Evaluation should be obtained at the end of the next consecutive cycle after initial documentation of either a PR or CR. Study drug should not be interrupted unless required by Section 6.1 or 6.2.

5 Patients with ALCL are required to have PET scans within 2 weeks prior to start of therapy and should also be followed with PET scans if positive at diagnosis. Patients with NB are required to have PET scans within 2 weeks prior to the start of therapy only if their disease is MIBG non-avid and should be followed with PET scans if baseline scans are positive.

6 Patients with neuroblastoma must have bilateral bone marrow aspirates and biopsies. These do not need to be repeated if negative at study enrollment and patient is responding to therapy.

7 Patients with ALCL must have bilateral bone marrow aspirates and biopsies. These do not need to be repeated if negative at study enrollment and patient is responding to therapy.

8 Phase 1: Part A – all ALCL patients, if clinically indicated; Part C – all ALCL patients

9 Phase 1: Part A – Neuroblastoma patients only; Part B – all neuroblastoma patients

10 Patients of childbearing potential require a negative pregnancy test prior to starting treatment and must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.

11 Snellen Eye Chart should be used to evaluate visual acuity. If a decline in visual acuity occurs or other visual symptoms occur, the patient should be referred for an ophthalmologic exam.

12 Review patient diary after completion of each treatment cycle and fax a copy, with the corresponding shuttle sheet, to the COG Statistics and Data Center (626) 447-2204. See Appendix XII and XIII.

13 See Section 8.2 and Appendix V for timing of PK studies.

14 See Section 8.3 and Appendix VI, VII, VIII, IX, and X for the nature and timing of correlative biology studies.

15 Patients with neuroblastoma must have both CT/MRI and MIBG scintigraphy performed prior to enrollment if the patient was enrolled with or has a history of MIBG avid tumor. Otherwise, the patient must have both CT/MRI and bone scan prior to enrollment. For patients with neuroblastoma and *measurable disease* by CT or MRI, lesions should be measured and followed using the same modality (CT or MRI) in addition to MIBG or bone scan. For patients with neuroblastoma with *evaluable disease* by MIBG scintigraphy or bone scan, use the same modality (MIBG scintigraphy or bone scan) to image patients; CT/MRI are not required but may be performed as clinically indicated.

16 For patients with positive bone marrow involvement at time of study enrollment, evaluate until negative per the schedule described in the table above.

17 For patients with ALCL and positive CSF involvement at time of study enrollment, evaluate until negative per the schedule described in the table above.

18 Baseline CNS imaging is required in patients with a prior history of CNS disease to ensure that the patient does not currently have CNS disease.

19 For consenting patients who are receiving the oral solution (OS). See Patient Taste Questionnaire on ADVL0912 Case Report Form.

20 Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to the first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.5.1.

21 Patients with ALCL currently enrolled on Part A of the study should follow the same evaluation schedule provided for patients on Part C (*i.e.* End of Cycle 3, 7, 11, 17, 23, and then yearly thereafter).

8.2 Pharmacokinetic Studies (for Parts A, B or C)

8.2.1 Description of Studies and Assay

Plasma will be collected for the purpose of determining PF-02341066 concentrations for pharmacokinetic analysis.

8.2.2 Sampling Schedule

Sampling schedule is based on adult PK data and the experience seen in children on this pediatric trial. For all patients, plasma samples will be obtained prior to the first dose on Day 1 of Cycle 1 and **at steady state**, defined as being between days 15 and 28 of BID dosing in Cycle 1 at the following time points: pre-dose (12 h after the last dose), 1 hr, 2 hr, 4 hrs, and 6-8 hrs.

8.2.3 Sample Collection and Handling Instructions

Blood samples (2 mL each) will be collected in K_2EDTA tubes. Record the exact date and time that the sample is drawn and the last dose of drug is administered on the Pharmacokinetic Study Form (see Appendix V). 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 4º C. Plasma samples will be stored at approximately -20°C within 1 hour of collection. Further details regarding pharmacokinetic sample processing, labeling, and shipping can be found in Appendix V.

8.3 Correlative Studies

8.3.1 Description of Studies

8.3.1.1 Pharmacogenomic Studies (for patients on Parts A, B or C):

Whole blood samples for pharmacogenomics will be obtained for the purpose of genotyping the alleles of cytochrome P450 enzymes and drug transport proteins. Instructions regarding sample collection, handling and shipping can be found in Sections 8.3.2.1, 8.3.3.1, and Appendix VI.

8.3.1.2 Tissue and Bone Marrow Studies for Neuroblastoma:

Tumor tissue from patients with neuroblastoma, if available, and bone marrow will be evaluated for correlative biology studies. Archival tumor tissue should be submitted for all patients with neuroblastoma, and extra effort should be expended to obtain consent for this tissue. **If a patient with neuroblastoma does not have tissue available, the study chair must be notified.** Details of this work are outlined in Appendix VII.

8.3.1.3 Bone Marrow and Peripheral Blood Studies for ALCL:

Minimal disease studies will be performed in children with ALCL. **These correlative studies are required and the study chair must be notified if these samples are not available.** RT-PCR will be performed on total RNA extracted from bone marrow and/or serial peripheral blood specimens, for detection of the t(2;5) NPM/ALK fusion transcript.

8.3.2 Sampling Schedule

8.3.2.1 Pharmacogenomic Studies (for patients on Parts A, B or C):

One peripheral blood sample (3 mL) will be collected at baseline prior to the first dose of PF-02341066.

8.3.2.2 Tissue and Bone Marrow Studies for Neuroblastoma:
Tissue (paraffin-embedded, or fresh frozen tissue) and bone marrow will be collected from original diagnosis, relapse, or any subsequent resection or biopsy prior to treatment with PF-02341066 from patients with neuroblastoma. If marrow is positive for tumor cells at time of study enrollment, a marrow will also be repeated at times of disease evaluations as described in Section 8.1 and sent to the laboratory in Appendix VIII for these correlative studies.

8.3.2.3 Bone Marrow and Peripheral Blood Studies for ALCL:
A single bone marrow sample will be obtained prior to starting Cycle 1 in patients with ALCL. In addition, peripheral blood samples will be obtained prior to starting Cycle 1, on day 15 of Cycle 1, at the beginning of Cycle 2, then once every cycle thereafter through cycle 11 and then every 3 cycles. The timing of collection of all specimens should coincide with routine laboratory evaluations and should be submitted to Dr. Megan Lim at the address listed in Appendix X.

8.3.3 Sample Collection and Handling Instructions

8.3.3.1 Pharmacogenomic Studies (for patients on Parts A, B or C):
Blood samples (3 mL) will be collected into one plastic K_2EDTA collection tube and stored at -70º C. Record the exact time that the sample is drawn on the Pharmacogenomic Study Form (see Appendix VI). Detailed instructions regarding pharmacogenomic sample processing, labeling, and shipping can be found in Appendix VI.

8.3.3.2 Tissue and Bone Marrow Studies for Neuroblastoma:
Tumor material should be sent to Dr. Yaël Mossé at room temperature by regular mail or using the institution's courier account at the address listed in Appendix IX.

Bone marrow should be sent to Dr. Yaël Mossé at room temperature by overnight Federal Express mail at the address listed in Appendix VIII. In patients with neuroblastoma, a bone marrow aspirate will be obtained (3-5 mL if ≤10 kg and 5 mL in children > 10 kg). Detailed instructions regarding sample processing, labeling, and shipping can be found in Appendix VIII.

8.3.3.3 Bone Marrow and Peripheral Blood Studies for ALCL:
Peripheral blood (15 mL if >10 kg and 10 mL in children ≤10 kg) and bone marrow (5 mL if > 10 kg and 3-5 mL in children ≤10 kg) will be collected in patients with ALCL. Record the exact time and date that the sample is drawn. Samples should be shipped room temperature, the same day as drawn. If the samples cannot be shipped immediately (i.e. is collected in the evening and will be shipped out the next morning via FedEx), they should be stored in a refrigerator until shipment. **Note: Samples should be sent within 24 hours from time drawn.**

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the study form in Appendix X, which must accompany the sample(s). Detailed instructions regarding sample processing, labeling, and shipping can be found in Appendix X. Samples will be sent at room temperature to Dr. Megan S. Lim at the address listed in Appendix X.

8.4 Radiology Studies

8.4.1 Central Radiology Review for Response:

Patients who respond to therapy (PR, CR) or have long term stable disease (SD) on protocol therapy ($\geq$ 6 cycles) will be centrally reviewed. COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into eRDE for review by the COG Operations Center.

The images are to be forwarded electronically to Imaging Research Center at Children's Hospital Los Angeles via the grid.

COG institutions that are not connected to the grid can send the images on hard copy film, CD ROM, or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL0912) and date and shipped to Syed Aamer at the address below:

Syed Aamer
Imaging Research Center
Data Administrator
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
Phone: (323) 361-3898
Fax: (323) 361-3054
E-mail: saamer@chla.usc.edu

8.4.2 Bone Age/Knee MRI

All tibial radiographs and knee MRIs (if obtained) should be submitted for review to the address listed above in Section 8.4.1.

8.5 Monitoring for Specific Toxicities

8.5.1 Growth Plate Toxicity

Patients will have a plain AP radiograph of a single proximal tibial growth plate obtained prior to the first dose of protocol therapy.

a. If patients are found to have a closed tibial growth plate, no further radiographs will be required.
b. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained at the end of Cycle 3 and then approximately every 6 months thereafter (timed with the nearest disease evaluation).
   - Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physeal pathology and undergo more frequent x-ray follow up. MRI should be performed without contrast.

- Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of PF-02341066 should be made after discussion with the Study Chair or Study Vice-Chair and DVL Leadership, taking into account the presence of any symptoms referable to the knee as well as the patient's response to PF-02341066. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue PF-02341066 or not.

9.0 AGENT INFORMATION

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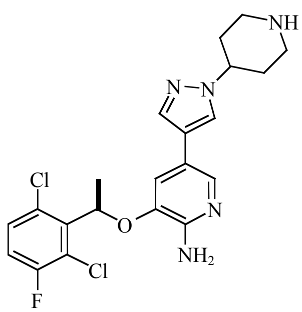

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10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination), laboratory (e.g., serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from study (See Section 6.0).
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Physician determines it is not in the patient's best interest.
f) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) and serum creatinine) are outside the parameters required for eligibility prior to the start of PF-02341066 (See Section 8.1).
g) Patients who develop a second malignant neoplasm.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RDE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any further data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study.

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Parts of the Study:

Part A1:	Patients with relapsed/refractory solid tumors or anaplastic large cell lymphoma (ALCL) – Phase 1 **COMPLETE**
Part A2:	Patients with recurrent/refractory malignancies who have confirmed ALK fusion proteins, ALK mutations, ALK amplification or evidence for MET mutation or amplification. Once Parts B and C are open to accrual, patients who are not eligible for either Part should enroll on Part A2, provided that they meet all other eligibility criteria for Part A2 (see Section 4.0).
Part A3:	Patients with recurrent/refractory neuroblastoma, who are not eligible for Part A1 or A2 or who cannot enroll on Part A1 because of stratum suspension or lack of available slots. **COMPLETE**
Part B:	Patients with ALK+ relapsed/refractory neuroblastoma – Phase 2
Part C:	Patients with ALK+ relapsed/refractory ALCL – Phase 2

There will be three parts of the study during the phase 1 component. Part A1 will be a standard phase 1 trial using the rolling 6 design for patients with relapsed/refractory solid tumors and ALCL. Part A2 will be patients with recurrent/refractory malignancies that have confirmed ALK fusion proteins, ALK mutations or amplification, or evidence for MET mutation or amplification who have exhausted all standard treatment options. Patients with confirmed ALK fusion proteins, ALK mutations or amplification or MET mutation or amplification will preferentially enroll in Part A1 when possible, and then Part A2 if not eligible for Part A1. Part A3 will be for patients with recurrent/refractory neuroblastoma, that do not have a confirmed ALK fusion protein, ALK mutation or ALK amplification, and are either not eligible for Part A1 or cannot enroll on Part A1 because of stratum suspension or lack of available slots. Accrual to Part A3 will begin at dose level 1, once initial accrual of Part A1 patients to dose level 1 has proceeded to dose level 2.

Patients in Parts A2 and A3 will be enrolled at one dose level below that of patients enrolled in Part A1. If dose escalation has not yet occurred, patients in Part A2 will be enrolled at the starting dose level (dose level 1). Intra-patient dose escalation of up to one dose level will be permitted in Part A1 (for patients with confirmed ALK or MET+ tumors), A2 and A3 in cycles of therapy subsequent to cycle 1 if the patient is tolerating the dose at which they began therapy and if the next higher dose level has been established as tolerable in Part A1.

Two to six evaluable patients with relapsed/refractory solid tumors and ALCL (Part A1) will be entered at each dose level for determination of maximum tolerated dose (see Section 11.3). The minimum sample size required to identify the MTD (Part A1) is 9 patients, which assumes the starting dose is the MTD and 2 of 3 patients in the next higher dose level experience a DLT. As of May 2011, 25 subjects have enrolled on Part A1. One additional non-CNS patient will be enrolled at dose level 4 for a total of 6 evaluable non-CNS patients at this dose level. If no DLT is experienced, we will dose-escalate to dose level 5. Assuming we will require only 1 more patient in dose level 4, and that we proceed with dose escalation and require 6 more evaluable patients in each of dose levels 5 and 6 before the MTD is reached, up to 17 additional patients will be required to complete this part of the study, assuming an inevaluability rate of 20%. In the unlikely event that all three of these dose levels will require expansion to 12 evaluable patients (see Section 11.2.2), a total of 39 additional patients will be required, assuming an inevaluability rate of 20%. With an observed accrual rate of 2-3 patients per month, we expect this part of the study to be complete within an additional 5-9 months.

Up to twenty patients may enroll onto Part A2 at each lagging dose level behind Part A1. In the case that an MTD is not achieved in Part A1, up to twenty patients may be enrolled onto Part A2 at the recommended phase 2 dose. If the dose is not tolerated in Part A2 at a given dose level (greater than 1/3 of patients in the dose level experience DLTs), the stratum will be closed to further accrual.

Once the MTD or recommended Phase 2 dose has been determined in Part A1, Part A2 will remain open at this dose for the duration of the Phase 2 part of the study. When Parts B and C are open to accrual, patients who are not eligible for either Part should enroll on Part A2, provided that they meet all other eligibility criteria for Part A2 (see Section 4.0). A total of 30 evaluable patients may enroll in Part A2 at the MTD or recommended Phase 2 dose. If 20 evaluable patients are accrued during this time with less than 3 observed responses, enrollment to this stratum will be discontinued. Additionally, if 0 responses are observed out of 10 evaluable patients with the same histologic tumor type treated at the recommended phase 2 dose, enrollment of that tumor type will be discontinued. A maximum of 45 patients is anticipated in this stratum, given the current number of enrollments. If greater than 1/3 of patients experience DLTs at this dose level, the stratum will be closed to further accrual. All patients enrolled on Part A2 who meet the eligibility criteria for Parts B or C of the study who are evaluable for response as described in Section 11.2.3 of this protocol will be included in the evaluation rule.

Up to three patients may enroll onto Part A3 at one dose level below the dose level that Part A1 patients are actively enrolling. If two out of three patients in Part A3 experience a DLT at a given dose level, the stratum will be closed to further accrual. A maximum of 15 patients is anticipated in this part.

Accrual to Parts B and C will only open once the MTD or recommended phase 2 dose has been determined for Part A1. Review of patient accrual onto recent Phase 2 solid tumor studies and ALK+ accruals to this study indicates the following entry rates for the various tumors under study can be achieved:

Disease Group/Part	Patients/Year
Neuroblastoma	15
ALCL	3-5

Assuming an inevaluability rate of 10%, a minimum of 11 patients and a maximum of 45 patients are expected to enroll in Parts B and C. We anticipate that the duration of the study (enrollment and evaluation) will require between 48 to 54 months.

11.2 Definitions

11.2.1 Evaluable For Adverse Effects

Any patient who receives the study drug will be evaluable for Adverse Effects. However, for the consideration of dose escalation, patients must be fully evaluable for toxicity. Any patient who experiences DLT at any time during protocol therapy is considered fully evaluable for Adverse Effects. Patients without DLT who receive at least 85% of the prescribed dose per protocol guidelines are also considered fully evaluable for Adverse Effects. Patients who are not fully evaluable for Adverse Effects at a given dose level will be replaced.

11.2.2 Maximum Tolerated Dose

The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy. In the event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), expansion of the cohort to 12 patients will be considered if all of the following conditions are met:

- One of the DLTs does not appear to be related to dose
- The Adverse Effects are readily reversible
- The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.

11.2.3 Evaluability for Response

Any patient who is enrolled and receives at least one dose of PF-02341066 will be considered evaluable for response provided: (1) the patient demonstrates progressive disease or death while on protocol therapy; or (2) the patient is observed on protocol therapy for at least one cycle and the tumor is not removed surgically prior to the time complete response or partial response is confirmed, or (3) the patient demonstrates a complete or partial response as confirmed according to protocol criteria. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in Section 11.4. Two objective status determinations are required to confirm best response (Section 12.8). All other patients will be considered non-responders. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. See Section 8.4 regarding shipping instructions. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.3 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of Part A1 of this study.[19] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	⩾ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	⩾ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	⩾ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	⩾ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped.

Since this agent is not expected to be associated with dose-limiting myelosuppression, at least 2 of every cohort of 3 or 5 of every cohort of 6 patients must be evaluable for hematologic toxicity. If hematologic dose limiting toxicity is observed, all subsequent patients who are enrolled in Part A1 must be evaluable for hematologic toxicity. Patients in Part A2 or A3 may be enrolled irrespective of whether or not they have bone marrow involvement.

In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

Results of pharmacokinetic testing will also be reported, including clearance, C_{max}, T_{max}, C_{ss}, and terminal half-life. Single-dose AUC, trough estimation, and estimate a t½ of accumulation will be obtained.

While the primary aim of this study is to evaluate the toxicity of PF-02341066, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

11.4 Phase 2 Evaluation in ALK+ Neuroblastoma (Part B) and ALK+ ALCL (Part C)

11.4.1 Study Design

The best response of disease to PF-02341066 will be examined separately in each of these two parts. In Parts B and C, the following Simon's optimal two stage design[20] will be used.

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 patients	0	Terminate the trial: agent ineffective
	1 or more	Inconclusive result, continue trial(proceed to stage 2)
Stage 2: Enter 10 additional patients	2 or less	Terminate the trial: agent ineffective
	3 or more	Terminate the trial: agent effective

PF-02341066 will not be considered of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If PF-02341066 has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If PF-02341066 has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

Once the trial has terminated in Part B, enrollment onto Part C will be evaluated for closure.

Response in all patients with solid tumors will be determined according to RECIST as defined in the protocol as either complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), or as described in Section 12.0 for other categories of responses assessment, and reported as final results. A report on the efficacy assessment will be posted on the completed disease stratum as part of the semi-annual study committee meeting book report.

It is anticipated that a multi-strata Phase 2 study will open group wide upon completion of stage 1 enrollment in Part B. Data collected from any patients enrolled at the MTD or recommended phase 2 dose or enrolled onto Parts B or C will be utilized in the Phase 2 study.

11.4.2 Method of Analysis

Response criteria are described in Section 12.0. Response rates will be calculated as the percent of patients whose best response is a CR or PR and confidence intervals will be constructed according to the method of Chang.[21] A responder is defined as a patient who achieves a best confirmed response (as defined in Section 12.8) of PR or CR on the study.

11.5 Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase I/II trial which will accrue a limited number of patients in the Phase I portion, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

11.6 Pharmacokinetic and Correlative Studies

A descriptive analysis of pharmacokinetic (PK) parameters of PF-02341066 will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

Due to small patient numbers, the correlative studies are expected to be descriptive and exploratory in nature. The results of these studies are expected to generate hypotheses for testing in future studies.

Pharmacogenomic data, ALK status, and MRD status will be reported descriptively. Where possible, we will attempt to preliminarily assess correlation between ALK status and response to PF-02341066, and MRD status and response to PF-02341066.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning October 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

12.2 Response Criteria

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor and measurable disease (Section 12.3); b) solid tumor and evaluable disease (Section 12.4); c) neuroblastoma with MIBG positive lesions (Section 12.5); d) neuroblastoma with bone marrow involvement (Section 12.6); or e) ALCL (Section 12.7). Note: Neuroblastoma patients who do not have MIBG positive lesions or bone marrow involvement should be assessed for response as solid tumor patients with measurable or evaluable disease.

12.3 Response Criteria for Patients with Solid Tumors and Measurable Disease

This study will use a minor modification of the (RECIST) Response Evaluation Criteria in Solid Tumors from the NCI for assessment of radiographic response.

12.3.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm. The investigator will identify up to 10 measurable lesions to be followed for response. Previously irradiated lesions that have not demonstrated clear progression post radiation do not qualify as being measurable or evaluable.

Serial measurements of lesions are to be done with appropriate imaging modalities. Bone scans or MIBG scans cannot be used to measure lesions (see Section 12.5 for response criteria for MIBG). The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

12.3.2 Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

12.3.3 End-of-Cycle Response

a) Complete Response (CR)
Disappearance of all target and non-target lesions. If immunocytology is available, no disease must be detected by that methodology.

b) Partial Response (PR)
At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment.

c) Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest disease measurement since the treatment started.

d) Progressive Disease (PD)
At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions, or evidence of laboratory or clinical progression.

12.3.4 Overall Best Response Assessment

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described in Section 12.8.

12.4 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.4.1 Evaluable Disease

The presence of at least one lesion that cannot be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

12.4.2 Complete Response (CR)

Disappearance of all evaluable disease.

12.4.3 Partial response

Partial responses cannot be determined in patients with evaluable disease.

12.4.4 Stable Disease (SD)

That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

12.4.5 Progressive Disease (PD)

The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

12.4.6 Overall Best Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described in Section 12.8.

12.5 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.5.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 4 weeks after radiation was completed and must show viable neuroblastoma.

12.5.2 The following criteria will be used to report MIBG response by the treating institution:

Complete response (CR)

Complete resolution of all MIBG positive lesions

Partial Response (PR)

Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions

Stable disease (SD)

No change in MIBG scan in number of positive lesions

Progressive disease (PD)

Development of new MIBG positive lesions

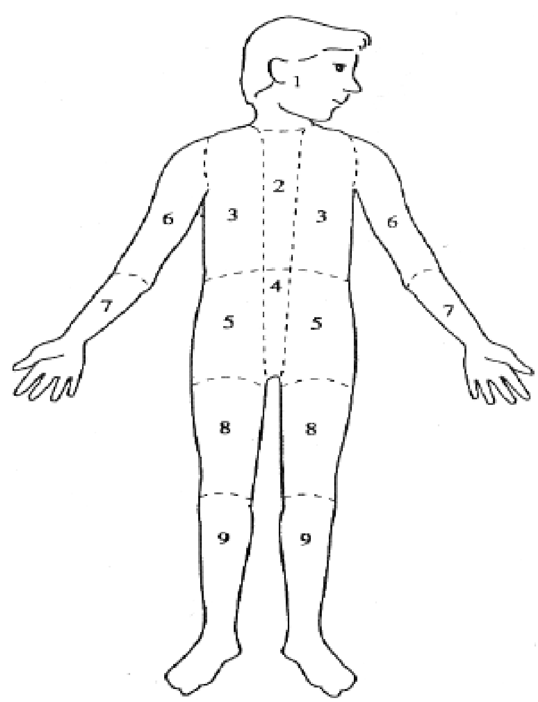
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.4 for details on transferring images to the Imaging Research Center.

NOTE: This scoring should also be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan. In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 3 weeks apart to be considered a **Complete Response**.

2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.5.4 Overall Best Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described in Table 3 in Section 12.8.

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.6.1 Bone Marrow Involvement

Bone marrow obtained within 2 weeks prior to study enrollment with tumor cells seen on routine morphology (not by NSE staining only) of bilateral aspirate or biopsy on at least one of the bone marrow samples.

Bone Marrow responses determined by H&E Staining of bilateral bone marrow biopsies and aspirates are defined as follows:

- Complete Response (CR)
  No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 4 weeks (± 5 days) apart.

- Progressive Disease (PD)
  - In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).
  - In patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 4 weeks (± 5 days) apart.

- Stable Disease
  Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

12.7 Response Criteria for Patients with ALCL

12.7.1 Complete Response

Disappearance of all evidence of disease from all sites for at least 4 weeks. This will be determined by PE and imaging. Bone marrow aspirate/biopsy must be normal and any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. PET scans must be negative if initially positive.

12.7.2 Complete Response Unconfirmed

A residual lymph node mass > 1.5 cm in greatest transverse diameter that has regressed by >75% in sum of the products of the greatest perpendicular diameters (SPD), or any residual lesions in organs that have decreased by >75% and with a negative PET scan and SUV <3. Patients with only residual positive bone lesions on PET scans will be considered in CRu. Patients with bone involvement may have positive lesions on PET scans for some time; therefore, these patients will be considered in CRu if the other residual lesions have disappeared, or of the residual lymph node mass or masses >1.5 cm in greatest transverse diameter have regressed by >75% in sum of the products of the greatest perpendicular diameters (SPD).

12.7.3 Partial Response

≥50% decrease in the SPD of the lesions. No new lesions.

12.7.4 No Response (Stable Disease)

Failure to qualify for a PR. No new lesions.

12.7.5 Progressive disease

≥25% increase in the size of any lesions or appearance of new lesions.

12.8 Best Response

Two objective status determinations of disease status, by CT or MRI, obtained on two consecutive determinations, separated by at least a 3 week time period, are required to determine the patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

Table 1. Sequences of objective statuses with corresponding best response.

1st Status	2nd Status	3rd Status	Best Response
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

Table 2: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	MIBG	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

Table 3: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only

For those patients in Part A or Part B that are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; and 3) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 4.0. The descriptions and grading scales found in the revised CTCAE version 4.0 will be used for AE reporting beginning October 1, 2011. All appropriate treatment locations should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAE.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
Unrelated, Unlikely, Possible, Probable, and Definite.
Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions above.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. **An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in bold font in the table of toxicities listed in the drug information section (Section 9.1.9) of the protocol.**

Step 5: Review Table A in this section to determine if:

- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

Table A: Phase 1 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2[3]	Grade 2	Grade 3[3]		Grade 3[3]		Grades 4 & 5[2, 3]
	Unexpected and Expected	Unexpected	Expected	Unexpected		Expected		Unexpected and Expected
				with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	5 Calendar Days	Not Required	24-Hour; 5 Calendar Days

1 **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification (via CTEP-AERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in non-CTEP IND studies) followed by complete report within 5 calendar days for:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

2 Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

3 **Please see exceptions below under section entitled "Additional Instructions or Exceptions."**

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS (via e-mail to COG AE Coordinator for agents in non-CTEP IND studies) within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, including Grade 4 lymphopenia, does not require expedited reporting whether it is expected or unexpected, unless it is associated with hospitalization.

As referenced in the CTEP Adverse Event Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at:
  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/CTEP-AERS.htm
  (Telephone the COG AE Coordinator at: **626-241-1545** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 calendar days** of learning of the event.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS) that can be found at http://ctep.cancer.gov.

An CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. If prompted to enter a sponsor e-mail address, please type in: COGCAdEERS@childrensoncologygroup.org.

Fax supporting documentation to COG (fax # 626-241-1795; attention: COG AE Coordinator). **ALWAYS include the ticket number on all faxed documents**.

13.4 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG data submission forms and do not alter the guidelines for CTEP-AERS reporting.

13.4.1 If an adverse event occurs more than once in a cycle of therapy only the most severe grade of the event should be reported.

13.4.2 If an adverse event progresses through several grades during one cycle of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 The resolution date of the AE is defined as the date at which the AE returns to eligibility criteria level or ≤ Grade 1 level, whichever level is greater (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.4.5 An adverse event that persists from one cycle to another should only be reported once unless the grade becomes more severe in a subsequent cycle. An adverse event which resolves and then recurs during a different cycle, must be reported each cycle it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2) should be reported at the end of each cycle using the forms provided in the data form packet (See Section 14.1).

13.5.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

13.5.3 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

13.6 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the following information within two weeks of an AML/MDS diagnosis occurring after treatment for cancer on NCI-sponsored trials:

- a completed CTEP-AERS report;
- Non-treatment related cases of AML/MDS for CTCAE v4.0 should be reported using "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify."
- To grade a non life-threatening event for "Myelodysplastic syndrome", use "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify" where the specified term is MDS.

Note: If a patient has been enrolled in more than one NCI-sponsored study, the

CTEP-AERS report must be submitted for the most recent trial.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports and Patient Taste Questionnaire. These forms are faxed, with the corresponding shuttle sheet, to the Statistics & Data Center at (626) 447-2204.
2. Reference Labs, Biopathology Reviews, and QARC data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.
3. Computerized Information Electronically Submitted: All other data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

14.3 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.3.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.3.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the Developmental Therapeutics Chair, Vice Chair and Statistician on a weekly conference call.

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: COMMON SUBSTRATES, INHIBITORS AND INDUCERS OF CYP3A4

The following lists describe medications which are common CYP3A4 substrates, inhibitors and inducers. This list should not be considered all inclusive; please refer to other resources such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx for additional information. Consult individual drug labels for specific information on metabolism by CYP3A4. Note: The topical use of these medications (if applicable), *e.g.* 2% ketoconazole cream, is allowed.

Substrates		
Macrolide Antibiotics	clarithromycin erythromycin NOT azithromycin	
Anti-arrhythmics	quinidine	
Benzodiazepines	alprazolam diazepam midazolam triazolam	
Immune Modulators	cyclosporine tacrolimus (FK506)	sirolimus
HIV Antivirals	indinavir nelfinavir ritonavir saquinavir	
Antihistamines	astemizole chlorpheniramine terfenidine	
Calcium Channel Blockers	amlodipine diltiazem felodipine lercanidipine	nifedipine nisoldipine nitrendipine verapamil
HMG CoA Reductase Inhibitors	atorvastatin cerivastatin lovastatin NOT pravastatin simvastatin	
Steroid 6beta-OH	estradiol hydrocortisone progesterone testosterone	
Other	alfentanyl buspirone cafergot caffeine=>TMU cocaine dapsone codeine-N-demethyl dextromethorphan eplerenone fentanyl finasteride imatinib	lidocaine methadone ondansetron pimozide propranolol quinine salmetrerol sildenafil tamoxifen paclitaxel trazodone vincristine

	haloperidol (in part) irinotecan	zaleplon zolpidem
Inhibitors		
HIV Antivirals	delaviridine indinavir nelfinavir ritonavir saquinavir	
Other	amiodarone NOT azithromycin cimetidine ciprofloxacin clarithromycin diethyl-dithiocarbamate diltiazem erythromycin fluconazole fluvoxamine gestodene	grapefruit juice itraconazole ketoconazole mifepristone nefazodone norfloxacin norfluoxetine mibefradil verapamil voriconazole
Inducers		
HIV Antivirals	efavirenz nevirapine	
Other	barbiturates carbamazepine glucocorticoids modafinil phenobarbital phenytoin	rifampin St. John's wort troglitazone pioglitazone rifabutin

APPENDIX IIIA: PF-02341066 DOSING TABLES
(FOR PATIENTS RECEIVING THE POWDER IN CAPSULE (PIC) FORMULATION)

Note: Patients enrolled on Phase 1 portion of the study that are receiving the Powder in Capsule (PIC) formulation must continue to follow the dosing nomograms below. For patients using the pediatric Oral Solution (OS), refer to Appendix IV.

PF-02341066 Dose Assignment: 100 mg/m^2/dose BID (DOSE LEVEL 1)

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m^2)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.40-0.43	80	40	40
0.44-0.55	100	50	50
0.56-0.65	120	60	60
0.66-0.75	140	70	70
0.76-0.85	160	80	80
0.86-0.94	180	90	90
0.95-1.06	200	100	100
1.07-1.16	220	110	110
1.17-1.26	240	120	120
1.27-1.36	260	130	130
1.37-1.44	280	140	140
1.45-1.56	300	150	150
1.57-1.66	320	160	160
1.67-1.76	340	170	170
1.77-1.87	360	180	180
≥ 1.88	400	200	200

PF-02341066 Dose Assignment: 130 mg/m^2/dose BID (DOSE LEVEL 2)

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m^2)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.30-0.33	80	40	40
0.34-0.42	100	50	50
0.43-0.50	120	60	60
0.51-0.58	140	70	70
0.59-0.66	160	80	80
0.67-0.72	180	90	90
0.73-0.81	200	100	100
0.82-0.89	220	110	110
0.90-0.97	240	120	120
0.98-1.04	260	130	130
1.05-1.10	280	140	140
1.11-1.20	300	150	150
1.21-1.28	320	160	160
1.29-1.35	340	170	170
1.36-1.44	360	180	180
1.45-1.58	400	200	200
1.59-1.67	420	210	210
1.68-1.74	440	220	220
1.75-1.83	460	230	230
1.84-1.97	500	250	250
≥ 1.98	520	260	260

PF-02341066 Dose Assignment: 165 mg/m²/dose BID (DOSE LEVEL 3)

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m²)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.30-0.33	100	50	50
0.34-0.39	120	60	60
0.40-0.46	140	70	70
0.47-0.52	160	80	80
0.53-0.56	180	90	90
0.57-0.64	200	100	100
0.65-0.70	220	110	110
0.71-0.76	240	120	120
0.77-0.82	260	130	130
0.83-0.87	280	140	140
0.88-0.95	300	150	150
0.96-1.00	320	160	160
1.01-1.06	340	170	170
1.07-1.13	360	180	180
1.14-1.25	400	200	200
1.26-1.31	420	210	210
1.32-1.37	440	220	220
1.38-1.45	460	230	230
1.46-1.55	500	250	250
1.56-1.61	520	260	260
1.62-1.71	540	270	270
1.72-1.85	600	300	300
1.86-1.92	620	310	310
≥1.93	640	320	320

PF-02341066 Dose Assignment: 215 mg/m²/dose BID (DOSE LEVEL 4)

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m²)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.30-0.35	140	70	70
0.36-0.39	160	80	80
0.40-0.44	180	90	90
0.45-0.49	200	100	100
0.50-0.54	220	110	110
0.55-0.58	240	120	120
0.59-0.63	260	130	130
0.64-0.67	280	140	140
0.68-0.72	300	150	150
0.73-0.77	320	160	160
0.78-0.82	340	170	170
0.83-0.86	360	180	180
0.87-0.95	400	200	200
0.96-1.00	420	210	210
1.01-1.05	440	220	220
1.06-1.11	460	230	230
1.12-1.19	500	250	250
1.20-1.23	520	260	260
1.24-1.32	540	270	270
1.33-1.42	600	300	300
1.43-1.47	620	310	310
1.48-1.55	640	320	320
1.56-1.65	700	350	350
1.66-1.76	720	360	360
1.77-1.89	800	400	400
≥ 1.90	820	410	410

PF-02341066 Dose Assignment: 280 mg/m^2/dose BID (DOSE LEVEL 5)

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m^2)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.30-0.33	180	90	90
0.34-0.37	200	100	100
0.38-0.41	220	110	110
0.42-0.45	240	120	120
0.46-0.48	260	130	130
0.49-0.51	280	140	140
0.52-0.55	300	150	150
0.56-0.58	320	160	160
0.59-0.62	340	170	170
0.63-0.66	360	180	180
0.67-0.69	380	190	190
0.70-0.73	400	200	200
0.74-0.76	420	210	210
0.77-0.80	440	220	220
0.81-0.83	460	230	230
0.84-0.87	480	240	240
0.88-0.91	500	250	250
0.92-0.94	520	260	260
0.95-0.98	540	270	270
0.99-1.03	560	280	280
1.04-1.09	600	300	300
1.10-1.12	620	310	310
1.13-1.16	640	320	320
1.17-1.21	660	330	330
1.22-1.26	700	350	350
1.27-1.30	720	360	360
1.31-1.37	740	370	370
1.38-1.44	800	400	400
1.45-1.48	820	410	410
1.49-1.55	840	420	420
1.56-1.62	900	450	450
1.63-1.71	920	460	460
1.72-1.80	1000	500	500
1.81-1.89	1020	510	510
≥ 1.90	1100	550	550

APPENDIX IIIB: PF-02341066 DOSING TABLES (FOR PATIENTS RECEIVING THE FORMULATED CAPSULES)

Note: The dosing tables in Appendix IIIB are for patients enrolled on Parts A2, B & C as of Amendment #6 who are receiving the Formulated Capsules (FC). For patients using the pediatric Oral Solution (OS), refer to Appendix IV.

PF-02341066 Dose Assignment: 280 mg/m²/dose BID
(DOSE LEVEL 5 and RECOMMENDED PHASE 2 DOSE)

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m²)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.63-0.80	400	200	200
0.81-0.98	500	250	250
0.99-1.16	600	300	300
1.17-1.33	700	350	350
1.34-1.51	800	400	400
1.52-1.69	900	450	450
1.70-1.87	1000	500	500
1.88-≥ 2.0	1100	550	550

For 1st **dose reduction** due to toxicity

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m²)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.63-0.80	300	150	150
0.81-0.98	350	200	150
0.99-1.16	400	200	200
1.17-1.33	500	250	250
1.34-1.51	600	300	300
1.52-1.69	650	350	300
1.70-1.87	700	350	350
1.88-≥ 2.0	800	400	400

For 2nd **dose reduction** due to toxicity

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m²)	**Total Daily Dose**	**mg q am**	**mg q hs**
0.63-0.80*	*	*	*
0.81-0.98*	*	*	*
0.99-1.16	300	150	150
1.17-1.33	350	200	150
1.34-1.51	400	200	200
1.52-1.69	450	250	200
1.70-1.87	500	250	250
1.88-≥ 2.0	600	300	300

*These patients will receive oral solution if 2nd dose reduction is required

APPENDIX IV: PF-02341066 PEDIATRIC ORAL SOLUTION CALCULATION

To calculate dosing volumes for each patient based on BSA, the following formula should be used:

$$\text{Dosing Volume (mL)} = \frac{\text{Prescribed Dose (mg/m}^2\text{) x BSA (m}^2\text{)}}{25 \text{ (mg/mL)}}$$

Calculated dosing volumes should be rounded up to the nearest 0.1 mL for the actual deliverable dose.

Examples:

- Patient BSA 0.75 m^2, Dose Level 1→ Dosing volume = 3.0 mL BID
  Dosing Volume (mL) = (100 mg/m^2 x 0.75 m^2) / (25 mg/mL) = 3 mL

- Patient BSA 0.75 m^2, Dose Level 3→ Dosing volume = 5.0 mL BID
  Calculated Volume (mL) = (165 mg/m^2 x 0.75 m^2) / (25 mg/mL) = 4.95 mL
  Dosing Volume (mL) = 5 mL (rounded up to nearest 0.1 mL)

Note: For patients receiving PF-02341066 PIC refer to Appendix IIIA and FC refer to Appendix IIIB.

APPENDIX V: PHARMACOKINETIC STUDY FORM

COG Pt ID # _______________ ACC # _______________
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Cycle 1, **Date of Steady State Sampling**: |__/__|__/__|__/__|

Dose Level: _______mg/m^2 Dose Administered: ______mg/day Body Surface Area: ______m^2

For all patients on Parts A, B or C, plasma samples (2 mL) will be obtained prior to the first dose on Day 1 of Cycle 1 and **at steady state**, defined as being between days 15 and 28 of BID dosing in Cycle 1 at the following time points: pre-dose (12 h after the last dose), 1 hr, 2 hr, 4 hrs, and 6-8 hrs. Record the exact date and time each sample is drawn and the last PF-02341066 dose is administered before the pharmacokinetic sample is drawn. Sample handling and processing instructions are described below and in Section 8.2.

Blood Sample No.	Time Point Cycle 1	Scheduled Collection Time	Date Dose Given	Actual Date Sample Collected	Actual Time Collected or Dose Given (24-hr clock)
1	Pre-Dose	Prior to the first dose on Day 1			|__|__| : |__|__|
		Last dose before Pre-Dose at Steady State Obtained			|__|__| : |__|__|
2	Pre-Dose at Steady State	12 h after the last dose recorded above			|__|__| : |__|__|
		Steady State Dose Given			|__|__| : |__|__|
3	Steady State	1 hr. after			|__|__| : |__|__|
4	Steady State	2 hrs. after			|__|__| : |__|__|
5	Steady State	4 hrs. after			|__|__| : |__|__|
6	Steady State	6-8 hrs. after			|__|__| : |__|__|

Sample Processing Procedures

1. **Label** the cryovial tube with the patient's study registration number, the study I.D. (ADVL0912), and the date and time the sample was drawn; please label as "**plasma**". Affix storage label to 2 mL cryovial (vertically).
2. **Draw 2 mL of blood** into a 4-mL K_2EDTA (lavender top) Vacutainer tube. Once collected, samples should be processed immediately and kept out of direct sunlight due to the light sensitive nature of PF-02341066.
3. **Mix** the blood with the anticoagulant by gently inverting the tube 6 to 8 times.
4. Place sample on wet ice.
5. **Centrifuge** the blood samples at approximately 1700g for 10 minutes at 4°C to harvest the **plasma.**
6. Remove the plasma by transfer pipette and **transfer ~1 mL of plasma** into the 2 mL pre-labeled cryovial. Cap the tubes tightly.
7. **Record the date and time of collection for each sample** on this form. A copy of this form must accompany the sample(s) at time of shipment.
8. **Place the cryovial containing the plasma inside the cryovial storage box provided and store the plasma at -20 to -70**°C within 1 hour of collection until shipment.

One copy of this Pharmacokinetic Study Form should be faxed to the study research coordinator with the corresponding shuttle sheet, to the Operations Center at (626) 447-2204. A second copy should be sent with the samples to Covance at the address listed in Appendix V-A. See Appendix V-A for detailed guidelines for packaging and shipping PK samples to Covance.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: ____ Date:_________________________
(site personnel who collected samples)

APPENDIX V-A:

Guidelines for Shipping Samples to Covance –Indianapolis

REGULATORY INFORMATION

Specific Federal and International Regulations define classes of "Hazardous Materials"1 and "Dangerous Goods"2. Specimens transported to the Covance Indianapolis - Bioanalytical Chemistry Department should be evaluated for their Hazardous Material Class and categorized, packaged, labeled, documented, and transported in accordance with the applicable regulations. Facilities shipping Hazardous Materials are required to maintain designated personnel trained in accordance with part 493 CFR-Subpart H within the last 36 months and International Air Transportation Association (IATA) regulations (if shipping by air) within the last 24 months. The IATA regulation manual also lists additional regulations imposed individually by a variety of Commercial Carriers and Airlines.

The information provided here are Covance Labs guidelines to assist in the proper and safe transport of samples for assay in this facility. They are not to be construed as a replacement or complete summary of applicable DOT (CFR) or IATA regulations.

GUIDELINES FOR PACKAGING SAMPLES

PACKAGING

A. Please organize samples by subject where possible (i.e. bag all of subject 001 together, all of subject 002 together, etc)
B. If shipping 2 or more studies in the same box, please clearly identify individual bags or boxes with client protocol number

1. Sample container caps should be securely fastened.
   a. Samples should not be transported in glass vials. Samples should be transferred to plastic tubes for transport.
      (If glass must be used, containers must be immobilized. Note: the use of glass greatly increases the risk of breakage and sample loss).
   b. Use labels that will not smear or fall off under cold or moist conditions.

2. Samples should be placed in a primary receptacle (insulated cooler), then into a secondary receptacle (sturdy cardboard box). These primary and secondary containers are available commercially as combination packaging. The package contents are placed in this order:
   a. Wrap the samples in enough absorbent material to absorb at least three times the contents should leakage occur.
   b. Place the wrapped samples in a plastic bag and seal (heat seal or zip lock)
   c. Place the sealed bag in the bottom of the primary receptacle.
   d. Add styrofoam peanuts or equivalent (barrier to dry ice and shock stabilizer)
   e. Add a sheet of cardboard
   f. If samples are to be frozen, adequate dry ice should be included in the container to last the duration of the journey. (48-72 hrs, at least 7 Kg or 15 pounds, approximately 4 pounds per day of transit).
   g. If there is room remaining, add filler material to avoid content movement during transport.
   h. The primary Styrofoam container should be taped shut and placed in the secondary cardboard container.

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1 Term used by Department of Transportation (DOT) in the Code of Federal Regulations (CFR)
2 Similar term used by the International Air Transportation Association (IATA), will use the term Hazardous Material in this document
3 Part 49 is "Hazardous Materials in Commerce" in the CFR

3. Complete the Pharmacokinetic Study Form located in Appendix V of the ADVL0912 protocol. **Please indicate sample storage conditions on this form.**

4. Seal the form in a protected plastic bag. Place the plastic bag containing the form on top of the secured styrofoam primary container lid so that it is immediately accessible upon opening the box.

5. Tape the shipping box securely closed. Use tape that is resistant to moisture and cold.

6. Place Biohazard warnings on outside of box (if applicable).

7. Label the box exterior in accordance with the applicable DOT CFR / IATA Regulations.

8. Complete an address label and attach it to the outside of the box.

****

GUIDELINES FOR SHIPPING SAMPLES

Send samples to:

Covance Bioanalytical Services, LLC **8211 SciCor Drive, Suite B** **Indianapolis, Indiana 46214** **Attn: BioA Sample Accession Mgr**

1. Samples should be shipped **least 2 days prior to a USA National Holiday.**

2. Call the Covance Bioanalytical Services Sample Management department **on the day prior to shipment (800-462-8887 Ext 3935 or Ext 3902),** as notification of the intended shipment, ***OR*** e-mail IndyBioSA@Covance.com with shipment information (tracking numbers and number of boxes sent).

3. **Samples to be shipped to the United States from outside the U.S.A**. should be shipped using an International carrier. The name of the carrier, shipping date, expected date of arrival, and tracking numbers should be e-mailed to IndyBioSA@Covance.com, prior to shipment.

4. Any questions regarding shipping instructions may be directed to the Sample Management Group at 1-800-462-8887 Ext. 3957, Ext 3902, or Ext. 3935, or via
Fax 317-616-2301. International phone code is 001.

****

SHIPPING

APPENDIX VI: PHARMACOGENOMIC STUDY FORM

COG Pt ID # _______________ ACC # _______________
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Body Surface Area: |__|°|__|__| m^2

Dose Level: ________mg/m^2 Total Dose: _______mg/day

- One peripheral blood sample (3 mL) will be obtained on Day 1 of Cycle 1 prior to the first dose of PF-02341066 for genotyping the alleles of cytochrome P450 enzymes and drug transport proteins.
- Record the exact time that the sample is drawn along with the exact time that the last dose is administered.

	Date	Time
Sample Obtained:	|__/__|__/__|__/__|	|___|___| : |___|___|
Drug Administered:	|__/__|__/__|__/__|	|___|___| : |___|___|

Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D. (ADVL0912), and the date and time the sample was drawn; please label as "**pharmacogenomic sample**".

Sample Processing Procedures

1. Draw 3 mL of blood into a 4-mL K_2EDTA (lavender top) Vacutainer tube.
2. Label the tube with the patient's study registration number, the study I.D. (ADVL0912), and the date and time the sample was drawn.
3. Gently mix the blood with the anticoagulant by gently inverting the tube (15 times).
4. Record the date and time of collection for each sample on this form.
5. After mixing the blood with the anticoagulant, place the blood collection tube inside the cryovial storage box provided **and store the blood at -20°C.**

Data should be recorded on this Pharmacogenomic Study Form, which must accompany the sample(s) at the time of shipment. One copy of the Pharmacogenomic Study Form should be faxed to the study Research Coordinator with the corresponding shuttle sheet, to the Operations Center at (626) 447-2204. A second copy should be sent with the sample to the laboratory at Pfizer, Inc. at the address below.

Sample Shipping

1. Ship all accumulated samples on dry ice. Shipments should be sent **Monday through Wednesday only** for priority overnight delivery. Do not ship on Thursday or Friday.
2. Genotype whole blood samples should be shipped to the address below. Please notify the laboratory of a pending shipment along with the FedEx tracking number by phone at (860) 686-3203 or by e-mail (PGxLab@pfizer.com).
3. Ship samples to:

CLIA PGx Lab
Pfizer, Inc.
Attn: Cheryl Tow-Keogh / Linda Wood
Building 118E, Room 261
Eastern Point Rd
Groton, CT 06355

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: ____ Date:___________________________
(site personnel who collected samples)

APPENDIX VII: NEUROBLASTOMA CORRELATIVE BIOLOGY STUDIES

1. **COMPREHENSIVE DNA RESEQUENCING OF ALK**
   Tumor tissue will be requested for all research subjects. The optimal sample will be tumor at the time of study enrollment, but tumor tissue from diagnosis or at any other point during therapy prior to treatment with PF-02341066 will be accepted. This can be archived tissue (frozen or paraffin) from the institution or from the Biopathology Center (BPC) for those subjects enrolled on ANBL00B1. If a tumor block is not available, unstained slides may be shipped instead. DNA extraction and Sanger-based re-sequencing of the 29 coding exons of ALK and 500bp of the promoter region will be performed at CHOP.

2. **DEFINE ALK ALLELIC STATUS**
   We will define whole genome DNA copy number status as well as *ALK* allelic using the Illumina HH550K Single Nucleotide Polymorphism (SNP) array.[6,22,23] The primary goal of this assay is to determine if the ALK and/or MYCN loci are amplified. For samples in which allelic gain or amplification exist in the context of a mutation, we will also design allele specific quantitative PCR probes to determine if the mutated allele is somatically gained.

3. **DEFINE ALK TRANSLOCATION STATUS*****
   We will perform FISH for *ALK* translocations using the LSI *ALK* Dual Color, Break Apart Rearrangement probe (Abbott-Vysis) either on touch preps or paraffin-embedded tumor from all available neuroblastoma primary tumors gather for experiments #1 and #2 above.
   ***These studies will only be pursued if ongoing investigations show that ALK translocations are a significant mechanism for ALK activation in neuroblastoma.

4. **DETERMINE THE MALIGNANT TRANSFORMING PROPERTIES OF ALL *ALK* MUTATIONS IDENTIFIED**
   To determine the functional consequences of various candidate *ALK* mutations, we will engineer mutant full-length *ALK* cDNAs using site-directed mutagenesis. We will then over-express these constructs in a mammalian neural-crest derived cell line and assay for malignant transformation. We will use a lentiviral system for stable integration of *alk* constructs into retinal pigment epithelial cells that express telomerase (RPE1-hTERT) and look for evidence of malignant transformation.[24] We will then screen for transformation *in vitro* using standard assays.

5. **DETERMINE THE BIOCHEMICAL CONSEQUENCES OF *ALK* ACTIVATION BY SURVEYING DOWNSTREAM SIGNALING PATHWAYS IN *ALK*-MUTANT SAMPLES**
   We will determine which of the major canonical signaling pathways are activated as a consequence of mutant ALK. Specifically, we will assess native and phosphorylated ALK, STAT3, AKT, ERK, and SHP2 expression on all available tumor tissue from patients enrolled on this trial. We will compare the signaling properties of the various mutations and look for differential signaling patterns that may predict increased sensitivity to growth inhibition by *ALK* inhibition.

6. **EXPLORE POTENTIAL MECHANISMS OF RESISTANCE TO PF-02341066 AT TIME OF DISEASE PROGRESSION ON THIS STUDY**
   We will collect bone marrow samples before and during treatment with PF-02341066, flow-sort for tumor cells, and establish cell lines in culture. These cell line models will then be used for direct re-sequencing of ALK as well as for in vitro and in vivo cytotoxicity assays to explore mechanisms of potential acquired drug resistance.

APPENDIX VIII:BONE MARROW STUDIES FORM (FOR PATIENTS WITH NEUROBLASTOMA ONLY)

Patient ID #: ____________________ Study ID: **ADVL0912**

BSA (m^2): ____________ Dose level (mg/m^2): ____________ Accession #: ____________

Actual Dose: ____________ Time dose taken: ____________ Date: ____________

Please do not write patient names on this form or on samples.

- In patients with neuroblastoma, a bone marrow aspirate will be obtained (5 mL sample). In children weighing ≤ 10 kg, this sample can be 3-5 mL.
- These samples will be obtained prior to starting Cycle 1 in patients with neuroblastoma. If marrow is positive for tumor cells at time of study enrollment, a marrow will also be repeated at times of disease evaluation (See Section 8.3.2.2).

Type of sample:	☑ bone marrow
Date Sample Collected:	

Collection of Bone Marrow

- Bone marrow aspiration:
  Collect 5 mL of bone marrow in preservative free heparin (100 units heparin/1 mL of bone marrow) by aspiration.

Shipment of Bone Marrow

- Place bone marrow in polypropylene screw top tube(s).
- Label tube with patient's registration number, the study ID (ADVL0912), and date and time it was drawn.
- Place tube(s) in container.
- Place the container with the conical tube in a styrofoam box.
- Package sample as appropriate for biologic material.
- Ship the sample **on the same day it was obtained** with **Federal Express overnight priority delivery** to:

  Attn: Dr. Yaël Mossé
  The Children's Hospital of Philadelphia
  The Colket Translational Research Building
  Room 3300
  3501 Civic Center Boulevard
  Philadelphia, PA 19104

- Do not ship samples for delivery on a weekend or Holiday.
- **Samples must be received within 24 hours of obtaining the sample.**

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: ________________________________ Date:____________________
(site personnel who collected samples)

APPENDIX IX: TISSUE STUDIES FORM
(FOR PATIENTS WITH NEUROBLASTOMA ONLY)

Patient ID #: ____________________ Study ID: **ADVL0912**

BSA (m^2): ____________ Dose level (mg/m^2): ____________ Accession #: ____________

Actual Dose: ____________ Time dose taken: ____________ Date: ____________

Tumor Sample Labeling:

Samples should be labeled with the following information:

Protocol number: **ADVL0912**
Institution: ____________________
Patient ID #: ____________________
Accession #: ____________________
Sample Date: ____________________
Site of Acquired Tissue: ____________________

Tissue obtained at (check one option below):
☐Diagnosis ☐Relapse

Shipment of Tumor Tissue:

Paraffin embedded tumor specimens must be packaged appropriately and shipped at room temperature to Dr. Yaël Mossé (at the address below). If a tumor block is not available, please send as many scrolls from the tumor block and/or a minimum of 10 unstained slides may be shipped instead. Please indicate above the date of the sample, site of tissue acquisition and whether it was obtained at diagnosis or relapse. Shipments should be sent **Monday through Thursday only** for priority overnight delivery using the COG FedEx account (do not ship on Friday). One copy of this form should be faxed to the study Research Coordinator with the corresponding shuttle sheet, to the Operations Center at (626) 447-2204.
A second copy should be sent with the tissue sample to lab address below.

Attn: Dr. Yaël Mossé
The Children's Hospital of Philadelphia
The Colket Translational Research Building
Room 3300
3501 Civic Center Boulevard
Philadelphia, PA 19104

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: ____ Date:______________________
(site personnel who collected samples)

APPENDIX X: BONE MARROW AND PERIPHERAL BLOOD STUDIES FORM (PATIENTS WITH ANAPLASTIC LARGE CELL LYMPHOMA)

Patient ID #: ____________________ Study ID: **ADVL0912** ____________

BSA (m^2): ____________ Dose level (mg/m^2): ____________ Accession #: ____________

Actual Dose: ____________ Time dose taken: ____________ Date: ____________

A single bone marrow sample will be obtained prior to starting Cycle 1 in patients with ALCL. In addition, peripheral blood samples will be obtained prior to starting Cycle 1, on day 15 of Cycle 1, at the beginning of Cycle 2, then as indicated in Section 8.1 for each subsequent cycle through cycle 11, and then every 3 cycles.

Type of sample (check one) :	☐ bone marrow ☐ peripheral blood
Date Sample Collected:	

- In ALCL patients, a bone marrow aspirate will be obtained (5 mL sample). In children weighing ≤ 10 kg, this sample can be 3-5 mL.
- In ALCL patients, peripheral blood will be collected (15 mL if weight > 10 kg, 10 mL if weight ≤10kg).

Collection of Bone Marrow or Peripheral Blood

Bone marrow or peripheral blood should be collected in a K+ EDTA (lavender-top) tube.

Shipment of Bone Marrow or Peripheral Blood

- Label tube with patient's registration number, the study ID (ADVL0912), and date and time it was drawn.
- Place tube(s) in container.
- Place the container with the conical tube in a styrofoam box.
- Package sample as appropriate for biologic material.
- Ship the sample **on the same day it was obtained** with **Federal Express overnight priority delivery** to:

Megan S. Lim, MD, PhD
109 Zina Pitcher Place
BSRB 2378, SPC 2200
Ann Arbor, MI 48109
Phone: (734) 615-4388
Fax: (734) 615-9666
E-mail: meganlim@umich.edu
fuzon@med.umich.edu

- Do not ship samples for delivery on a weekend or Holiday.
- **Samples must be sent within 24 hours of time drawn.**
- Notify Fuzon Chung and Dr. Lim at the e-mail addresses above prior to shipping samples and include the tracking number for the shipment.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: ____ Date:____________________
(site personnel who collected samples)

APPENDIX XI: CORRELATIVE STUDIES GUIDE

Correlative Study	Appendix	Blood Volume				Tube Type
		≤ 10 kg		>10 kg		
		Volume per sample	Total Cycle 1	Volume per sample	Total Cycle 1	
Pharmacokinetics[a]	V	2 ml	12 ml	2 ml	12 ml	K+ EDTA
Pharmacogenomics	VI	3 ml	3 ml	3 ml	3 ml	K+ EDTA
Bone Marrow[b]	VIII	3-5 ml	3-5 ml	5 ml	5 ml	Preservative free heparin tubes
Bone Marrow[c]	X	3-5 ml	3-5 ml	5 ml	5 ml	K+ EDTA
Peripheral Blood[c]	X	10 ml	20 ml	15 ml	30 ml	K+ EDTA
Tumor Tissue[b]	IX					
Total Blood Volume in Cycle 1		-	**35 ml**	-	**45 ml**	
Total Bone Marrow Volume		-	**6-10 ml**	-	**10 ml**	

[a] Required for all patients (Parts A, B or C)
[b] Additional Studies for Patients with Neuroblastoma
[c] Additional Required Studies for Patients with ALCL

APPENDIX XII: PF-02341066 PATIENT DIARY (CAPSULES)

COG Patient ID:___________ **ACC # :** _____ **Institution :**_________________________________
Please do not write patient names on this form.

Complete each day with the time and dose of PF-02341066 given. Make note of other drugs and supplements taken. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle. Your institution will fax this document with the corresponding shuttle sheet, to the COG Statistics & Data Center at (626) 447-2204 after each treatment cycle.

Note: If patients are receiving the PIC formulation, please enter 10mg, 50mg, and 100mg for the capsule strengths below. If patients are receiving the formulated capsules, please enter 150mg, 200mg, and 250mg for the capsule strengths below.

EXAMPLE (PIC formulation)				***Number of capsules taken***			***Comments***
WEEK 1	***Date***	***Time***		***10 mg***	***50 mg***	***100 mg***	*He felt nauseated an hour after taking the drug but did not vomit.*
Day 1	*1/15/13*	*8:30*	*AM*	2	1	0	
		8:30	*PM*	2	1	0	

EXAMPLE (Formulated Capsules)				***Number of capsules taken***			***Comments***
WEEK 1	***Date***	***Time***		***150 mg***	***200 mg***	***250 mg***	*He felt nauseated an hour after taking the drug but did not vomit.*
Day 1	*1/15/13*	*8:30*	*AM*	0	1	0	
		8:30	*PM*	0	1	0	

Cycle #: _____ **Dose:** ________ **Start Date**: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

WEEK 1	**Date**	**Time**		**mg**	**mg**	**mg**	**Comments**
Day 1			**AM**				
			PM				
Day 2			**AM**				
			PM				
Day 3			**AM**				
			PM				
Day 4			**AM**				
			PM				
Day 5			**AM**				
			PM				
Day 6			**AM**				
			PM				
Day 7			**AM**				
			PM				

WEEK 2	Date	Time		mg	mg	mg	Comments
Day 8			AM				
			PM				
Day 9			AM				
			PM				
Day 10			AM				
			PM				
Day 11			AM				
			PM				
Day 12			AM				
			PM				
Day 13			AM				
			PM				
Day 14			AM				
			PM				

WEEK 3	Date	Time		mg	mg	mg	Comments
Day 15			AM				
			PM				
Day 16			AM				
			PM				
Day 17			AM				
			PM				
Day 18			AM				
			PM				
Day 19			AM				
			PM				
Day 20			AM				
			PM				
Day 21			AM				
			PM				

WEEK 4	Date	Time		mg	mg	mg	Comments
Day 22			AM				
			PM				
Day 23			AM				
			PM				
Day 24			AM				
			PM				
Day 25			AM				
			PM				
Day 26			AM				
			PM				
Day 27			AM				
			PM				
Day 28			AM				
			PM				

CHILDREN'S ONCOLOGY GROUP

APPENDIX XIII: PF-02341066 PATIENT DIARY (ORAL SOLUTION)

COG Patient ID:___________ **ACC # :** _____ **Institution :**_________________________________

Please do not write patient names on this form.

Complete each day with the time and dose of PF-02341066 given. Make note of other drugs and supplements taken. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle. Your institution will fax this document with the corresponding shuttle sheet, to the COG Statistics & Data Center at (626) 447-2204 after each treatment cycle.

EXAMPLE				***Amount of oral solution taken***	***Comments***
WEEK 1	***Date***	***Time***		***(total mL per dose)***	*He felt nauseated an hour after taking the drug but did not vomit.*
Day 1	*1/15/09*	*8:30*	*AM*	*2*	
		8:30	*PM*	*2*	

Cycle #: _____ **Dose:** ________ **Start Date**: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

WEEK 1	**Date**	**Time**		**mL**	**Comments**
Day 1			**AM**		
			PM		
Day 2			**AM**		
			PM		
Day 3			**AM**		
			PM		
Day 4			**AM**		
			PM		
Day 5			**AM**		
			PM		
Day 6			**AM**		
			PM		
Day 7			**AM**		
			PM		

WEEK 2	**Date**	**Time**		**mL**	**Comments**
Day 8			**AM**		
			PM		
Day 9			**AM**		
			PM		
Day 10			**AM**		
			PM		
Day 11			**AM**		
			PM		
Day 12			**AM**		
			PM		
Day 13			**AM**		
			PM		
Day 14			**AM**		
			PM		

WEEK 3	Date	Time		mL	Comments
Day 15			AM		
			PM		
Day 16			AM		
			PM		
Day 17			AM		
			PM		
Day 18			AM		
			PM		
Day 19			AM		
			PM		
Day 20			AM		
			PM		
Day 21			AM		
			PM		

WEEK 4	Date	Time		mL	Comments
Day 22			AM		
			PM		
Day 23			AM		
			PM		
Day 24			AM		
			PM		
Day 25			AM		
			PM		
Day 26			AM		
			PM		
Day 27			AM		
			PM		
Day 28			AM		
			PM		

APPENDIX XIV: ORAL SOLUTION ADMINISTRATION INSTRUCTIONS

ADMINISTRATION INSTRUCTIONS

1	Study Site Staff should review information contained on drug label as well as dosing and administration instructions with patient and/or patient caregiver to ensure proper dispensing of medication. Particular attention should be focused on how to accurately draw desired dose into correct oral syringe(s) and how to read syringe graduations to avoid patient mis-dosing. Note that oral solution will be packaged together with a press-in-bottle adaptor and re-usable dosing syringes.
2	Each morning and evening dose should be taken at about the same time each day, approximately 12 hours apart. The dose may be taken with or without food or beverage.
3	Remove the bottle from the refrigerator and gather the appropriate oral syringe(s) and any other supplies as directed by Study Site Staff. Before using dosing syringes, ensure that each syringe and its components are clean and dry. The plunger within each syringe should be pressed all the way closed. Note once a bottle of oral solution has been opened, it should only be used for 90 days unless additional in-use stability data has been made available.
4	When using a bottle for the first time, unscrew the bottle cap and insert the press in bottle adaptor (PIBA) into the bottle opening to help withdraw the medication. Once inserted the press in bottle adaptor will not be taken out.
5	Open the bottle and ensure that the bottle adaptor is securely in place.
6	Select a clean, dry dosing syringe and insert the syringe tip into the bottle adaptor.
7	Pick up the bottle with one hand while holding the dosing syringe firmly in place with the other hand. It is recommended that the thumb of the hand holding the dosing syringe be placed against the top of the syringe barrel while the fingers grip the sides of the barrel. The dosing syringe tip should still be firmly inserted into the bottle adaptor.
8	Turn bottle and syringe set-up upside down so bottle is on top of syringe. Slowly pull back on the plunger to draw a small amount of solution into the syringe (about 2 mL). Check the syringe for trapped air bubbles. If air bubble(s) are present in the syringe, return the bottle to the upright position and then remove the dosing syringe from the adaptor.
9	Expel trapped air bubble(s) in the syringe by holding the syringe with the tip pointed upwards and gently tap on the side of the syringe barrel to move air bubbles into the tip of the syringe. Slowly depress the syringe plunger to expel the air from the syringe tip. Ensure that no further air bubbles are present and that the solution in the syringe completely fills the tip of the syringe. Note that trapped air in the syringe will cause an inaccurate volume of medication to be delivered.
10	Re-insert the dosing syringe tip into the bottle adaptor and invert the bottle and syringe set-up again. Continue to slowly pull back on the plunger and withdraw the prescribed amount of solution into the syringe.
11	When the desired amount of solution is contained within the syringe, return the bottle to the upright position and remove the syringe.
12	If additional dose syringes need to be prepared, repeat steps 6 -11.
13	After preparing dosing syringe(s), medication should be delivered promptly to patient.

	If the patient cannot be dosed immediately with medication in syringes, wrap each syringe with aluminum foil to protect medication from light exposure and place in refrigerator. Oral solution may be stored in supplied syringes for no more than 24 hours. If the patient has sensitivity to cold temperatures, then the oral solution may be held in syringes for up to 24 hours at room temperature. As mentioned above, the syringes must be wrapped with aluminum foil to protect medication from light exposure.
14	To deliver the dose, place the tip of the oral dosing syringe into the patient's mouth. With the patient's head tilted slightly back, slowly push the plunger to expel the solution. To avoid choking, be careful not to expel the dose directly into the back of the throat.
15	Recap the bottle and return it to refrigerator.
16	Complete Crizotinib Oral Solution Taste Feedback Questionnaire (see the ADVL0912 Case Report Forms) within 10 minutes of dosing patient. Questionnaire is to be completed on the following schedule to capture patients taste responses to the oral solution after dose administration. • First administration of oral solution • Once a week during first month of administration of oral solution • Every visit to treating institution after first month of administration of oral solution
17	Wash hands. Clean the syringe by removing the plunger and rinsing the barrel and plunger with water. Allow the barrel and plunger to air dry or use a clean paper towel or clean cloth to dry. When dry, push the plunger back into the syringe barrel in preparation for next dose.
18	As per guidance from Study Site Staff, bring any unused medication and used syringes in a sealed plastic bag to your next clinic appointment for appropriate disposal. The sealable plastic bag should be labeled as "waste" and kept away from the reach of children or pets.

NOTE:

- **If the patient vomits the dose, do not repeat the dose at that time. Wait until the next regularly scheduled time to administer the dose.**
- **If a dose is missed, take a dose as soon as you remember, but never more than 6 hours after the time it was originally due.**
- **If you have any questions, contact your provider.**

APPENDIX XV: POTENTIAL DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

PF-02341066 (Crizotinib)

Drugs that may interact with PF-02341066 (Crizotinib)

• Antibiotics
    • Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
    • Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine
• Antifungals
    • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
    • Leflunomide, tofacitinib
• Anti-rejection medications
    • Cyclosporine, sirolimus, tacrolimus
• Antiretrovirals and antivirals
    • Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
    • Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
    • Amiodarone, amlodipine, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
    • Aprepitant, artemether/lumefantine, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements* that may interact with PF-02341066 (Crizotinib)
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

CHILDREN'S ONCOLOGY GROUP

APPENDIX XVI: NON-MEMBER COLLABORATOR (NMC) INSTITUTIONS

MA036/ Dana-Farber Cancer Institute **PI: Carlos Rodriguez-Galindo, MD/27475**

Treating Physician	CTEP ID	Treating Physician	CTEP ID	Treating Physician	CTEP ID
Prasanna Ananth, MD	48366	Holcombe Grier, MD	13310	Steven Margossian, MD	37140
Daniel Bauer, MD	43560	Eva Guinan, MD	28044	Jonathan Marron, MD	50289
Amy Billett, MD	19386	Alejandro Gutierrez, MD	41524	Elizabeth Mullen, MD	28067
Melissa Burns, MD	50335	Inga Hofmann, MD	43767	Allison O'Neill, MD	48196
Susan Chi, MD	35547	Andrew Hong, MD	48363	Andrew Place, MD	44535
Julia Chu, MD	50288	Katherine Janeway	41525	Scott Pomeroy, MD	28062
Natalie Collins, MD	48367	Lisa Kenney, MD	24997	Gayle Pouliot, MD	50122
Brian Crompton, MD	49046	Jennifer Kesselheim, MD	41865	Charles Willard Roberts, MD	35955
Kimberly Davies, MD	28026	Mark Kieran, MD	27594	Stephen Sallan, MD	9495
Barbara Degar, MD	33238	Birgit Knoechel, MD	43768	Suzanne Shusterman, MD	35265
Lisa Diller, MD	20709	Michelle Lee, MD	43770	Lewis Silverman, MD	27566
Christine Duncan, MD	39635	Leslie Lehmann, MD	27565	Kimberly Stegmaier, MD	33629
Anne Frazier, MD	28022	Jennifer Mack, MD	37489	Christina Ullrich, MD	41526
Natasha Frederick, MD	50151	Peter Manley, MD	42343	Lynda Vrooman, MD	41863
Paola Friedrich, MD	50058	Brenton Mar, MD	44534	Joanne Wolfe, MD	33724
Rani George, MD	35655	Karen Marcus, MD	30102	Jennifer Wu, MD	50017

OH006/ Nationwide Children's Hospital **PI: Mark Anthony Ranalli, MD / 43014**

Treating Physician	CTEP ID	Treating Physician	CTEP ID	Treating Physician	CTEP ID
Rolla Abu-Arja, MD	44498	Terri Guinipero, MD	47128	Melissa Rose, MD	43511
Anthony Audino, MD	50420	Sarita Joshi, MD	36300	Bhuvana Setty, MD	48357
Jeffery Auletta, MD	37809	Riten Kumar, MD	43957	Nilay Shah, MD	52595
Rajinder Bajwa, MD	40813	Stephen Lessnick, MD	32641	Keri Streby, MD	53680
Robyn Dennis, MD	48385	Sarah O'Brien, MD	48846	Susan Vear, MD	52596
Amy Dunn, MD	52975	Randal Olshefski, MD	43174	Anthony Villella, MD	37199
Jonathan Finlay, MD	12359	Diana Osorio, MD	54470		

CO011/ Children's Hospital Colorado **PI: Kelly Maloney, MD/36571**

Treating Physician	CTEP ID	Treating Physician	CTEP ID	Treating Physician	CTEP ID
Kathrin Bernt, MD	43774	Lia Gore, MD	33572	Tobias Neff, MD	43564
Carrye Cost, MD	43026	Douglas Graham, MD	37791	Christopher Porter, MD	43031
John Craddock, MD	43521	Brian Greffe, MD	19670	Lisa Reaves, MD	43816
Kathleen Dorris, MD	43973	Gerald Haase, MD	24468	Christopher Silliman, MD	21481
Nicholas Foreman, MD	43629	Michael Handler, MD	44270	Thomas Smith, MD	21774
Timothy Garrington, MD	37792	Joanne Hilden, MD	25124	Michael Wang, MD	37794
Roger Giller, MD	13372	Margaret Macy, MD	43409		

TX011/ UT Southwestern/Simmons Cancer Center-Dallas PI: Patrick Leavey, MD/ 36518

Treating Physician	CTEP ID	Treating Physician	CTEP ID	Treating Physician	CTEP ID
Victor Aquino, MD	26554	Kathleen (Wiertel) Ludwig, MD	55619	Martha Stegner, MD	43019
Daniel Bowers, MD	43077	Tiffany Simms-Waldrip, MD	47408	Gail Tomlinson, MD	24631
Laura Klesse, MD	43064	Stephen Skapek, MD	24814	Jonathan Wickiser, MD	43071
Andrew Koh, MD	42245	Tamra Slone, MD	43063	Naomi Winick, MD	14049

TN008/ Vanderbilt University/Ingram Cancer Center PI: Howard Katzenstein, MD/35354

Treating Physician	CTEP ID	Treating Physician	CTEP ID	Treating Physician	CTEP ID
Scott Borinstein, MD	42939	Richard Ho, MD	36287	Devang Pastakia, MD	49192
Adam Esbenshade, MD	43299	Austin Kirschner, MD	53988	Emmanuel Volanakis, MD	46599
Debra Friedman, MD	27336	Heather McDaniel, MD	48471		

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This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document, which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be filed with the COG Group Operations Center's Regulatory Compliance Office before a patient may be registered on this study.

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

[FOR PART A2 (PHASE 2 COMPONENT) OF THE STUDY ONLY]

ADVL0912*, A Phase 1/2 Study of PF-02341066, an Oral Small Molecule Inhibitor of Anaplastic Lymphoma Kinase (ALK) and c-MET, in Children with Relapsed/Refractory Solid Tumors and Anaplastic Large Cell Lymphoma*

When we use "you" and "I" in this consent form, we mean you or your child.

This study is a clinical trial (a research study involving patients, or protocol) of an experimental new drug for cancer. We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point. Clinical trials only include patients who choose to take part. Your participation in this study is entirely voluntary. Please read the consent form carefully. You will be given a copy of it to keep if you decide to participate in this study. You may discuss your decision with your friends and family if you would like.

This study is being carried out by the Children's Oncology Group (COG) Phase I Consortium. COG is an international research group that consists of more than 200 hospitals that treat children with cancer in the United States, Canada, Australia, and Switzerland, and The Phase I Consortium is the group of 21 hospitals within COG that does phase 1/2 studies like this one. It is common medical practice to treat children with cancer on research studies like this one. Participation in this study will be limited to the Consortium institutions and five additional hospitals within COG.

This is a Phase 1/2 study of a drug called PF-02341066. PF-02341066 is a drug that in laboratory studies can block or inhibit two proteins called c-met and Alk. These proteins may be important in the growth of certain types of cancer cells. PF-02341066 is considered experimental because the Food and Drug Administration (FDA) have not approved it.

You are participating in the phase 2 portion of this trial. In this part of the trial, we use the highest tolerable dose studied in the phase 1 portion to assess the anti-tumor effect of PF-02341066 in patients with an abnormality in the ALK gene that cannot be cured by any known standard treatment

You are being asked to participate in this study because you have a recurrent or progressive tumor or lymphoma that cannot be cured by any known standard treatment. When a cancer comes back (recurs) or does not respond to therapy, your doctor may recommend other anti-cancer drugs (chemotherapy), surgery, or radiation therapy. For certain cancers, a combination of one or more of these approaches is considered standard treatment. However, for other cancers, for cancers that again come back, or for cancer for which therapy is no longer working, the best treatment is not known.

Why is this study being done?

We are testing new experimental drugs such as PF-02341066 in the hopes of finding a drug that may be effective against recurrent tumors or lymphoma.

The goals of this study are:

- **To learn what kind of side effects PF-02341066 can cause;**
- **To learn more about the pharmacology (how your body handles the drug) of PF-02341066;**
- **To learn more about the biology of PF-02341066;**
- **To determine whether PF-02341066 is a beneficial treatment for your tumor.**

How many people will take part in the study?

There will be up to 45 patients participating in Part A2 of this study. About ___ will be treated at this hospital.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A medical history
- Physical exam
- Eye exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests
- Test of bone marrow (if you have lymphoma)
- Pregnancy test (if you are a woman who could have children)
- Plain X-ray of one or both of your lower legs
- Electrocardiogram (EKG, which tests the electrical impulses of your heart)
- We will also do whatever X-rays, CT scans, MRI or other tests are needed to check your tumor or to check whether tumor has spread to your brain since those patients may not participate in the study.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, PF-02341066 will be given by mouth twice a day for 28 days. This entire period is called a cycle. You may continue to receive PF-02341066 unless you develop serious side effects or your tumor worsens.

You will also have the following tests and procedures during the study. They are part of regular cancer care. They are being done more often because you are in this study.

- Physical exam
- Eye exam
- Blood tests
- Urine tests

- Tests to evaluate the status of your tumor based on your tumor type and location (e.g., CT or MRI scans, MIBG scans, PET scans, bone marrow aspirates and biopsies)

These tests are all necessary to make sure that you are not having unsafe side effects and to see whether or not your tumor is responding to PF-02341066.

Copies of the films used to check your child's disease may be sent to central review centers as part of COG quality control. Your name and other identifying information will be removed from these films prior to review.

In addition, we will monitor one or both of your lower legs with a plain X-ray prior to starting treatment with PF-02341066. If your bones have stopped growing, no further X-rays of the lower legs will be taken. If your bones are still growing, we will check your lower legs for changes at the end of Cycle 3, and then approximately every 6 months thereafter with a plain X-ray. Should we detect changes, we may perform an MRI to better describe the changes. These tests are performed, because in some growing animals that received PF-02341066 and other related drugs, changes in the structure of the growing bones were observed.

You will be given a Patient Diary at the beginning of each cycle of PF-02341066. Use the diary to record the date and time you take the drug, side effects you experience and other medications you are taking. This diary should be returned to clinic, along with the medication bottle (even if it is empty) before starting another cycle. This will help us to know how much of the drug you take and how it made you feel.

The PF-02341066 will be given as a capsule or liquid solution by mouth. Since we do not have information on how well the medicine is absorbed, if you vomit the medication it should not be taken again.

<u>Questionnaire:</u>

If you are receiving the PF-02341066 as a liquid by mouth, we would like to ask you to fill out a short questionnaire at the time of the first dose, and then once per week for the first month, and then at every visit thereafter so we can learn more about how the drug tastes. This questionnaire will take about 20 minutes to fill out each time. The study staff will collect some information from your chart about your age and what kind (if any) of PF-02341066 capsules or liquid you may have received in the past. The questionnaire is optional. The information learned would not change the way you are treated, and the results will not be returned to you.

______/______ Yes, I agree to take part in the questionnaire.

______/______ No, I do not agree to take part in the questionnaire.

We would also like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about PF-02341066 and may help children who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be returned to you. The pharmacokinetic studies are required and the biology studies are optional. You do not have to do those tests if you do not want to. Although these tests are a very important part of how we will better learn to use this drug, it is your decision as to whether or not you agree to participate in these tests.

Pharmacokinetic Studies

During the study blood samples will be collected to determine how much of the PF-02341066 is in your blood (pharmacokinetics). These samples are about 2 mL (approximately ½ teaspoon) of blood each. A single sample will be obtained before your first dose of the drug on Day 1 and additional samples will be obtained between day 15 and day 28 after you begin taking the drug in Cycle 1. These additional samples will be obtained before and at 1 hour, 2 hours, 4 hours, and 6-8 hours after the dose is given after approximately the middle of the first cycle (between day 15 and day 28). These additional samples may require that a small intravenous tube (catheter or IV) be placed if you do not have a central line. If you have a central line then you will not require an IV for these studies. A total of 12 mL (less than 3 teaspoons) of blood will be drawn for these studies. This amount of blood is safe even for small children. *These blood samples are required from all participants in this study.*

Biology Studies
If you consent to the biology study, one blood sample (3 ml, which is less than one teaspoon) will be collected before you take the first dose of PF-02341066 on Day 1 of Cycle 1.

______/______ Yes, I agree to participate in the biology studies.

______/______ No, I do not agree to participate in the biology studies.

A total of 15 mL will be drawn (approximately 3 teaspoons) for all the pharmacokinetic and biology study tests described above. This amount of blood is safe to draw even from small children.

How long will I be in the study?
Your doctor may decide to take you off study if any of the following occur:

- The side effects of PF-02341066 are too harmful for you
- You need a treatment that is not allowed on this study
- Your tumor does not improve or worsens
- You are not able to follow study-related treatment instructions
- New information becomes available
- The study is not in your best interest
- The study is stopped

After you are finished taking PF-02341066, the study doctor will ask you to visit the office for follow-up exams as they would normally do for patients with solid tumors or lymphoma.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from PF-02341066 can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side

effects. Many side effects go away soon after you stop taking the PF-02341066. In some cases, side effects can be serious, long lasting, may never go away, or possibly result in death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to PF-02341066 (crizotinib) include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving PF-02341066, more than 20 and up to 100 may have:
• **Vision Changes*** • **Constipation, diarrhea, nausea, vomiting** • **Loss of appetite** • **Swelling of the body** • **Tiredness** • **Dizziness** • **Changes in taste** • **Damage to nerves that may interfere with walking or organ function which may cause numbness, tingling, weakness or pain in the muscles**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving PF-02341066, from 4 to 20 may have:
• **Anemia which may require blood transfusion** • **Heartburn** • **Sores in the mouth** • **Abnormal heartbeat** • **Change in the heart rhythm** • **Headache** • **Rash** • **Belly pain** • **Infection, especially when white blood cell count is low** • **Sores in the mouth**

RARE, AND SERIOUS In 100 people receiving PF-02341066, 3 or fewer may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Difficulty swallowing** • **Damage to the lungs which may cause shortness of breath** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Fluid collection in the kidney that may be irregular and could be benign or could become cancerous** • **A tear or hole in the stomach that may require surgery** • **Blood clot which may cause swelling, pain, shortness of breath** • **Fainting**

*Vision changes may include blurred vision, double vision, discomfort in the eyes from light, swelling and redness of the eyelids, impaired vision, seeing spots before the eyes (floaters), flashing lights, brightness, rings, shadows, and/or streaking.

Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription or over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be

avoided.

*If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the blood stream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied by or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S (acquired immune deficiency syndrome) and other infections.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. A pregnancy test will be obtained in female patients before beginning treatment with PF-02341066.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

Risks of blood drawing or placing an intravenous catheter for blood drawing:

Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Risks of bone marrow aspirate and biopsy:

Risks associated with having a bone marrow aspirate or biopsy include: pain, bleeding, infection, or bruising.

Risks of Imaging Scans

The following imaging scans are part of routine care for many types of cancer and are performed to assess the size and/or location of your tumor(s).

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

The potential benefit of the treatment with PF-02341066 is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. Because there is not much information about the PF-02341066 effect on cancers in humans, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **No further treatment, and comfort care only**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **The drug company partner (the company that makes the drug PF-02341066) and its staff**
- **Health Canada***

* -Health Canada will only be able to see and/or copy reports describing bad side effects you may experience on this trial. If you are being treated at a Canadian institution, Health Canada will be able to see and/or copy all of your medical records.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Pfizer, Inc. is supplying PF-02341066 at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the PF-02341066.

If, during the study, PF-02341066 becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

You will not be charged for the costs of the special blood studies that are being done for research purposes only, such as the pharmacokinetic and biology studies. You may receive up to $100 (maximum) for the required pharmacokinetic studies for PF-02341066 to compensate for your inconvenience (i.e., travel, parking, meals reimbursement, etc).

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/learning/insurance-coverage/. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ *[name(s)]* at __________________ *[telephone number].*

For questions about your rights while taking part in this study, call the ________________________ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at __________________ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org

If you are in the United States, you may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. You will be given a copy of the protocol (full study plan) upon request. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all 10 pages of this form (including the study chart).
I have read it or it has been read to me.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant ____

Signature of Participant / Parent (or Guardian) ____

Date ____

Signature of Physician or Responsible Investigator ____

Date ____

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document, which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be filed with the COG Group Operations Center's Regulatory Compliance Office before a patient may be registered on this study.

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

[FOR PARTS B OR C (PHASE 2 COMPONENT) OF THE STUDY]

ADVL0912, *A Phase 1/2 Study of PF-02341066, an Oral Small Molecule Inhibitor of Anaplastic Lymphoma Kinase (ALK) and c-MET, in Children with Relapsed/Refractory Solid Tumors and Anaplastic Large Cell Lymphoma*

When we use "you" and "I" in this consent form, we mean you or your child.

This study is a clinical trial (a research study involving patients, or protocol) of an experimental new drug for cancer. We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point. Clinical trials only include patients who choose to take part. Your participation in this study is entirely voluntary. Please read the consent form carefully. You will be given a copy of it to keep if you decide to participate in this study. You may discuss your decision with your friends and family if you would like.

This study is being carried out by the Children's Oncology Group (COG) Phase I Consortium. COG is an international research group that consists of more than 200 hospitals that treat children with cancer in the United States, Canada, Australia, and Switzerland, and The Phase I Consortium is the group of 21 hospitals within COG that does phase 1/2 studies like this one. It is common medical practice to treat children with cancer on research studies like this one. Participation in this study will be limited to the Consortium institutions and five additional hospitals within COG.

This is a Phase 1/2 study of a drug called PF-02341066. PF-02341066 is a drug that in laboratory studies can block or inhibit two proteins called c-met and ALK. These proteins may be important in the growth of certain types of cancer cells. PF-02341066 is considered experimental because the Food and Drug Administration (FDA) have not approved it.

You are participating in the phase 2 portion of this trial. In this part of the trial, we use the highest safe dose studied in the phase 1 portion to assess the anti-tumor effect of PF-02341066 in patients with neuroblastoma or anaplastic large cell lymphoma.

You are being asked to participate in this study because you have a recurrent or progressive neuroblastoma or lymphoma that shows an abnormality in the ALK gene and that cannot be cured by any known standard treatment. When a cancer comes back (recurs) or does not respond to therapy, your doctor may recommend other anti-cancer drugs (chemotherapy), surgery, or radiation therapy. For certain cancers, a combination of one or more of these approaches is considered standard treatment. However, for other cancers, for cancers that again come back, or for cancer for which therapy is no longer working, the best treatment is not known.

Why is this study being done?

We are testing new experimental drugs such as PF-02341066 in the hopes of finding a drug that may be effective against recurrent neuroblastoma or lymphoma.

The goals of this study are:

- **To determine whether PF-02341066 is a beneficial treatment for your tumor;**
- **To learn what kind of side effects PF-02341066 can cause;**
- **To learn more about the pharmacology (how your body handles the drug) of PF-02341066;**
- **To learn more about the biology of PF-02341066.**

How many people will take part in the study?

There will be about 11-45 patients participating in Part B and C of this study. About ___ will be treated at this hospital.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A medical history
- Physical exam
- Eye exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests
- Test of bone marrow (lymphoma or neuroblastoma) and spinal fluid (lymphoma)
- Pregnancy test (if you are a woman who could have children)
- Plain X-ray of one or both of your lower legs
- Electrocardiogram (EKG, which tests the electrical impulses of your heart)
- We will also do whatever X-rays, CT scans, or other tests are needed to check your tumor

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, PF-02341066 will be given by mouth twice a day for 28 days. This entire period is called a cycle. You may continue to receive PF-02341066 unless you develop serious side effects or your tumor worsens.

You will have the following tests and procedures during the study. They are part of regular cancer care. They may be done more often because you are in this study.

- Physical exam
- Eye exam
- Blood tests
- Urine tests

- Tests to evaluate the status of your tumor based on your tumor type and location (e.g., CT or MRI scans, MIBG scans, PET scans, bone marrow aspirates and biopsies)

These tests are all necessary to make sure that you are not having unsafe side effects and to see whether or not your tumor is responding to PF-02341066.

Copies of the films used to check your child's disease may be sent to central review centers as part of COG quality control. Your name and other identifying information will be removed from these films prior to review.

In addition, we will monitor one or both of your lower legs with a plain X-ray prior to starting treatment with PF-02341066. If your bones have stopped growing, no further X-rays of the lower legs will be taken. If your bones are still growing, we will check your lower legs for changes at the end of Cycle 3, and then approximately every 6 months thereafter with a plain X-ray. Should we detect changes, we may perform an MRI to better describe the changes. These tests are performed, because in some growing animals that received PF-02341066 and other related drugs, changes in the structure of the growing bones were observed.

You will be given a Patient Diary at the beginning of each cycle of PF-02341066. Use the diary to record the date and time you take the drug, side effects you experience and other medications you are taking. This diary should be returned to clinic, along with the medication bottle (even if it is empty) before starting another cycle. This will help us to know how much of the drug you take and how it made you feel.

The PF-02341066 will be given as a capsule or liquid solution by mouth. Since we do not have information on how well the medicine is absorbed, if you vomit the medication it should not be taken again. Since this medicine can make you sleepy, you can take this medicine at bedtime.

Questionnaire:

If you are receiving the PF-02341066 as a liquid by mouth, we would like to ask you to fill out a short questionnaire at the time of the first dose, and then once per week for the first month, and then at every visit thereafter so we can learn more about how the drug tastes. This questionnaire will take about 20 minutes to fill out each time. The study staff will collect some information from your chart about your age and what kind (if any) of PF-02341066 capsules or liquid you may have received in the past. The questionnaire is optional. The information learned would not change the way you are treated, and the results will not be returned to you.

______/______ Yes, I agree to take part in the questionnaire.

______/______ No, I do not agree to take part in the questionnaire.

We would also like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about PF-02341066 and may help children who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be returned to you. The pharmacokinetic studies are required and the biology studies are optional, except in patients with ALCL in whom some specific correlative biology tests are required. You do not have to do these tests if you do not want to. Although these tests are a very important part of how we will better learn to use this drug, it is your decision as to whether or not you agree to participate in these tests.

Pharmacokinetic Studies
During the study blood samples will be collected to determine how much of the PF-02341066 is in your blood (pharmacokinetics). These samples are about 2 mL (approximately ½ teaspoon) of blood each. A single sample will be obtained before your first dose of drug on Day 1 and additional samples will be obtained between day 15 and day 28 after you begin taking the drug in Cycle 1. These additional samples will be obtained before and at 1 hour, 2 hours, 4 hours, and 6-8 hours after the dose is given after approximately the middle of the first cycle (between day 15 and day 28). These additional samples may require that a small intravenous tube (catheter or IV) be placed if you do not have a central line. If you have a central line then you will not require an IV for these studies. A total of 12 mL (less than 3 teaspoons) of blood will be drawn for these studies. This amount of blood is safe even for small children. *These blood samples are required from all participants in this study.*

Biology Studies
If you consent to the biology study, one blood sample (3 ml, which is less than one teaspoon) will be collected before you take the first dose of PF-02341066 on Day 1 of Cycle 1.

______/______ Yes, I agree to participate in the biology studies.

______/______ No, I do not agree to participate in the biology studies.

A total of 15 mL will be drawn (approximately 3 teaspoons) for all the pharmacokinetic and biology study tests described above. This amount of blood is safe to draw even from small children.

Additional Tissue Studies to Consider for Patients with Neuroblastoma Only
As part of your regular care, your doctor may have removed some body tissue (tumor tissue or bone marrow) to see if you have cancer. We would like to keep some of the tissue that is left over and test how much a gene called ALK can be found in the tissue. If you weigh more than 10 kg, the bone marrow sample is 5 mL (about 1 teaspoon). If you weigh equal to or less than 10 kg, the bone marrow sample is 3-5 mL (about 1 teaspoon or less). The ALK gene testing may help us learn more about how the drug, PF-02341066, works in the tissues in your body. If the results are positive, the bone marrow sample will be repeated with each disease evaluation. The tissue and/or bone marrow will be sent directly to the lab for testing and will not be sold. The ALK gene testing in the tumor and bone marrow is done for research and we will not disclose these results to you. However, if you are interested in genetic screening for neuroblastoma, you should talk with your doctor about a new molecular diagnostic test that is available.

______/______ Yes, I agree to participate in the biology tumor tissue studies.

______/______ No, I do not agree to participate in the biology tumor tissue studies.

______/______ Yes, I agree to participate in the biology bone marrow studies.

______/______ No, I do not agree to participate in the biology bone marrow studies.

Additional Studies to Consider for Patients with Anaplastic Large Cell Lymphoma (ALCL) Only
For patients with ALCL, we would like to test your blood and bone marrow before you begin therapy for minimal residual disease (MRD). MRD is the presence of very small amounts of cancer in the blood and bone marrow and we would see if the MRD test can help us determine early signs of whether or not your tumor is responding to the drug. These tests are done for research and the results will not be disclosed to you. The bone marrow sample (5 mL, about 1 teaspoon if you weigh more than 10 kg, or 3-5 mL, about 1

teaspoon or less if you weigh equal to or less than 10 kg) will be drawn before your first dose of PF-02341066. The blood samples (15 mL, about 3 teaspoons if you weigh more than 10 kg, or 10 mL, about 2 teaspoons if you weigh equal to or less than 10 kg) will be drawn before your first dose of PF-02341066, on Day 15 of Cycle 1, at the beginning of Cycle 2, once in each additional cycle through Cycle 11, and then every 3 cycles. These samples would be drawn at the same time as routine blood tests. These samples will be sent directly to the lab for testing and will not be sold. *These blood and bone marrow samples are required from all patients with ALCL.*

How long will I be in the study?

Your doctor may decide to take you off study if any of the following occur:

- The side effects of PF-02341066 are too harmful for you
- You need a treatment that is not allowed on this study
- Your tumor does not improve or worsens
- You are not able to follow study-related treatment instructions
- New information becomes available
- The study is not in your best interest
- The study is stopped

After you are finished taking PF-02341066, the study doctor will ask you to visit the office for follow-up exams as they would normally do for patients with solid tumors or lymphoma.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from PF-02341066 can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the PF-02341066. In some cases, side effects can be serious, long lasting, may never go away, or possibly result in death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to PF-02341066 (crizotinib) include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving PF-02341066, more than 20 may have:
• **Vision Changes*** • **Constipation, diarrhea, nausea, vomiting** • **Loss of appetite** • **Swelling of the body** • **Tiredness** • **Dizziness** • **Changes in taste** • **Damage to nerves that may interfere with walking or organ function which may cause numbness, tingling, weakness or pain in the muscle**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving PF-02341066, from 4 to 20 may have:
• **Anemia which or may require blood transfusion** • **Heartburn** • **Sores in the mouth** • **Change in the heart rhythm** • **Headache** • **Rash** • **Belly pain** • **Infection, especially when white blood cell count is low** • **Sores in the mouth**

RARE, AND SERIOUS In 100 people receiving PF-02341066, 3 or fewer may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Difficulty swallowing** • **Damage to the lungs which may cause shortness of breath** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Fluid collection in the kidney that may be irregular and could be benign or could become cancerous** • **A tear or hole in the stomach that may require surgery** • **Blood clot which may cause swelling, pain, shortness of breath** • **Fainting**

*Vision changes may include blurred vision, double vision, discomfort in the eyes from light, swelling and redness of the eyelids, impaired vision, seeing spots before the eyes (floaters), flashing lights, brightness, rings, shadows, and/or streaking.

Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription or over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

*If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the blood stream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied by or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S (acquired immune deficiency syndrome) and other infections.

<u>Reproductive risks</u>: **You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study.** Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. A pregnancy test will be obtained in female patients before beginning treatment with PF-02341066.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

<u>Risks of blood drawing or placing an intravenous catheter for blood drawing</u>:

Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

<u>Risks of bone marrow aspirate and biopsy</u>:

Risks associated with having a bone marrow aspirate or biopsy include: pain, bleeding, infection, or bruising.

<u>Risks of spinal tap (For patients with ALCL)</u>:

Spinal taps are part of routine care for patients with lymphoma and for some types of brain tumors. **A spinal tap is a procedure where a special needle is inserted in the lower back through the space between the bones that surround the spinal canal. This procedure has a slight risk of infection, bleeding, nerve damage, or headache. Patients will be given medications to numb the pain and blur the memory before the test since it is painful. The pain is usually brief but occasionally may linger. Sometimes this procedure is done while the patient is under general anesthesia.**

<u>Risks of Imaging Scans</u>

The following imaging scans are part of routine care for many types of cancer and are performed to assess the size and/or location of your tumor(s).

<u>Risks associated with having a PET-CT scan (For patients with ALCL)</u>:

For the PET-CT scan you will get a radioactive sugar (FDG) by vein. This exposes your body to radiation like a chest X-ray or CT scan. The amount of FDG that you get depends on what you weigh. The radiation exposure for the PET scan is about the same to about half that of a standard CT scan. You will also get x-rays from the CT portion of the PET-CT scan. The total amount of radiation you get from the combined PET and CT scan will not be more than 2 to 6 times the amount of radiation that everyone gets in a year from natural sources like the atmosphere. The risk from this amount of radiation is considered to be small when compared with other everyday risks.

<u>Risks associated with having a MIBG scan (For Patients with Neuroblastoma)</u>:
A MIBG scan is an imaging test that involves exposure to radiation and uses a special camera to take pictures of specific tissues in the body after a radioactive tracer is injected in a vein in the arm. The risks associated with having a MIBG scan include pain at the injection site, bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

The potential benefit of the treatment with PF-02341066 is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. Because there is not much information about the PF-02341066 effect on cancers in humans, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **No further treatment, and comfort care only**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The Children's Oncology Group**

- **Representatives of the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **The drug company partner (the company that makes the drug PF-02341066) and its staff**
- **Health Canada***

* -Health Canada will only be able to see and/or copy reports describing bad side effects you may experience on this trial. If you are being treated at a Canadian institution, Health Canada will be able to see and/or copy all of your medical records.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Pfizer, Inc. is supplying PF-02341066 at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the PF-02341066.

If, during the study, PF-02341066 becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

You will not be charged for the costs of the special blood studies that are being done for research purposes only, such as the pharmacokinetic and biology studies. You may receive up to $100 (maximum) for the required pharmacokinetic studies for PF-02341066 to compensate for your inconvenience (i.e., travel, parking, meals reimbursement, etc).

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/learning/insurance-coverage/. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ *[name(s)]* at __________________ *[telephone number]*.

For questions about your rights while taking part in this study, call the ________________________ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at __________________ *(telephone number)*. *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org

If you are in the United States, you may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. You will be given a copy of the protocol (full study plan) upon request. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all 12 pages of this form (including the study chart).
I have read it or it has been read to me.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant ____

Signature of Participant / Parent (or Guardian) ____

Date ____

Signature of Physician or Responsible Investigator ____

Date ____

STUDY CHART
(FOR ALL PATIENTS ON PARTS A, B OR C OF THIS STUDY)

You will receive PF-02341066 twice a day for 28 days. This 28-day period of time is called a cycle. The chart below shows what will happen to you during Cycle 1 and subsequent cycles.

Cycle 1		Subsequent Cycles	
DAY	**WHAT YOU DO**	**DAY**	**WHAT YOU DO**
Before starting study	**Come into the clinic and do the following:** • Get routine blood tests • Get urine tests • Get a physical exam by your doctor • Get an eye exam by your doctor • Get CT/MRI, MIBG or PET imaging scans (if required) • Get a test of bone marrow (if required) • Get a test of spinal fluid (if required) • Get an EKG • Get a bone X-ray test • Get a disease evaluation that will be done by your doctor. Depending on the results of this evaluation, your doctor will tell you whether or not you may begin this study.		
Day 1	**Come into the clinic and do the following:** • Get routine blood tests • Get a physical exam by your doctor • Begin taking PF-02341066 twice a day. Keep taking PF-02341066 for 28 days, unless told to stop by your health care team	**Day 1**	**Come into the clinic and do the following:** • Get routine blood tests • Get urine tests • Get a physical exam by your doctor • Keep taking PF-02341066 twice a day for 28 days if you have no bad side effects and cancer is not getting worse. Call the doctor at ____________ *[insert phone number]* if you do not know what to do.
Days 2-28	• Continue taking PF-02341066 twice a day until Day 28 • For the required pharmacokinetic studies in all patients, you will need to come into the clinic between day 15 and day 28 to get blood tests done.	**Day 2-28**	• Continue taking PF-02341066 twice a day until Day 28
Day 28	**Come into the clinic and do the following:** • Return to your doctor's office at _______ *[insert appointment time]* for your next exam and to begin the next cycle. • Get routine blood tests • Get a physical exam by your doctor • Get an eye exam by your doctor • Get CT/MRI, MIBG or PET imaging scans (if required) • Get a test of bone marrow (if required) • Get a test of spinal fluid (if required) • Get a disease evaluation that will be done by your doctor. Depending on the results of this evaluation, your doctor will tell you whether or not you may continue to the next cycle and continue to receive PF-02341066. If you continue, please follow the schedule listed in the column under "Subsequent Cycles".	**Day 28**	**Come into the clinic and do the following:** • Get routine blood tests • You will get an eye exam at the end of Cycles 3, 5 and 7 and then every 3 cycles • You will get a bone marrow and disease evaluation at the end of Cycles 3, 5 and 7 and then every 3 cycles if you are enrolled on Part B. • You will get a bone marrow and disease evaluation at the end of Cycles 3, 7, 11, 17, 23 and then yearly thereafter if you are enrolled on Part C. • Get imaging scans (if required) • Get a bone X-ray test at the end of Cycle 3 and then approximately every 6 months thereafter (if required) • Depending on the results of your evaluation, your doctor will tell you whether or not you may continue to the next consecutive cycle. If you continue, please repeat this schedule as listed under "Subsequent Cycles".