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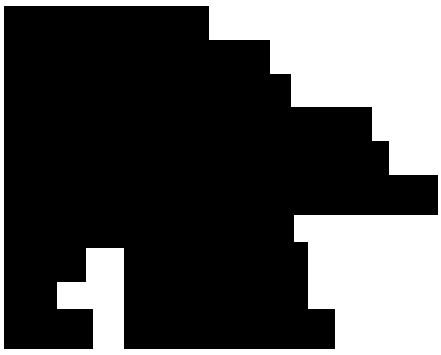
CHILDREN'S ONCOLOGY GROUP

ADVL1212

A PHASE 1 STUDY OF CRIZOTINIB ([redacted]) IN COMBINATION WITH CONVENTIONAL CHEMOTHERAPY FOR RELAPSED OR REFRACTORY SOLID TUMORS OR ANAPLASTIC LARGE CELL LYMPHOMA

Participation Limited to the COG Phase 1 Consortium



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For COG Phase 1/Pilot Consortium Operations Contacts See:
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AGENT NSC# AND IND#'s

Investigational Agent
Crizotinib (NSC# 749005, [redacted]

Commercial Agents
Topotecan (NSC# 609699)
Cyclophosphamide (NSC# 26271)

The following are no longer study agents effective 02/16/2016:
Vincristine (NSC# 67574)
Doxorubicin (NSC# 123127)
Dexrazoxane (NSC# 169780)

IND Sponsor: COG

SEE APPENDIX VIII, IX, X-A, XI, and XII FOR SPECIMEN SHIPPING ADDRESSES.

ABSTRACT

Crizotinib is an orally bioavailable small molecule inhibitor of the c-Met/HGFR and ALK receptor tyrosine kinase (RTK) that has been studied extensively pre-clinically and is currently being investigated in early phase clinical trials for children with relapsed and refractory solid tumors and anaplastic large cell lymphoma (ALCL). C-Met/HGFR and ALK are two tyrosine kinases implicated in the development of multiple adult and pediatric malignancies. The c-Met RTK is frequently altered or dysregulated in advanced cancers and has been implicated in tumor progression, and therefore represents an attractive novel therapeutic target. It has been shown that the Met receptor plays a role in PAX3-PKHR-mediated transformation in rhabdomyosarcomas, and that MET can serve as a therapeutic target in this disease. The anaplastic lymphoma kinase gene (ALK) is an orphan tyrosine kinase transmembrane receptor with homology to neurotrophin receptors and the MET oncogene. 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, 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 translocation in a fraction of non-small-cell lung cancers and in other solid tumors. ALK also 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. Finally, it was previously shown that a substantial percentage of human-derived neuroblastoma cell lines express ALK transcripts and ALK proteins. More recently, however activating mutations in the tyrosine kinase domain of the ALK oncogene were found to be the cause of hereditary neuroblastoma and these mutations can also be somatically acquired.

This phase 1 study is conducted in several parts to evaluate crizotinib in combination with cytotoxic chemotherapy in patients with recurrent or refractory solid tumors and ALCL. In Part A, crizotinib oral solution is administered in combination with topotecan and cyclophosphamide, a cytotoxic chemotherapy regiment with activity against solid tumors including neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma. In Part B, crizotinib oral solution is administered in combination with vincristine and doxorubicin/dexrazoxane, a cytotoxic chemotherapy with activity in most solid tumors and ALCL. Part C combines crizotinib formulated capsule and cyclophosphamide and topotecan and Part D combines crizotinib microsphere formulation in combination with cyclophosphamide and topotecan. Crizotinib will be administered orally twice daily at a starting dose of 165 mg/m^2/dose and will be escalated in increments of ~30% to 280 mg/m^2/dose, which is the recommended phase 2 dose in the single-agent phase 1 trial of

crizotinib (ADVL0912). Topotecan and cyclophosphamide will be administered daily x 5 every 3 weeks. Vincristine and doxorubicin/dexrazoxane will be administered once every 21 days. Pharmacokinetic and correlative biology studies will also be performed.

The overarching goal of this study is to provide safety and tolerability data for the use of crizotinib in combination with chemotherapy in order to move forward with integrating crizotinib into upfront therapy for children with high-risk neuroblastoma, ALCL, and other malignancies with ALK aberrations. In addition, crizotinib may be beneficial in the upfront therapy for children with c-Met amplified or mutated tumors, such as rhabdomyosarcoma.

As of February 16, 2016, Parts A and B of the study have been completed, no new patients will be enrolled to these cohorts, and all have been removed from the protocol.

EXPERIMENTAL DESIGN SCHEMA

Part C and D: Crizotinib + Topotecan/Cyclophosphamide

Part D- Cycle 1 Only

Cycle Day							
1	2	3	4	5	6	7-21	21
CRIZ QD (PM)	CRIZ BID →						Evaluation
CPM	CPM	CPM	CPM	CPM			
TOPO	TOPO	TOPO	TOPO	TOPO			
					MGF		

Part C# and Part D*

Cycle Day							
1	2	3	4	5	6	7-21	21
CRIZ BID →							Evaluation
CPM	CPM	CPM	CPM	CPM			
TOPO	TOPO	TOPO	TOPO	TOPO			
					MGF		

CRIZ: crizotinib (PO)
CPM: Cyclophosphamide (IV)
TOPO: Topotecan (IV)
MGF: Myeloid Growth Factor (filgrastim [G-CSF] or biosimilar or PEG-filgrastim)
All cycles
*Cycle 2+ for Part D

Treatment with crizotinib will be discontinued on Part C or Part D if there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from therapy. Therapy may otherwise continue for up to approximately 24 months.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the recommended phase 2 dose (RP2D) or maximum tolerated dose (MTD) of crizotinib administered orally twice daily in combination with topotecan and cyclophosphamide in children with refractory/relapsed solid tumors or anaplastic large cell lymphoma (ALCL).

1.1.2 To define and describe the toxicities of crizotinib in combination with topotecan and cyclophosphamide administered on this schedule.

1.1.3 To characterize the pharmacokinetics of crizotinib in children with relapsed/refractory cancer when combined with either topotecan and cyclophosphamide or vincristine and doxorubicin/dexrazoxane.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of crizotinib in combination with either topotecan and cyclophosphamide or vincristine and doxorubicin/ dexrazoxane within the confines of a Phase 1 study.

1.2.2 To preliminarily examine the relationship between ALK status in patients with neuroblastoma or ALCL and response to crizotinib in combination with either topotecan and cyclophosphamide or vincristine and doxorubicin/dexrazoxane.

1.2.3 To preliminarily examine the relationship between MRD status and clinical response to crizotinib in combination with either topotecan and cyclophosphamide or vincristine and doxorubicin/dexrazoxane in patients with ALCL.

1.2.4 To examine ALK and c-Met expression, copy number and mutations status in archival tumor tissue from solid tumor and ALCL patients.

1.2.5 To use a questionnaire to gather information on the acceptability of the crizotinib capsule formulation.

1.2.6 To use a questionnaire to gather information on the acceptability of the crizotinib microsphere formulation.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Rationale For Part A Chemotherapy Backbone

The regimen of intravenous topotecan and cyclophosphamide has been studied in multiple pediatric cancers. It was initially studied in a Phase 1 clinical trial conducted by the Pediatric Oncology Group. The combination was determined to be safe, with neutropenia being the dose limiting toxicity. Responses were seen in patients with Wilms' tumor, neuroblastoma, rhabdomyosarcoma and osteosarcoma.[1] This was followed by a Phase 2 study in children with recurrent or

refractory solid tumors. Again, the therapy was found to be well tolerated with responses (CR+PR) in children with rhabdomyosarcoma (10/15), neuroblastoma (6/13) and Ewing sarcoma (6/17). Stabilization of disease was seen in osteosarcoma, although objective responses were rare.[1]

The Children's Oncology Group (COG) conducted a randomized Phase 2 trial of topotecan and cyclophosphamide compared to topotecan alone in children with recurrent or refractory neuroblastoma and found progression free survival (PFS) to be significantly better for patients receiving the combination versus topotecan alone.[2] A pilot study through COG (ANBL02P1) has demonstrated the feasibility/tolerable toxicity of the dose-intensive topotecan/cyclophosphamide administration and ability to harvest peripheral blood stem cells following this regimen. This combination is now embedded into the induction chemotherapy regimen in the COG phase III (ANBL0532) trial for treatment of patients with high-risk neuroblastoma.

The combination of topotecan and cyclophosphamide was also studied in a Phase 2 window trial for children with newly diagnosed metastatic rhabdomyosarcoma. The overall response rate (complete + partial response) to the combination was 47%, demonstrating that it is a combination that is active against newly diagnosed rhabdomyosarcoma.[3] While not necessarily curative, the combination of topotecan and cyclophosphamide induces a response in patients with a variety of tumor types, is well tolerated and can be administered as an outpatient. As these agents are particularly active in tumors that have been shown to be affected by alterations in c-Met and/or ALK, it is a rational backbone to combine with crizotinib in order to assess toxicity.

2.1.2 Rationale For Part B Chemotherapy Backbone

Vincristine and Doxorubicin are active agents in the treatment of most solid tumors, leukemias and lymphomas.

Weinstein and colleagues studied 29 patients treated for large cell lymphoma with APO therapy. The protocol included induction with vincristine, adriamycin and prednisone (APO), followed by a consolidation stage adding mercatopurine and asparaginase to APO and maintenance with APO plus 6-MP and Methotrexate. Overall survival and event free survival were 83% and 76% respectively; thus, this regimen was subsequently adopted as standard of care of large cell lymphoma.[4] Further studies by the Pediatric Oncology Group found that the addition of cyclophosphamide did not improve outcomes, whereas the addition of intermediate dose methotrexate and high dose cytarabine was inconclusive due to insufficient power in the study to detect a difference between the two arms.[5] Based on these results, APO has been chosen as the standard of care for children with ALCL and ongoing studies continue to look at the addition of other conventional chemotherapeutic agents to this combination.

Upfront therapy for solid tumors including Ewing sarcoma, neuroblastoma, osteosarcoma, rhabdomyosarcoma and many others includes either vincristine or doxorubicin, if not both. Based on the vast amount of pediatric malignancies in which these two agents have activity, vincristine and doxorubicin are a logical combination for which to add crizotinib.

2.1.3 Rationale for the use of Crizotinib

Crizotinib is an orally bio-available, selective small molecule inhibitor of c-Met/HGFR and ALK receptor tyrosine kinase. In preliminary biochemical screens, crizotinib inhibited HGF-stimulated or constitutive total tyrosine phosphorylation of wild type c-Met/HGFR with a mean IC_{50} value of 11nm across a panel of human tumor cell lines. In addition, crizotinib demonstrated potent activity against NPM-ALK in a human lymphoma cell line (IC_{50} 24 nM).[6]

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. 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. 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.[7] Activating mutations in c-Met have been identified in multiple adult solid tumors. In addition, C-Met is widely expressed in both alveolar and embryonal rhabdomyosarcoma. High levels of expression are associated with unfavorable clinical features and tumor marrow involvement.[8]

Anaplastic lymphoma kinase (ALK) is an orphan receptor tyrosine kinase first identified as part of the t(2;5) chromosomal translocation associated with most ALCLs and a subset of T-cell non-Hodgkin lymphomas.[9] ALK and its mutant translocation with the nucleophosmin gene (NPM-ALK) results in a constitutively active ALK receptor tyrosine kinase expressed in 80% of ALCLs.[10] Crizotinib has demonstrated potent activity against NPM-ALK in both *in vitro* and *in vivo* models.

In addition to its role in ALCL, it has recently become clear that several other human cancers activate ALK signaling. This is achieved by creating unique oncogenic fusions of the ALK gene at chromosomal band 2p23 with a variety of partners through chromosomal translocation events, resulting in the generation of oncogenic ALK fusion genes and their encoded proteins. These oncogenic fusion proteins lead to constitutive activation of the ALK kinase domain and have been identified in various solid tumors including myofibroblastic tumors, squamous cell carcinomas, and non-small cell lung cancers.[10] Most notably, in a phase 1 trial of crizotinib in a pretreated population of patients with ALK+ NSCLC that generally has a 10% response rate to conventional chemotherapy, treatment with crizotinib yielded an overall response rate of 55% and estimated 6-month progression-free survival rate of 72%.[11,12]

It has recently been discovered that germline mutations in ALK are the major cause of hereditary neuroblastoma and can also be somatically acquired in 8-10% of sporadic cases.[13-16] ALK mutations are also present in a substantial subset of high-risk neuroblastoma due to somatic mutation. Preclinical data in neuroblastoma confirm the oncogenic potential of mutated ALK, and pharmacologic inhibition of ALK validates feasibility of a targeted approach in this tumor type.[17] These data have also established the differential sensitivity between various mutations, with reduced sensitivity of F1174-expressing cells secondary to an increased affinity for ATP,[17] providing the rationale for an increase in dosage to overcome the relative difference in ATP-affinity.

Recent studies have suggested an oncogenic role for full-length ALK in thyroid cancer [18] and rhabdomyosarcoma.[19] It is clear that ALK is one of the few oncogenes activated in both hematopoietic and non-hematopoietic malignancies and represents a tractable target for innovative therapies on the basis of selective inhibition of its tyrosine kinase activity.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Consistent with its predicted mechanism of action, crizotinib inhibits target dependent tumor cell proliferation or invasion, induces tumor cell apoptosis, and inhibits angiogenesis in preclinical tumor models. Furthermore, oral administration of crizotinib demonstrated efficacy, including marked cytoreductive antitumor activity, in several tumor models that expressed activated c-Met/HGFR or NPM-ALK.

Preclinical *in vitro* and *in vivo* data demonstrate that crizotinib 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, crizotinib potently inhibited human GTL-16 gastric carcinoma cell growth, HGF-stimulated human NCI-H441 lung carcinoma cell migration and invasion with IC_{50} ranging from 6.1 to 16 nM.[20]

In Karpas 299 ALCL, cells that express an NPM-ALK fusion protein due to a t(2;5) chromosomal translocation, crizotinib inhibited proliferation at an IC_{50} of 60 nM. Growth inhibition in these NPM-ALK positive lymphoma cells was associated with G0/G1 cell cycle arrest and induction of apoptosis.[6] When investigated for potential anti-angiogenic activity, crizotinib inhibited HGF-mediated HUVEC endothelial cell survival (IC_{50}-11nM) and matrigel invasion (IC_{50}=35nM) as well as HMVEC endothelial cell tubulogenesis in fibrin gels, with IC_{50}'s of 11nM to approximately 80nM.[20]

In the Karpas 299 NPM-ALK positive human ALCL lymphoma tumor model, administration of crizotinib at 100 mg/kg/day resulted in complete regression of tumors for all mice in this dosing cohort within 15 days of the initial compound administration. After 17 days, crizotinib was stopped, resulting in tumor re-growth. When tumors grew to a larger size (> 600 mm^3), crizotinib treatment was re-initiated for an additional 13 days and complete regression of tumor was once again demonstrated.[6]

The antitumor activity of crizotinib has also been evaluated in a variety of human tumor xenograft models in which dysregulation of c-Met/HGFR is implicated. Crizotinib 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. It also demonstrated near complete tumor growth inhibition in both the U87MG glioblastoma (97% growth inhibition) and PC-3 prostrate carcinoma (87% growth inhibition) at 50mg/kg/day. In models in which multiple dose levels were evaluated, 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.[20]

Preliminary Activity of Crizotinib in Neuroblastoma

Mutations in the ALK proto-oncogene are the major cause of hereditary neuroblastoma and are also somatically acquired in sporadic primary tumors. Systematic re-sequencing of 1600 sporadic neuroblastoma tumors obtained at diagnosis and representative of the natural spectrum of this disease confirms that ALK is mutated in 8% of cases and mutations are distributed across the spectrum of phenotypes, as shown in a prior meta-analysis.[21] The R1275 mutation occurs most frequently, as it does in the germline of patients with hereditary predisposition,[13] and is detected in close to 50% of tumors with an ALK mutation followed by F1174 and F1245, with these 3 amino acid locations accounting for 86% of all mutations and all reported to be constitutively active.[17,22] Other predictive valuable biomarkers have been proposed for ALK tyrosine kinase inhibition in neuroblastoma, notably mRNA ALK expression,[23] and native ALK protein expression measured by immunohistochemistry,[24,25] suggesting that these are biomarkers of mutation-independent ALK activation.

Neuroblastoma cell lines driven by an ALK mutation or amplification are sensitive to crizotinib. Cell lines and xenografts that express R1275Q-ALK, one of the two most commonly occurring mutations, are highly sensitive. By contrast, those expressing the F1174L-ALK are more resistant to crizotinib *in vitro* and *in vivo*. Biochemical analyses linked the reduced susceptibility of F1174L-mutated ALK to crizotinib 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.[17]

2.2.2 Animal Toxicology

The primary 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 treatment at 20 mg/kg/day. Repeated administration of crizotinib 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 rates. Crizotinib 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 crizotinib 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.

2.2.3 Preclinical Pharmacokinetic Studies

The pharmacokinetics of a single oral dose of crizotinib 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-compartmental 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_{0-24h}	116	mcg•h/mL
$AUC_{0-\infty}$	147	mcg•h/mL
Steady state trough concentration (C_{12h})	8.8	mcg/mL
Half-life ($t_{1/2}$)	12	H

One cannot directly extrapolate from the mouse model to the human given the marked intra-species differences in protein binding between mice and humans (96% versus 91%). Once you correct for protein binding, then the free drug concentration is still 5-fold higher than the free drug concentration in humans. When these differences are taken into consideration, exposures required for preclinical anti-tumor activity are achievable in children. Specifically, the free drug exposure in mice treated at 200 mg/kg, which is equivalent to ~80 mg/m^2, is achievable in pediatric patients. Please refer to Section 2.4.2 for further discussion of the pharmacokinetics of crizotinib in children.

2.3 Adult Studies

2.3.1 Phase 1 Studies

Crizotinib was studied in a Phase 1 clinical trial for patients with refractory solid tumors in order to determine toxic effects and maximum tolerated dose of single agent crizotinib. This was 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, crizotinib was administered under fasting conditions QD or BID on a continuous schedule. Thirty-seven patients were treated in the dose escalation part of the trial. Three DLT's were 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. In the expanded cohort, patients were treated with 250 mg twice daily. Grade 1 nausea and diarrhea were the most commonly reported side effects. Nausea and emesis were independent of dose or duration of treatment and were effectively managed using IV or oral antiemetics. Diarrhea was effectively controlled by anti-diarrheals. In addition, Grade 1 visual disturbances were reported in 41% of patients consisting mainly of seeing shadows or streaks during changes in light. 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 experienced Grade 3 or Grade 4 increases in ALT. These events occurred within the first cycle 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.[11]

In a review of safety for crizotinib, Pfizer has determined that there are 4 potential cases of pneumonitis in patients with NSCLC, which may be related to crizotinib. The frequency of non-radiation recall as of September 2012 is 1.6%. One of the 4 cases was fatal. The 3 other patients were permanently discontinued from the study and fully recovered. Interpretation of the 4 non-radiation recall cases was complicated by the underlying non-small cell lung cancer for which patients were being treated. In addition, 3 cases were complicated by the co-administration of other drugs known to potentially cause pneumonitis and/or other pulmonary complications.

With more than 1400 patients who have been treated with crizotinib, there are 2 cases of fatal hepatic failure reported as serious adverse events related to crizotinib treatment.

To date, there have been no phase 1 studies of crizotinib in combination with chemotherapy in adults.

2.3.2 Phase 2 Studies

There is currently an on-going phase 2 trial of crizotinib in adults with locally advanced or metastatic non-small cell lung carcinoma.

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.[26] After oral administration of crizotinib 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 AUC_{tau} 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. Crizotinib showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In order to assess the effect of crizotinib 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 crizotinib at 250 mg BID in 13 patients.[26] A 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A.

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

The Children's Oncology Group is currently conducting a Phase 1/2 study of crizotinib in children with relapsed/refractory solid tumors and Anaplastic Large Cell Lymphoma (ADVL0912). The Phase 1 dose escalation started at 100 mg/m^2/dose BID and has escalated to dose level 6 (365 mg/m^2/dose). In the Phase 1 trial, there were not any hematologic DLTs observed during the first cycle at 100, 130, or 165 mg/m^2/dose BID; at dose level 4 (215 mg/m^2/dose BID), 1 subject experienced grade 3 dizziness, probably related to study drug, and 1 subject with a CNS tumor experienced grade 5 intra-tumoral CNS hemorrhage, possibly related to study drug. During cycle 2 of therapy, one subject at dose level 2 (130 mg/m^2/dose BID) with a CNS tumor experienced a grade 4 intra-tumoral CNS hemorrhage, with an attribution of unlikely related to study drug. More than 300 adult patients with tumor metastases to the brain have been treated with crizotinib without experiencing an intra-tumoral hemorrhage. One subject at dose level 6 (365 mg/m^2/dose BID) experienced grade 4 ALT, AST, GGT and Alkaline Phosphatase, likely related to study drug; a second subject at this dose-level experienced grade 4 neutropenia also likely related to study drug. As a result, the maximum tolerated dose on the phase 1 trial of crizotinib is 280 mg/m^2/dose BID.

The A2 portion of the ADVL0912 phase 1 trial has enrolled patients with ALK+ relapsed or refractory neuroblastoma, ALCL, and other tumors activated by ALK or MET. Nine patients with ALK-translocated anaplastic large cell lymphoma were enrolled and eight of the nine patients had measurable radiographic disease. Six of these patients had a complete response, one had a partial response and one had stable disease. Eleven patients with neuroblastoma with known ALK mutations were enrolled with one patient experiencing a complete response and two with stable disease. An additional 23 patients with neuroblastoma and unknown ALK status were treated with one patient experiencing a complete response and five additional patients with prolonged stable disease.[27]

Part B, the phase 2 portion of ADVL0912 for patients with neuroblastoma and a known ALK aberration has been completed and results are being analyzed.

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Nineteen children enrolled on the pediatric phase 1 trial had adequate pharmacokinetic sampling after the first dose of crizotinib. The disposition of crizotinib 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 crizotinib 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 215mg/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, the ongoing Phase 1/2 trial is performing steady state PK, which can be compared to the exposures in preclinical models. Data is currently available for all 6 patients at dose level 5 and for 4 patients at dose level 6. The data show peak crizotinib concentrations of 2 μM at the highest dose level and greater than 1.5 μM average concentrations. These levels are expected to result in inhibition of growth in ALK driven neuroblastomas. Preclinical data in a wide range of ALK mutated neuroblastoma models demonstrated that average concentrations of ≥ 1 μM are necessary to obtain significant anti-tumor activity.

2.5 **Overview of Proposed Pediatric Study**

This will be a phase 1 study of crizotinib in combination with either topotecan and cyclophosphamide or vincristine and doxorubicin/dexrazoxane for children with relapsed or refractory solid tumors or ALCL. The primary aim of this study will be to determine if these combinations are safe and tolerable. Crizotinib will be administered orally twice daily with the starting dose of 165 mg/m^2/dose. We will then dose escalate to target the MTD of 280 mg/m^2/dose BID established in the single-agent phase 1 trial of crizotinib (ADVL0912).

Children will be enrolled on either Part A or Part B per the treating physician's choice and availability of a reservation. Children enrolled on Part A will receive topotecan 0.75 mg/m^2/dose IV x 5 days and cyclophosphamide 250 mg/m^2/dose IV x 5 days every 3 weeks in addition to the crizotinib. Children on Part B will receive vincristine 1.5 mg/m^2/dose IV and doxorubicin 45 mg/m^2 IV on day 1 every 3 weeks in addition to the crizotinib. Dexrazoxane (450 mg/m^2) will be administered for children who have had an anthracycline exposure ≥ 350 mg/m^2. Doxorubicin will be omitted after cycle 2 for patients who have had a total anthracycline dose ≥ 750 mg/m^2. Patients may continue on therapy until there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from therapy. Therapy may otherwise continue for up to 24 months. Eligibility will include all patients with relapsed/refractory solid tumors or ALCL.

To assess potential biological correlates of efficacy, we will examine (when available) banked tumor DNA as well as tissue blocks from diagnosis or relapse 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. In addition, IHC for ALK and c-Met expression will be performed in participating subjects with sarcomas.

2.6 **Amendment #3 to allow Crizotinib Formulated Capsules (FC) (February 2014)**

As of February 2014, a total of 21 patients have been treated on ADVL1212. Ten subjects were enrolled on Part A and 11 subjects on Part B.

On Part A, Dose Level 1 was expanded to 6 subjects after 1 subject experienced a hematologic DLT of Grade 3 febrile neutropenia and Grade 4 neutropenia. There were no additional hematologic DLTs at this dose level and ultimately the patient with Grade 3 febrile neutropenia and Grade 4 neutropenia was found to be inevaluable for hematologic DLT due to bone marrow involvement of their disease. Additionally, following this, Amendment #1 was approved to exclude Grade 3 and 4 febrile neutropenia as a DLT as this is an expected event given the combination chemotherapy backbones. At Dose Level

1, 1 of 6 patients experienced a non-hematologic DLT of Grade 3 nausea. Given this, the dose was escalated. At Dose Level 2, 1 of 3 evaluable patients thus far has experienced a non-hematologic DLT of Grade 3 diarrhea. There have been no hematologic DLTs on Part A at Dose Level 2.

On Part B, an initial cohort of 3 subjects were enrolled; however, 2 were found to be inevaluable for DLT as their eligibility studies were performed outside the required time frame, so an additional 2 subjects were enrolled. None of the 3 evaluable subjects experienced a hematologic or non-hematologic DLT. Thus, Part B was escalated to Dose Level 2. Again, there were no hematologic or non-hematologic DLTs at Dose Level 2. At Dose Level 3, 2 out of 3 subjects experienced non-hematologic DLT of Grade 3 nausea in 1 subject and Grade 4 QTc prolongation and Grade 3 dehydration in another subject. The third subject at this dose level was found to be ineligible for the study.

Due to the possibility that many of the non-hematologic DLTs observed to date on the study are related to the palatability of the OS rather than due to true toxicity of the investigational agent, Amendment #3 will only allow the administration of FCs to patients with a BSA of ≥ 1.07 m^2 (Part C). To ensure that the non-hematologic DLTs are truly due to the palatability of the OS, the starting dose for Amendment #3 will be 165 mg/m^2 BID, the same starting dose as for Parts A and B. With Amendment #3 we will no longer utilize the vincristine/doxorubicin/dexrazoxane chemotherapy backbone and will study the investigational agent in combination with topotecan and cyclophosphamide only (Part C). The ongoing COG study ANHL12P1 is utilizing crizotinib at 165 mg/m^2 BID in combination with a multi-agent chemotherapy backbone that includes doxorubicin. The data regarding the safety and tolerability of crizotinib in combination with chemotherapy from the ANHL12P1 trial and Part C of this trial will be utilized to inform the recommended dosing of crizotinib for future studies.

With Amendment #3, patients will no longer be accrued to Parts A and B of the study; an additional 29 patients to Parts C may be required to determine the MTD/ RP2D of this three-drug regimen (Section 11.1), assuming a 20% inevaluability rate. The study was expected to accrue a maximum of 50 patients.

2.7 **Amendment #4 to allow the Crizotinib Microspheres (cMS) (2015)**

With Amendment #4, the newly developed crizotinib coated microsphere sprinkle formulation will be studied at the MTD/ RP2D determined from Part C. Pfizer has developed this formulation to address the poor taste of the oral solution and eliminate this factor as a barrier to medication administration for children. The microsphere sprinkles have a pH coated trigger membrane designed to taste neutral in the mouth ($pH > 6$), and to lose their coating and be absorbed in the stomach ($pH < 5.5$). The microphere sprinkles will be dispensed onto a dosing spoon and subsequently mixed with water for administration.

A taste and relative bioavailability study of the coated microsphere (cMS) formulation has been completed in adult healthy subjects. While the limited number of subjects (n=12) in this study was not designed for an bioequivalence, results showed that the cMS formulation almost met the bioequivalence criteria, with a relative bioavailability of 94.28% (90% CI: 83.88%, 105.97%) in AUC_{inf} and 90.58% (90% CI: 79.88%, 102.72%) in C_{max}, compared with the commercial formulated capsule (FC) formulation. Based on the evaluation of taste sensory attributes (overall liking, mouth feel, bitterness and tongue/mouth burn) using a "swirl and spit" technique and oral administration, the cMS formulation performed

significantly better than an equivalent dose of oral solution (OS) formulation that were used previously

Of note, at a pH ≥ 5.5, the dissolution of the cMS barrier membrane is delayed and at even higher pH levels will likely be shut down. This is of significant consideration for patients taking agents elevating gastric pH including proton pump inhibitors (PPIs) and histamine-2 receptor (H_2) antagonists/ blockers. Therefore, patients should avoid taking PPIs and H_2 antagonists/ blockers when adiminstered with crizotinib cMS formulation.

2.8 **Amendment #6 to reflect requests made by CTEP and the FDA of Amendments #4 and #5 (October 2016)**

As of February 16, 2016, Part A (Crizotinib (OS) and Topotecan/Cyclophosphamide) and Part B (Crizotinib (OS) and Vincristine/Doxorubicin/Dexrazoxane) were completed. No patients are currently enrolled or receiving protocol therapy. The relevant sections have been removed from the protocol. Additionally, language has been revised to clarify the completion and closure of Parts A and B of study.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

Access requirements for OPEN:
Investigators and site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >). This is the same account (user id and password) used for credentialing in the CTSU members' web site. To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

3.1 Current Study Status

Investigators should refer to the CTSU OPEN (Oncology Patient Enrollment Network) 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://open.ctsu.org/open/
2. Click the **Slot Reservation** Tab. *The Site Patient page opens.*
3. Click the **Report** Tab. *The Slot Reservation Report opens. Available Slots are detailed per study strata.*

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 and other required regulatory documents 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).

Regulatory 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.

Study centers can check the status of their registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

3.3 **Patient Registration in the COG Registry**

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained.

3.4 **Reservation and Contact Requirements**

Before enrolling a patient on study, a reservation must be made in OPEN and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID 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 OPEN website.

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) an IRB-approved institutional screening protocol or b) 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 uploaded into RAVE immediately following enrollment.

3.8 **Institutional Pathology Report**

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report 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.

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 CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUCOntact.aspx or the ADVL1212 COG Research Coordinator. 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 OPEN 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. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and biopsy must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

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 Diagnosis: Patients must have had histologic verification of malignancy at original diagnosis or relapse. All patients with relapsed or refractory solid tumors or anaplastic large cell lymphoma (ALCL) are eligible except for patients with primary or metastatic CNS tumors or patients with primary cutaneous ALCL.

4.1.3 Disease Status: Patients must have either measurable or evaluable disease (see Sections 12.2 and 12.3 for definitions).

4.1.4 Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

Performance Level: Karnofsky ≥ 60% 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.

4.1.5 Prior Therapy

4.1.5.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

a. Myelosuppressive chemotherapy:
   i. *Solid Tumors*: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
   ii. *ALCL:*
   - Patients with ALCL who relapse while receiving standard maintenance chemotherapy will not be required to have a waiting period before enrollment onto this study.
   - Patients who relapse while they are not receiving standard maintenance therapy, must have fully recovered from all acute toxic effects of prior therapy. At least 14 days must have elapsed after the completion of cytotoxic therapy.

b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. 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.

c. Biologic (anti-neoplastic agent): At least 7 days after the last dose of 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. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.

e. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

f. Corticosteroids: See Section 4.2.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

g. XRT:
   i. *Solid Tumors*: At least 14 days after local palliative XRT (small port); ≥ 6 weeks must have elapsed since treatment with therapeutic doses of MIBG; At least 150 days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; At least 42 days must have elapsed if other substantial BM radiation.
   ii. *ALCL*: At least 14 days after local palliative XRT (small port); At

least 84 days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; At least 42 days must have elapsed if other substantial BM radiation.

h. Stem Cell Infusion without TBI: No evidence of active graft vs. host disease and at least 84 days must have elapsed after transplant and ≥ 42 days for autologous stem cell infusion after I^{131}-MIBG therapy.

i. Patients must not have received prior therapy with crizotinib.

4.1.6 Organ Function Requirements

4.1.6.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors or ALCL without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.6.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

4.1.6.2 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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.6.3 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.

4.1.6.4 Adequate Cardiac Function Defined as:

- QTc ≤ 480 msec;

Note: Patients should avoid concomitant medication known or suspected to prolong QTc interval or cause Torsades De Pointes. If possible, alternative agents should be considered. Patients who are receiving drugs that prolong the QTc are eligible if the drug is necessary and no alternatives are available. See Appendix XV for drugs that may prolong the QTc. Patients with Grade 1 prolonged QTc (450-480 msec) at the time of study enrollment should have correctable causes of prolonged QTc addressed if possible (i.e., electrolytes, medications). Patients with bradyarrhythmias, electrolyte abnormalities, or who receive concomitant medications that may prolong the QTc should be carefully monitored.

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

4.1.8 Body Surface Area (BSA):

4.1.8.1 **Part C:** Patients must have a BSA ≥ 1.07 m^2 at the time of study enrollment.

4.1.8.2 **Part D**: Patients must have a BSA ≥ 0.43 m^2 at the time of study enrollment.

4.1.9 Tumor tissue must be sent per Section 8.5. If tumor tissue is unavailable, the study chair must be notified prior to enrollment.

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 may be fetal risks 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 during treatment and for 3 months after stopping treatment.

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 at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.5.1.f).

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 are not eligible.

4.2.2.4 Anti-GVHD agents post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

4.2.2.5 CYP3A4 Substrates with Narrow Therapeutic Indices:
As crizotinib 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.

4.2.2.6 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.

4.2.2.7 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.

4.2.2.8 Proton Pump Inhibitors (PPIs) or H_2 blockers: Patients receiving PPIs and H_2 blockers are not eligible for Part D.

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

4.2.4 Patients who have received a prior solid organ transplantation are not eligible.

4.2.5 Patients who have a primary or metastatic CNS tumor at the time of study enrollment are not eligible. A prior history of metastatic CNS tumor is allowed as long as there is no evidence of CNS disease at study enrollment.

4.2.6 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.

4.2.7 Drug Administration:

4.2.7.1 **Part C:** Patients must be able to swallow intact capsules.

4.2.7.2 **Part D:** Patients must be able to swallow liquid.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Part C and Part D: Crizotinib + Topotecan/Cyclophosphamide

Part D - Cycle 1 Only

Cycle Day							
1	2	3	4	5	6	7-21	21
CRIZ QD (PM)	CRIZ BID →						Evaluation
CPM	CPM	CPM	CPM	CPM			
TOPO	TOPO	TOPO	TOPO	TOPO			
					MGF		

Part C# and Part D*

Cycle Day							
1	2	3	4	5	6	7-21	21
CRIZ BID →							Evaluation
CPM	CPM	CPM	CPM	CPM			
TOPO	TOPO	TOPO	TOPO	TOPO			
					MGF		

CRIZ: crizotinib (PO)
CPM: Cyclophosphamide (IV)
TOPO: Topotecan (IV)
MGF: Myeloid Growth Factor (filgrastim [G-CSF] or biosimilar or PEG-filgrastim)
All cycles
*Cycle 2+ for Part D

- **Crizotinib** will be administered orally twice daily, approximately 12 hours apart, **except on Day 1 of Cycle 1 when crizotinib will be administered once daily in the evening (PART D patients only;** refer to Section 5.1.2 for details**)**. If a patient vomits a dose of crizotinib, it will not be repeated. Dose escalation will occur as described in Section 5.3.1. Crizotinib should be administered at least one hour prior to chemotherapy on Day 1 through 5, **except for Part D when Day 1 chemotherapy during Cycle 1 will be administered in the morning independent of the Day 1 crizotinib dose**. Refer to Section 5.1.1 (FC) and Section 5.1.2 (cMS) for crizotinib formulation and treatment information.
- **Cyclophosphamide** will be administered intravenously (250 mg/m^2/dose) over 15-30 minutes once daily x 5 days every 3 weeks. The use if Mesna is not required with low dose cyclophosphamide. Hydrate per institutional guidelines.
- **Topotecan** will be administered intravenously (0.75 mg/m^2/dose) over 30 minutes once daily x 5 days every 3 weeks.
- **Myeloid growth factor** (filgrastim or biosimilar or pegylated filgrastim) should be initiated 24-48 hours after the completion of topotecan and cyclophosphamide for all patients. Myeloid growth factor should continue until the post-nadir absolute neutrophil count is ≥ 2,000/mm^3, and the administration of myeloid growth factor to the patient should cease at least 24 hours prior to starting Day 1 chemotherapy of subsequent cycles.

5.1.1 **Part C: For patients receiving the crizotinib capsule formulation (FC)**

Patients will receive the FC formulation only. Refer to the dosing nomogram (see Appendix IV-B).

Patients should also be instructed to swallow the capsules whole and not to chew the capsule prior to swallowing. Patients should be instructed not to ingest crizotinib capsules that are broken, cracked, or otherwise not intact.

Pre-Amendment #4 Part C patients should continue to receive their current formulation (FC).

5.1.2 **Part D: For patients receiving the crizotinib microsphere formulation (cMS)**

- **Cycle 1 Day 1**: Crizotinib should be given in the evening with water so that a 12 hour trough concentration can be collected in the morning of Day 2.

- **Cycle 1 Days 2-21 and Subsequent Cycles (Days 1-21):** The dose can only be administered with water. After the dose has been taken, the patient should drink a small glass of water to ensure that the microspheres are rinsed from the mouth and to prevent residual taste.

  Note: On scheduled pharmacokinetic study days during Cycle 1 (Day 2 and between Days 15 and 21) the crizotinib morning dose should be administered in the clinic.

Patients will receive the crizotinib cMS formulation. Refer to the dosing nomogram in Appendix IV-C and administration guidelines in Appendices III-B and III-C.

For All Parts of the Study

5.1.3 A cycle of therapy is considered to be 21 days. A cycle may be repeated up to a total of 35 cycles of therapy, for a total of 24 months.

5.1.4 Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 21 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0.

5.3 Dose Escalation Schema

5.3.1 Part C: Inter-Patient Escalation (Crizotinib FC)

The starting dose of crizotinib will be at 165 mg/m^2/dose BID. The dose of topotecan will be fixed at 0.75 mg/m^2/dose. The dose of cyclophosphamide will be fixed at 250 mg/m^2/dose. Dose levels for subsequent groups of patients are as follows:

Dose Level	Crizotinib	Cyclophosphamide	Topotecan
-1	130 mg/m^2/dose	250 mg/m^2/dose	0.75 mg/m^2/dose
1*	**165 mg/m^2/dose**	**250 mg/m^2/dose**	**0.75 mg/m^2/dose**
2	215 mg/m^2/dose	250 mg/m^2/dose	0.75 mg/m^2/dose
3	280 mg/m^2/dose	250 mg/m^2/dose	0.75 mg/m^2/dose

*Starting Dose Level

There will be no escalations beyond Dose Level 3, which is the MTD established in the pediatric phase 1 trial of single agent crizotinib.

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 130 mg/m^2/dose BID (Dose Level -1).

With Amendment #4, Part C patients will be treated at the recommended Phase 2 dose (R2PD) which was determined to be Dose Level 2: 215 mg/m^2/dose for crizotinib, 0.75 mg/m^2/dose for topotecan, and 250 mg/m^2/dose for cyclophosphamide.

5.3.2 Part D (Crizotinib cMS):

Patients will be treated at the RP2D which was determined to be 215 mg/m^2/dose for crizotinib, 0.75 mg/m^2/dose for topotecan, and 250 mg/m^2/dose for cyclophosphamide from Part C.

Dose Level	Crizotinib	Cyclophosphamide	Topotecan
-2	130 mg/m^2/dose	250 mg/m^2/dose	0.75 mg/m^2/dose
-1	165 mg/m^2/dose	250 mg/m^2/dose	0.75 mg/m^2/dose
1*	**215 mg/m^2/dose**	**250 mg/m^2/dose**	**0.75 mg/m^2/dose**

*Starting Dose Level

There will be no dose escalation beyond Dose Level 1.

If the MTD is exceeded at Dose Level 1, then a subsequent cohort of Part D patients will be treated at the next lower dose level of 165 mg/m^2/dose for crizotinib (cMS), 0.75 mg/m^2/dose for topotecan, and 250 mg/m^2/dose for cyclophosphamide (Dose Level -1).

If the MTD is exceeded at Dose Level -1, then a subsequent cohort of Part D patients will be treated at the next lower dose level of 130 mg/m^2/dose for crizotinib (cMS), 0.75 mg/m^2/dose for topotecan, and 250 mg/m^2/dose for cyclophosphamide (Dose Level -2).

5.3.3 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

5.4 **Grading of Adverse Events**

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. 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 protocol therapy. 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 3 or 4 non-hematological toxicity with the specific **exclusion** of:
  - Grade 3 nausea and vomiting of less < 3 days duration
  - Grade 3 liver enzyme elevation, including ALT/AST/GGT, that return to levels that meet initial eligibility criteria within 7 days of study drug interruption. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
  - Grade 3 or 4 fever < 5 days duration
  - Grade 3 infection < 5 days duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation

- QTc prolongation > 500 ms that persists despite correction of serum electrolyte abnormalities will be considered dose-limiting.

- 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.

- **Note:** Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.5.2 Hematological dose limiting toxicity

- Hematological dose limiting toxicity will be defined as neutropenia or thrombocytopenia that precludes initiation of the next cycle of therapy within 7 days of the scheduled start date.

- **Note:** Grade 3 or 4 febrile neutropenia will not be considered a dose limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modifications.

Note: These dose modifications apply to all patients in all Parts of the study.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who have dose-limiting hematological toxicity should receive subsequent cycles at the same crizotinib dose level. However, both the dexrazoxane and doxorubicin, or both the topotecan and cyclophosphamide doses will be reduced so that patients receive 75% of the full dose.

6.1.2 Patients who have dose-limiting hematological toxicity that does not resolve to baseline or eligibility within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.1.3 If hematological dose-limiting toxicity recurs at the reduced dose, the patient must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients who have dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements or baseline but should receive subsequent doses of crizotinib at the next lower dose level. In addition, the dexrazoxane, doxorubicin and vincristine or topotecan/cyclophosphamide doses will be reduced so that patients receive 75% of the full dose.

6.2.1.1 For patients enrolled in Part C, if any non-hematological dose-limiting toxicity occurs at Dose Level -1, the patient will be removed from protocol therapy.

6.2.1.2 For patients enrolled in Part D, if any non-hematological dose-limiting toxicity occurs at Dose Level -2, the patient will be removed from protocol therapy.

6.2.2 If any non-hematological dose-limiting toxicity recurs at the reduced dose, the patient must be removed from protocol therapy.

6.2.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or eligibility within 21 days after the planned start of the next treatment cycle will be removed from protocol therapy.

6.2.4 Patients with Grade 3 liver enzyme elevation, including ALT/AST/GGT, will have crizotinib held until levels meet initial eligibility criteria.

- If levels meet initial eligibility criteria within 7 days of study drug interruption, this is not considered a DLT and crizotinib will be continued at the same dose.
- If levels meet initial eligibility criteria >7 days after interruption of study drug, but <21 days from the planned start of the next cycle, this is a DLT and

the patient may continue on protocol therapy but should receive subsequent doses of crizotinib at the next lower dose level. In addition, the dexrazoxane, doxorubicin and vincristine or topotecan/cyclophosphamide doses will be reduced so that patients receive 75% of the full dose.

6.2.4.1 For patients enrolled in Part C, if any non-hematological dose-limiting toxicity occurs at Dose Level -1, the patient will be removed from protocol therapy.

6.2.4.2 For patients enrolled in Part D, if any non-hematological dose-limiting toxicity occurs at Dose Level -2, the patient will be removed from protocol therapy.

6.2.5 Patients who develop ≥ Grade 3 QTc prolongation at any time must be removed from protocol therapy.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol 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 7.5 for drugs that should not be used concomitantly due to potential interactions with crizotinib. The use of mesna is allowed if the patient has had a history of hemorrhagic cystitis or develops hemorrhagic cystitis while on study.

7.4 Growth Factors

Growth factors that support white cell number should be used for all patients enrolled on study (see Section 5.1).

7.5 Concomitant Medications

The metabolism of crizotinib 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 crizotinib 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 crizotinib until treatment discontinuation (See Sections 4.2.2.6 and 4.2.2.7). The list of potent CYP3A4 inhibitors and inducers in Sections 4.2.2.6 and 4.2.2.7 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 4.2.2.6 and 4.2.2.7 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 crizotinib. Please see Appendix II for a list of common substrates, inhibitors, and inducers of CYP3A4.

Crizotinib 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 crizotinib administration at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A. Therefore, caution must be exercised in subjects receiving crizotinib in combination with drugs that are predominantly metabolized by CYP3A. In particular, chronic co-administration of crizotinib with CYP3A4 substrates with narrow therapeutic indices must be avoided from the time of the first dose of crizotinib until treatment discontinuation. See Section 4.2.2.5 for the list of CYP3A4 substrates with narrow therapeutic indices. Crizotinib has minimal potential to inhibit other human CYP isoforms such as CYP1A2, 2C8, 2C9, 2C19 and 2D6.

Drugs that prolong the QTc may be used only if the drug is necessary and no alternatives are available. See Appendix XV for drugs that may prolong the QTc.

Additionally, the concurrent use of non-prescription drugs (excluding vitamins) or herbal supplements is not recommended (see Appendix XIV). **The use of PPIs and H_2 blockers are prohibited for patients enrolled on Part D.**

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and biopsy must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Height, weight, BSA	X		X
Performance Status	X		
CBC, differential, platelets[3]	X	Twice Weekly (every 3 to 4 days)	Weekly
Pharmacokinetics[1]	X	X	
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Tumor Disease Evaluation[4,14]	X	End of Cycle 1	Every other cycle x2 then q 3 cycles
PET scan[6]	X	End of Cycle 1	Every other cycle x2 then q 3 cycles
Bone Marrow Evaluation[7, 8]	X	End of Cycle 1	Every other cycle x2 then q 3 cycles
CSF cytology[9]	X	End of Cycle 1	As clinically indicated
Urine HVA/VMA[10]	X		X
Pregnancy Test[2]	X		
Snellen Eye Chart[11]	X		End of Cycle 3 then q 3 cycles
Patient Diary[5]		Weekly	X
Correlative biology studies[12]	X	X	X
EKG[18]	X		
CNS imaging (CT or MRI)[13]	X		
Tumor Tissue[15]	X		
Capsule Acceptability Questionnaire (optional)[16]		Day 1, then Weekly	X
Microsphere Taste Feedback Questionnaire (optional)[17]		Day 1, then Weekly	X

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

1 See Section 8.3 for timing of PK studies.

2 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable

method of birth control.

3 If patient develops Grade 4 neutropenia, then CBCs should be checked at least every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

4 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

5 Patient diary (see Appendix V-B and Appendix V-C) should be reviewed and uploaded into RAVE weekly during Cycle 1 and then after completion of each treatment cycle.

6 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.

7 Patients with neuroblastoma or 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 For patients with positive bone marrow involvement at time of study enrollment, evaluate at end of cycle 1 and then as described in the table above until negative.

9 For all patients with ALCL, if clinically indicated. If patients with ALCL have CSF involvement at the time of study enrollment, evaluate at the end of cycle one and then every other cycle until negative.

10 Neuroblastoma patients only.

11 Snellen eye chart should be used to assess visual acuity. If a decline in visual acuity occurs or other visual symptoms occur, the patient should be referred to an ophthalmologist for an examination.

12 See the Correlative Studies Guide in Appendix VI and see Sections 8.4, 8.5, 8.6, 8.7 and Appendix VII for the nature and timing of correlative biology studies.

13 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.

14 Patients with neuroblastoma must have both CT/MRI and MIBG scintigraphy prior to enrollment if the patient was enrolled with or has a history of having 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 and *evaluable disease* by MIBG scintigraphy or bone scan, use the same modality (MIBG scintigraphy or bone scan) to image and follow patients; CT/MRI are not required but may be performed as clinically indicated.

15 Archival tumor tissue should be submitted if available for all patients and extra effort should be expended to obtain consent for this tissue (See Section 8.5). If a patient does not have tissue available, the study chair must be notified.

16 See Capsule Acceptability Questionnaire on ADVL1212 Case Report Form. The questionnaire should be administered to children or adults, preferably by the clinician or the nurse at the time of the first dose. After that, the questionnaire should be completed as stated in the above table.

17 See Microsphere Taste Feedback Questionnaire on ADVL1212 Case Report Form. The questionnaire should be administered to consenting patients at the time of the first dose. After that, the questionnaire should be completed as stated in the above table.

18 If an initial QTc reading of > 500 msec is obtained, then a second confirmatory consecutive EKG must be performed. The guideline in Section 6.2.5 should be followed if a patient develops Grade 3 QTc prolongation at any time. Patients with prolonged QTc should have correctable causes of prolonged QTc addressed if possible, including medications (see Appendix XV) and correction of electrolyte abnormalities (including Ca++ and Mg++).

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response: Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy 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 RAVE for review by the COG Operations Center and for data analysis.

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

COG institutions that are not connected to the ImageInBox can send the images on hard copy film, CD ROM, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1212) and date and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CRP
Administrator, 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

8.3 Pharmacology (Required)

8.3.1 Description of Studies and Assay:

Plasma will be collected for the purpose of determining crizotinib concentrations for pharmacokinetic analysis.

8.3.2 Sampling Schedule

- **Part C**: 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 21 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 hours.

- **Part D:**
  - **Days 1 and 2 of Cycle 1**: Plasma samples will be obtained prior to the first dose of crizotinib (Day 1 pre-dose) and at 12 hours after the first dose on Cycle 1 Day 1 (Day 2 pre-dose). The first dose should be administered in the evening so that the 12 hour trough level can be drawn pre-dose on Day 2.

  - **Between Days 15 and 21 of Cycle 1**: In addition, samples will be collected at steady state, scheduled around one dose between days 15 and 21 of BID dosing in Cycle 1 at the following time points: pre-dose (12 hours after the last dose), 1 hr, 2 hr, 4 hr and 6-8 hrs.

8.3.3 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 X).

Once collected, samples should be processed immediately and kept out of direct sunlight due to the light sensitive nature of crizotinib. 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 to -70°C within 1 hour of collection.

Further details regarding pharmacokinetic sample processing, packaging, and shipping can be found in Appendix X and X-A.

8.3.4 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D. (ADVL1212), and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

8.4 Pharmacogenomic Studies

8.4.1 Description of Studies

Whole blood samples for pharmacogenomics will be obtained for the purpose of genotyping the alleles of cytochrome P450 enzymes and drug transport proteins.

8.4.2 Sampling Schedule
One peripheral blood sample (3 mL) will be collected at baseline prior to the first dose of crizotinib.

8.4.3 Sample Collection, Handling Instructions
The blood sample (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 (Appendix VIII). Detailed instructions for sample processing and shipping can be found in Appendix VIII.

8.4.4 Sample Labeling
Each tube must be labeled with the patient's study registration number, the study I.D. (ADVL1212), and the date and time the sample was drawn. Data should be recorded on the Pharmacogenomic Study Form (Appendix VIII), which must accompany the sample(s).

8.5 Tumor Tissue Studies

8.5.1 Description of Studies
Tumor tissue will be evaluated for correlative biology studies assessing ALK and cMET expression, copy number and mutations status. Archival tumor tissue should be submitted for all patients and extra effort should be expended to obtain consent for this tissue. **If a patient does not have tissue available, the study chair must be notified.** Details are outlined in Appendix VII.

8.5.2 Sampling Schedule
Tissue (paraffin-embedded, or fresh frozen tissue) will be collected from original diagnosis, relapse, or any subsequent resection or biopsy prior to treatment with crizotinib.

8.5.3 Sample Collection, Handling, and Shipping Instructions
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 on the Tissue Studies Form (see Appendix IX).

8.5.4 Sample Labeling
Each tube must be labeled with the patient's study registration number, the study I.D. (ADVL1212), and the date and time the sample was drawn. Data should be recorded on the Tissue Studies Form (Appendix IX), which must accompany the sample(s).

8.6 Correlative Studies for Patients with Neuroblastoma (Required)

8.6.1 Description of Studies
Bone marrow from patients with neuroblastoma will be evaluated for correlative biology studies. Details of this work are outlined in Appendix VII.

8.6.2 Sampling Schedule
A fresh bone marrow specimen will be collected prior to treatment with crizotinib from patients with neuroblastoma. If marrow is positive for tumor cells at time of study enrollment, a marrow will also be repeated every other cycle and at times of disease evaluations and submitted for correlative biology studies.

8.6.3 Sample Collection and Handling Instructions

Bone marrow should be sent to Dr. Yaël Mossé at room temperature by overnight Federal Express mail at the address listed on the Bone Marrow Studies Form for patients with neuroblastoma in Appendix XI.

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 XI.

8.6.4 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D. (ADVL1212), and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s).

8.7 Correlative Studies for Patients with ALCL (Required)

8.7.1 Description of Studies

Minimal disease studies will be performed in patients 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.

8.7.2 Sampling Schedule

Bone Marrow Studies

Bone marrow samples (5 mL if >10 kg and 3-5 mL in children ≤10 kg) will be obtained prior to starting Cycle 1 and repeated until negative in patients with ALCL.

Peripheral Blood Studies

Peripheral blood samples (15 mL if >10 kg and 10 mL in children ≤10 kg) will be obtained at the following time points: prior to starting Cycle 1, on day 15 of Cycle 1, and then prior to each subsequent cycle.

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 XII.

8.7.3 Sample Handling and Labeling Instructions

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. (ADVL1212), and the date and time the sample was drawn. Data should be recorded on the study form in Appendix XII, which must accompany the sample(s). Detailed instructions regarding sample processing, labeling, and shipping can be found in Appendix XII. Samples will be sent at room temperature to Dr. Megan S. Lim at the address listed in Appendix XII.

9.0 AGENT INFORMATION

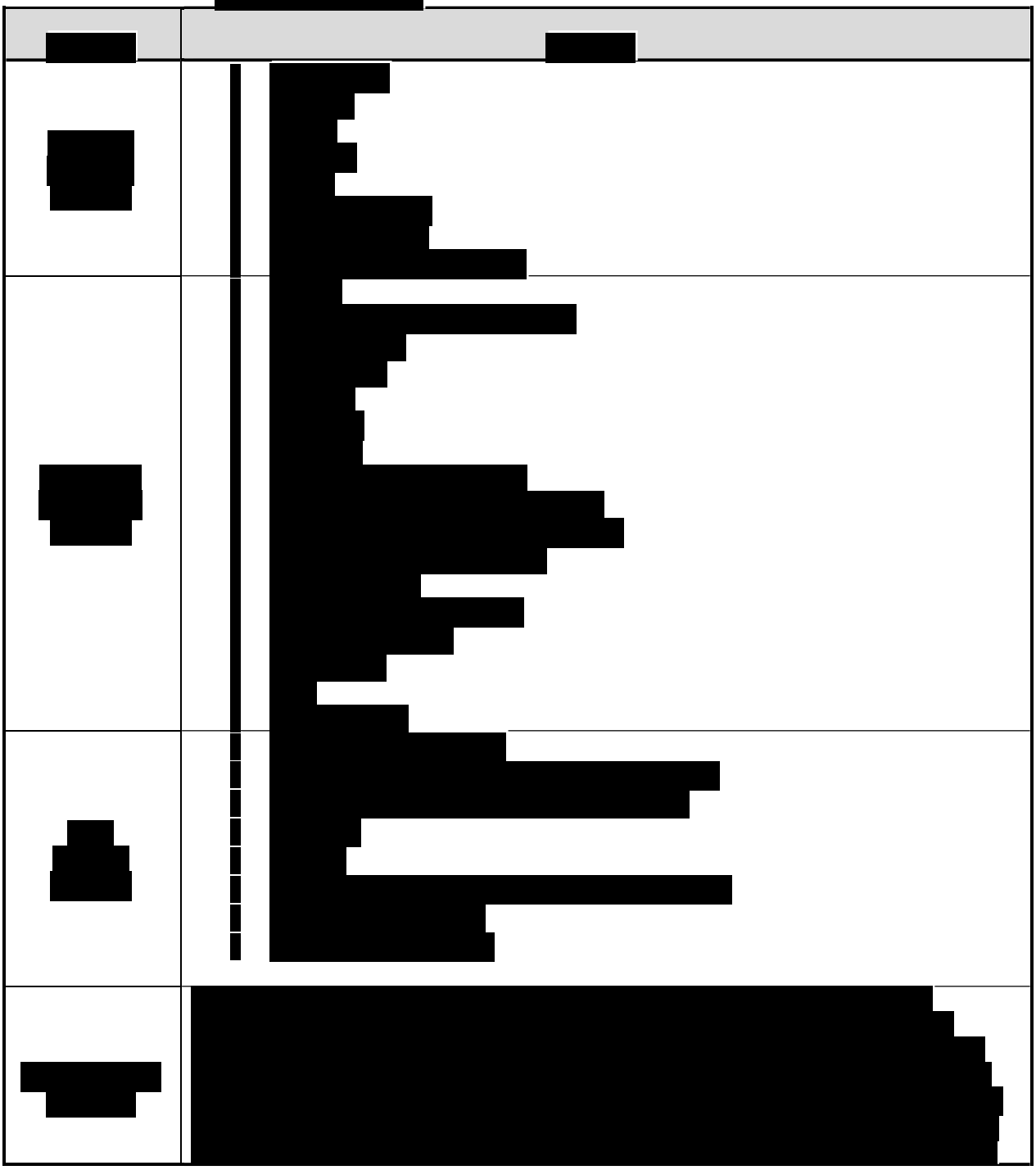
[redacted]

[redacted]

Formulated capsule-specific information for patients and/or caregivers:

[redacted]

[redacted]



9.2 **TOPOTECAN**
(SKF-104864, Hycamtin®) NSC #609699 **(06/03/13)**

9.2.1 Source and Pharmacology:

Topotecan hydrochloride is a semi-synthetic derivative of camptothecin (an alkaloid derived from the camptothecin tree which grows widely throughout Asia) and is an anti-tumor drug with topoisomerase I-inhibitory activity. Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents re-ligation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks. Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤ 4, the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at physiologic pH. *In vitro* studies in human liver microsomes indicate that metabolism of topotecan to an N-demethylated metabolite represents a minor metabolic pathway. Topotecan exhibits multi-exponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

In humans, about 30% of the dose is excreted in the urine and renal clearance is an important determinant of topotecan elimination. In patients with mild renal impairment (Cl_{cr} of 40 to 60 mL/min.), topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function. In patients with moderate renal impairment (Cl_{cr} of 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control patients, with an increase in half-life. Dosage adjustment is recommended for these patients. Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in patients without hepatic impairment. Topotecan half-life increased slightly, from 2 hours to 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen.

9.2.2 Topotecan Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, diarrhea (L), constipation, fever, pain (abdominal, skeletal, back pain)	Anorexia, headache, asthenia, rash (urticaria, pruritis, bullous eruption) (L), asymptomatic hypotension, dyspnea	Anaphylaxis, angioedema, chest pain, rigors
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression, fatigue, febrile neutropenia	Stomatitis/mucositis, increased SGOT (AST)/SGPT (ALT)/alkaline phosphatase, sepsis	Elevated bilirubin, paresthesias, myalgia, arthralgia, intratumoral bleeding
Delayed: Anytime later during therapy	Alopecia		Microscopic hematuria, increased creatinine, proteinuria
Unknown Frequency and Timing:	Teratogenic effects of topotecan have been noted in animal models at doses ≤ to those used in humans. It is not known if topotecan is excreted into human breast milk.		

(L) Toxicity may also occur later.

9.2.3 Formulation and Stability:

Topotecan is available as a lyophilized powder for reconstitution and as a solution concentrate. Each vial of lyophilized powder contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. Inactive ingredients are mannitol 48 mg, and tartaric acid 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. Topotecan concentrate solution for injection is supplied as a sterile, non-pyrogenic, clear, yellow to yellow-green solution at a topotecan free base concentration of 4 mg/4 mL (1 mg/mL) available in single use vials. Each mL of topotecan injection contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base, 5 mg tartaric acid, NF and water for injection, USP. Hydrochloric acid and/or sodium hydroxide may be used for pH adjustment. The pH of the solution is approximately 2.6 to 3.2; both products must be further diluted prior to administration in a minimum of 50 mL of compatible fluid for infusion. Both types of vials should be protected from light in the original cartons and stored at controlled room temperature between 20° and 25°C (68° and 77°F).

9.2.4 Guidelines for Administration:

See Treatment and Dose Modifications sections of the protocol.

Reconstitute each topotecan 4 mg vial with 4 mL SWFI to concentration of 1 mg/mL. Further dilute in 50-250 mL D5W or NS. Reconstituted vials of topotecan diluted for infusion are stable at approximately 20°-25°C (68°-77°F) and ambient lighting conditions for 24 hours.

9.2.5 Supplier:

Commercially available. See package insert for further information.

9.3 CYCLOPHOSPHAMIDE

(Cytoxan) NSC #26271 **(03/13/13)**

9.3.1 Source and Pharmacology:

Cyclophosphamide is an alkylating agent related to nitrogen mustard.

Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

9.3.2 Cyclophosphamide Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1] *Dependent on dose, age, gender, and degree of pubertal development at time of treatment.*
[2] *Risk increased with pulmonary chest irradiation and higher doses.*
(L) Toxicity may also occur later.

9.3.3 Formulation and Stability:

Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30ºC (86ºF).

9.3.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

Cyclophosphamide for Injection: If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution, cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

9.3.5 Supplier:
Commercially available from various manufacturers. See package insert for further information

9.4 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio®) NSC #614629 (09/09/15)

9.4.1 Source and Pharmacology:
Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor, which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). Filgrastim exhibits nonlinear pharmacokinetics with clearance dependent on filgrastim concentration and neutrophil count. Filgrastim is cleared by the kidney. The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2-8 hours.

9.4.2 Filgrastim Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subq):skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, rash or exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)

Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS
Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

9.4.3 Formulation and Stability:
Neupogen® supplied as a clear solution of 300 mcg/mL in 1 mL or 1.6 mL vials. Neupogen® vials are preservative free single use vials. Discard unused portions of open vials.

Neupogen®, Granix®, and Zarxio® are also available as single use prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim for subcutaneous administration.

Store refrigerated at 2º-8ºC (36º-46ºF). Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Avoid freezing and temperatures > 30ºC.

For IV use, dilute filgrastim (Neupogen®) and tbo-filgrastim (Granix®) in D5W only to concentrations >15 mcg/mL. Filgrastim-sndz (Zarxio®) may be diluted in D5W to concentrations between 5 mcg/mL and 15 mcg/mL. At concentrations below 15 mcg/mL, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/mL) in order to minimize the adsorption of filgrastim to plastic infusion containers and equipment for all 3 products (communication on file from Teva Pharmaceuticals USA). Filgrastim or filgrastim-sndz dilutions of 5 mcg/mL or less are not recommended. Tbo-filgrastim dilutions below 2 mcg/mL are not recommended. Diluted filgrastim biosimilar products should be stored at 2º-8ºC (36º-46ºF) and used within 24 hours. Do not shake.

Do not dilute with saline-containing solutions at any time; precipitation will occur.

9.4.4 Guidelines for Administration:
See Treatment, Dose Modifications and Supportive Care sections of the protocol. Filgrastim biosimilar products should not be administered within 24 hours of (before AND after) chemotherapy.

9.4.5 Supplier: Commercially available from various manufacturers. See package insert for further information.

9.5 PEGFILGRASTIM

(pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®) NSC #725961 **(01/30/10)**

9.5.1 Source and Pharmacology:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD)

monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period postchemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years-old, and 21.2 (+/- 16) hours in children 12 to 21 years-old.

9.5.2 Pegfilgrastim Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site (pain, induration, and local erythema), headache	Low grade fever, allergic reactions (anaphylaxis, angioedema, or urticaria), generalized erythema and flushing,
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, sickle cell crises in patients with sickle cell disease (SCD), excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			ARDS
Unknown frequency and timing:	Fetal toxicities and teratogenic effects of pegfilgrastim in humans are unknown. Conflicting data exist in animal studies. It is unknown whether the drug is excreted in breast milk.		

9.5.3 Formulation and Stability:

Supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex). Store refrigerated at 2º-8ºC (36º-46ºF) and in the carton to protect from light. Prior to injection, pegfilgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

9.5.4 Guidelines for Administration**:** See Treatment and Dose Modifications sections of the protocol.

Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy. Do not shake. The manufacturer does not recommend use of the 6-milligram (mg) fixed-dose formulation of pegfilgrastim in infants, children, or adolescents under 45 kilograms.

9.5.5 Supplier: Commercially available from various manufacturers. See package insert for further information.

9.6 Agent Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, and use by each patient will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Pfizer. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers.

To ensure adequate records, all study drug will be accounted for in the patient diary (see Appendix V-A, Appendix V-B, and Appendix V-C) and drug accountability inventory forms. Unless otherwise authorized, at the end of the clinical trial all drug supplies unallocated or unused by the subjects must be disposed at the study site and documented. Patients must return all containers to a designated study center participant. All containers of crizotinib that were sent to the investigator throughout the study must be disposed at the study site and documented, whether they are used or unused, and whether they are empty or not.

All used, unused or expired study drug will be disposed of at the study site and documented. All material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.7 Agent Ordering

Crizotinib will be supplied by Pfizer Pharmaceuticals, Inc. Study drug can be obtained by following the instructions on the agent request form provided on the ADVL1212 protocol page of the COG website.

Information on drug ordering is posted on the protocol web site. The drug supply must be stored in a locked limited access area. Crizotinib is for investigational use only, and is to be used only within the context of this study. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol.

9.8 Agent Inventory Records

Patients will be required to return all bottles of study medication at the beginning of each cycle. The number of capsules remaining will be documented and recorded. Patients who are considered non-compliant will be withdrawn from study.

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 or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from protocol therapy (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) Completion of 35 cycles of therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of crizotinib (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care as outlined in Section 10.2 (a).

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 RAVE 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 required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

There will be four parts to the study (Parts A-D). As of February 16, 2016, Parts A and B of the study have been completed and will no longer have patients enrolled on protocol therapy. The relevant sections referencing Parts A and B have been removed from the protocol for clarity:

Part C: Crizotinib (FC) + Topotecan/Cyclophosphamide
Part D: Crizotinib (cMS) + Topotecan/Cyclophosphamide

A minimum of 3 evaluable patients will be entered at each dose level to Part C of the study for the determination of the MTD. Once the MTD or recommended Phase 2 dose (RP2D) has been defined in Part C, up to 6 additional patients with relapsed/refractory solid tumors or ALCL without heme restrictions may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Review of the enrollment rate into previous COG new agent studies indicates that 1-2 patients per month are available, which will permit completion of enrollment to Part C of the study within 15-30 months. An additional 29 patients to Part C may be required to determine the MTD, assuming a 20% inevaluability rate. A maximum of 50 patients is anticipated. (Fifty-one patients to Part C may be required if all dose levels in Part C require expansion to 12 patients per Section 11.2.2; enrollment may require 26-51 months and a maximum of 72 patients is anticipated in that scenario).

Part D: The starting dose level for Part D will be the RP2D determined from Part C, Dose Level 2: 215 mg/m^2/dose for crizotinib, 0.75 mg/m^2/dose for topotecan, and 250 mg/m^2/dose for cyclophosphamide. Once the MTD/RP2D has been defined for Part D, up to 6 additional patients with relapsed/refractory solid tumors or ALCL without restrictions on hematologic evaluability may be enrolled to acquire PK data in a representative number of young patients (e.g 6 patients < 12 years old and 6 patients ≥ 12 years old). A minimum of 4 patients will be required for this Part. A maximum of 22 patients would be required for this Part if 6 are required at both dose levels, 6 more are required for PK analysis in a representative number of young patients, and 20% inevaluability is observed. Part D and the Part C PK expansion are expected to be concluded within 11-22 months.

At the time of Amendment #4, 35 patients enrolled onto the study (10 patients on Part A, 11 patients on Part B, and 14 patients on Part C). The entire study is therefore expected to accrue a maximum of 65 patients within 41-52 months, accounting for the determination of MTD/RP2D of Part D and the PK expansion cohorts to Parts C and D.

11.2 Definitions

11.2.1 Evaluable For Adverse Effects

Any patient who experiences DLT at any time during protocol therapy is considered evaluable for Adverse Effects. Patients without DLT who receive at least 85% of the prescribed dose per protocol guidelines and had the appropriate toxicity monitoring studies performed are also considered evaluable for Adverse Effects. Patients who are not evaluable for Adverse Effects at a given dose level during Cycle 1 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, as described in Section 11.3.
- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:
  - One of the DLTs does not appear to be dose-related
  - 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

  Expansion will proceed according to the rules of the 3+3 design (see Section 11.3): Three additional patients will be studied. If none of the initial three additional patients experiences DLT, the dose will be escalated. If one of the initial three additional patients experiences DLT, expansion to a total of 12 patients will continue. If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.
- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.3 Dose Escalation and Determination of MTD (Parts A to D)

11.3.1 Three patients are studied at the first dose level.

11.3.2 If none of these three patients experience DLT, then the dose is escalated to the next higher level in the three subsequent patients.

11.3.3 If one of three patients experiences DLT at the current dose, then up to three more patients are accrued at the same level.

a) If none of these three additional patients experience DLT, then the dose is escalated in subsequent patients. If there are no further dose escalations, then the RP2D has been confirmed.

b) If one or more of these three additional patients experiences DLT, then patient entry at that dose level is stopped. (See Section 11.2.2 for exception to rule). Up to three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose).

11.3.4 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 (see Section 11.2.2 for exception to rule). Up to three more patients are treated at the next lower dose (unless six or more patients have already been treated at that prior dose). The highest dose with less than two DLTs out of six evaluable patients will be the estimated MTD.

11.3.5 Using this dose escalation scheme, the probability of escalating to the next dose level, based on the true rate of DLT at the current dose, is given by the following table when there are 6 evaluable patients at the current dose:

	True Adverse Effects at a Given Dose					
	10%	20%	30%	40%	50%	60%
Probability of Escalating	.91	.71	.49	.31	.17	.08

Thus, if the true underlying proportion of toxic events is 30% at the current dose, there is a 49% chance of escalating to the next dose.

In addition to determination of the MTD or RP2D, a descriptive summary of all toxicities will be reported.

11.4 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 1 trial which will accrue a limited number of patients, 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.

11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of crizotinib at steady state will be performed and compared with data from the single agent phase 1 study of crizotinib (ADVL0912). The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of crizotinib in combination with conventional chemotherapy, 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.

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

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. 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 for Patients with Solid Tumors

See the table in Section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained 60 days following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor and measurable disease (Section 12.2); b) solid tumor and evaluable disease (Section 12.3); c) neuroblastoma with MIBG positive lesions (Section 12.4); d) neuroblastoma with bone marrow involvement (Section 12.5); or e) ALCL (Section 12.6).

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.

12.2.1 Definitions

12.2.1.1 Evaluable for objective response: Patients who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable for response. For all other patients, only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response.

12.2.1.2 Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2.2 Disease Parameters

12.2.2.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must

be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

12.2.2.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

12.2.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.2.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

12.2.2.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence,

absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.2.3.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.2.3.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

12.2.3.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

12.2.3.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.2.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.2.3.6 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.2.3.7 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (**Note:** the appearance of one or more new

lesions is also considered progressions). **Note:** in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.2.4.2**Evaluation of Non-Target Lesions**

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

12.2.5 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.3.1 Evaluable Disease

The presence of at least one lesion, with no lesion that can 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.

12.3.2 Complete Response

Disappearance of all evaluable disease.

12.3.3 Partial response

Partial responses cannot be determined in patients with evaluable disease

12.3.4 Stable Disease (SD)

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

12.3.5 Progressive Disease

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

12.3.6 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.4.1 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 28 days after radiation was completed and must show viable neuroblastoma.

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

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

12.4.3

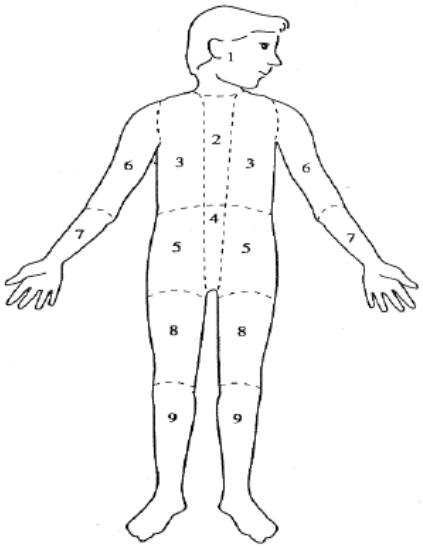
The response of MIBG lesions will be assessed on central review using the Curie scale[14] as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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 21 days 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.

12.4.4 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 5 in Section 12.7.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 28 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: 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 21 days apart.

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

12.5.2 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Section 12.7.

12.6 Response Criteria for Patients with ALCL

12.6.1 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.

12.6.2 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).

12.6.3 Partial Response

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

12.6.4 No Response (Stable Disease)

Failure to qualify for a PR. No new lesions.

12.6.5 Progressive disease

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

12.6.6 Overall Response Assessment

The overall response assessment takes into account response in both target and non-target lesions, the appearance of new lesions and normalization of markers (where applicable), according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, marker and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall Response**
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**
CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.7 Best Response

12.7.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 1: **For Patients with Measurable Disease (i.e., Target Disease)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥28 days Confirmation**
CR	Non-CR/Non-PD	No	PR	≥28 days Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥28 days from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2: **For Patients with Non-Measurable Disease (i.e., Non-Target Disease)**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Table 3. **Sequences of overall response assessments with corresponding best response**

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

Table 4: **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 5: **Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only**
If patients 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

12.7.2 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

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 Case Report Forms (CRFs) 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) whether the adverse event is considered serious; 3) the *grade* (severity); and 4) 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. 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).

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

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- 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.

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 in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found below under the section entitled "Additional Instructions or Exceptions".

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

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- 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 clearly due to progressive disease 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 unless it is associated with hospitalization.

- Grade 3 and Grade 4 febrile neutropenia (regardless of hospitalization) does not require expedited reporting via CTEP-AERS.

- Grade 1 and 2 adverse events listed in the table below **do not require** expedited reporting via CTEP-AERS:

Category	Adverse Events
EYE DISORDERS	Eye disorders- Other (blurred vision, diplopia, visual impairment, vision brightness, vision field defect, shadows/streaking) Eye pain Flashing lights (photopsia) Floaters Photophobia
GASTROINTESTINAL DISORDERS	Abdominal pain Constipation Diarrhea Nausea Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue Edema face Edema limbs Localized edema

Category	Adverse Events
INVESTIGATIONS	Alanine aminotransferase increased Aspartate aminotransferase increased GGT increased Neutrophil count decreased White blood cell count decreased
METABOLISM AND NUTRITION DISORDERS	Anorexia
NERVOUS SYSTEM DISORDERS	Dizziness Dysgeusia Neuropathy
PSYCHIATRIC DISORDERS	Insomnia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Periorbital edema

As referenced in the CTEP Adverse Events 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 (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 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

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

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

If prompted to enter a sponsor email address, please use: COGCADEERS@childrensoncologygroup.org.

Email supporting documentation to the ADVL1212 COG Research Coordinator. **ALWAYS include the ticket number on all emailed 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 course (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 course 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 baseline or less than Grade 1, whichever level is higher (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 course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course 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 Case report form (CRF) 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 and non-NCI-sponsored trials following their chemotherapy for cancer must be reported via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after treatment for cancer on NCI-sponsored and non-NCI-sponsored trials.

Secondary Malignancy: A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an NCI IND/IDE or a non-NCI IND must be reported via CTEP-AERS. Three options are available to describe the event:

1) Leukemia secondary to oncology chemotherapy(e.g., acute myelocytic leukemia [AML]),
2) Myelodysplastic syndrome (MDS), or
3) Treatment-related secondary malignancy.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A *second malignancy* is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

13.7 **Reporting Pregnancy, Fetal Death, and Death Neonatal**

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed along with any additional medical information to the ADVL1212 COG Research Coordinator (Appendix XIII). The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as "Pregnancy, puerperium and perinatal conditions - Other (Pregnancy) under the Pregnancy, puerperium and perinatal conditions SOC and reported as Grade 3.

- Pregnancy should be followed until the outcome is known.

13.7.2 Fetal Death

- Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

- Any fetal death should be reported expeditiously, as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions SOC.

- A fetal death should NOT be reported as "Fetal death," a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

- A neonatal death should be reported expeditiously as Grade 4 "General disorders and administration- Other (neonatal loss)" under the General disorders and administration SOC.

- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all follow-ups. If the baby is born with a birth defect or other anomaly, then a second CTEP-AERS report is required.

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: e.g. Roadmaps, Pathology Reports, Surgical Reports, and Patient Questionnaire. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center 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 RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the CRF packet.

See separate CRF Packet, which includes submission schedule.

14.2 Access to Rave for Data Submission/ Data Reporting

Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the COG or COGC roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com, or by email to the COG Study Assigned Research Coordinator.

14.3 **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.

14.4 **Data and Safety Monitoring Plan**

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

14.4.1 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.

14.4.2 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.

REFERENCES

1. Saylors RL, 3rd, Stine KC, Sullivan J, et al: Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol 19:3463-9, 2001
2. London WB, Frantz CN, Campbell LA, et al: Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a Children's Oncology Group study. J Clin Oncol 28:3808-15, 2010
3. Walterhouse DO, Lyden ER, Breitfeld PP, et al: Efficacy of topotecan and cyclophosphamide given in a phase II window trial in children with newly diagnosed metastatic rhabdomyosarcoma: a Children's Oncology Group study. J Clin Oncol 22:1398-403, 2004
4. Weinstein HJ, Lack EE, Cassady JR: APO therapy for malignant lymphoma of large cell "histiocytic" type of childhood: analysis of treatment results for 29 patients. Blood 64:422-6, 1984
5. Laver JH, Kraveka JM, Hutchison RE, et al: Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. J Clin Oncol 23:541-7, 2005
6. Christensen JG, Zou HY, Arango ME, et al: Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther 6:3314-22, 2007
7. Christensen JG, Burrows J, Salgia R: c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. Cancer Lett 225:1-26, 2005
8. Diomedi-Camassei F, McDowell HP, De Ioris MA, et al: Clinical significance of CXC chemokine receptor-4 and c-Met in childhood rhabdomyosarcoma. Clin Cancer Res 14:4119-27, 2008
9. Mosse YP, Wood A, Maris JM: Inhibition of ALK signaling for cancer therapy. Clin Cancer Res 15:5609-14, 2009
10. Pulford K, Lamant L, Espinos E, et al: The emerging normal and disease-related roles of anaplastic lymphoma kinase. Cell Mol Life Sci 61:2939-53, 2004
11. Kwak EL, Bang YJ, Camidge DR, et al: Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363:1693-703, 2010
12. Ou SH, Bazhenova L, Camidge DR, et al: Rapid and dramatic radiographic and clinical response to an ALK inhibitor (crizotinib, PF02341066) in an ALK translocation-positive patient with non-small cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 5:2044-6, 2010
13. Mosse YP, Laudenslager M, Longo L, et al: Identification of ALK as a major familial neuroblastoma predisposition gene. Nature 455:930-5, 2008
14. Janoueix-Lerosey I, Lequin D, Brugieres L, et al: Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. Nature 455:967-70, 2008
15. George RE, Sanda T, Hanna M, et al: Activating mutations in ALK provide a therapeutic target in neuroblastoma. Nature 455:975-8, 2008
16. Chen Y, Takita J, Choi YL, et al: Oncogenic mutations of ALK kinase in neuroblastoma. Nature 455:971-4, 2008
17. Bresler SC, Wood AC, Haglund EA, et al: Differential inhibitor sensitivity of anaplastic lymphoma kinase variants found in neuroblastoma. Science translational medicine 3:108ra114, 2011
18. Murugan AK, Xing M: Anaplastic thyroid cancers harbor novel oncogenic mutations of the ALK gene. Cancer research 71:4403-11, 2011
19. van Gaal JC, Flucke UE, Roeffen MH, et al: Anaplastic lymphoma kinase aberrations in rhabdomyosarcoma: clinical and prognostic implications. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30:308-15, 2012
20. Zou HY, Li Q, Lee JH, et al: An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic

mechanisms. Cancer research 67:4408-17, 2007

21. De Brouwer S, De Preter K, Kumps C, et al: Meta-analysis of neuroblastomas reveals a skewed ALK mutation spectrum in tumors with MYCN amplification. Clinical cancer research : an official journal of the American Association for Cancer Research 16:4353-62, 2010

22. Schonherr C, Ruuth K, Yamazaki Y, et al: Activating ALK mutations found in neuroblastoma are inhibited by Crizotinib and NVP-TAE684. The Biochemical journal 440:405-13, 2011

23. Schulte JH, Bachmann HS, Brockmeyer B, et al: High ALK receptor tyrosine kinase expression supersedes ALK mutation as a determining factor of an unfavorable phenotype in primary neuroblastoma. Clinical cancer research : an official journal of the American Association for Cancer Research 17:5082-92, 2011

24. Passoni L, Longo L, Collini P, et al: Mutation-independent anaplastic lymphoma kinase overexpression in poor prognosis neuroblastoma patients. Cancer Res 69:7338-46, 2009

25. Duijkers FA, Gaal J, Meijerink JP, et al: Anaplastic lymphoma kinase (ALK) inhibitor response in neuroblastoma is highly correlated with ALK mutation status, ALK mRNA and protein levels. Cellular oncology 34:409-17, 2011

26. Kwak EL, Camidge DR, Clark J, et al: Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066. ASCO Meeting Abstracts 27:3509, 2009

27. Mosse YP, Lim MS, Voss SD, et al: Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol 14:472-80, 2013

28. Diskin SJ, Li M, Hou C, et al: Adjustment of genomic waves in signal intensities from whole-genome SNP genotyping platforms. Nucleic Acids Res, 2008

29. Maris JM, Mosse YP, Bradfield JP, et al: Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. N Engl J Med 358:2585-93, 2008

30. Jiang XR, Jimenez G, Chang E, et al: Telomerase expression in human somatic cells does not induce changes associated with a transformed phenotype. Nat Genet 21:111-4, 1999

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical references. 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	
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 simvastatin	
Steroid 6beta-OH	estradiol hydrocortisone progesterone testosterone	
Other	alfentanyl buspirone cafergot caffeine=>TMU cocaine dapsone codeine-N-demethyl dextromethorphan eplerenone fentanyl finasteride imatinib haloperidol (in part)	lidocaine methadone ondansetron* pimozide propranolol quinine salmetrerol sildenafil tamoxifen paclitaxel trazodone vincristine zaleplon

	irinotecan	zolpidem
Inhibitors		
HIV Antivirals	delaviridine indinavir nelfinavir ritonavir saquinavir	
Other	amiodarone 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

***Ondansetron may be given for emesis or anti-emetic prophylaxis**

APPENDIX III-B: CRIZOTINIB MICROSPHERE ADMINISTRATION INSTRUCTIONS

CRIZOTINIB INSTRUCTIONS: Please take the prescribed dose of Crizotinib microspheres twice a day, in the morning and evening. **The only exception to this instruction is during Day 1 of Cycle 1 when crizotinib should be taken once during the evening** (see the Patient Diary in Appendix V-C). The dose can only be administered with water. After the dose has been taken, the patient should drink a small glass of water to ensure that the microspheres are rinsed from the mouth and to prevent residual taste. Take the dose at approximately the same time twice daily, **except during Day 1 of Cycle 1 crizotinib should be taken once during the evening**.

To be completed by Study Clinic:

COG Patient ID: _____ Acc#:_____ Date Dispensed: _____
Please do not write patient names on this form.

Insititution: _____

Study Clinic Telephone Number: _____ Diary provided by (staff initials): _____

- Do not swallow the capsule whole. Only take as described in the instructions below.
- Administer the microspheres immediately following preparation
- Do not take more than the prescribed dose at any time.
- Select a clean area to prepare the dose according to the instructions below
- The person preparing the dose should wash their hands before and after the dose is administered
- The dosing spoon provided with the drug must be used for giving Crizotinib
- Do not use the dosing spoon for any other medications
- The microsphere capsules should be handled and administered with care. Any spills of coated microspheres during dose preparation or administration should be cleaned up with water.

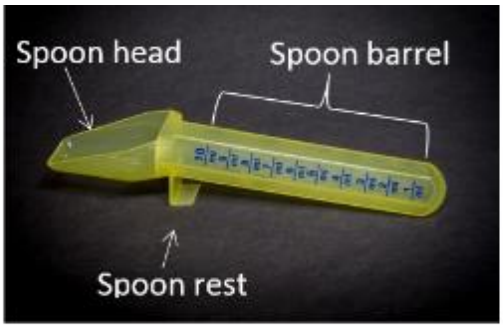
On days that you have a scheduled study visit (including on pharmacokinetic study days), do not take your morning dose at home. Instead, bring your study medication bottle and the Patient Diary with you to your scheduled visit and await further instruction from your doctor.

STUDY MEDICATION STORAGE: Keep the Crizotinib microsphere capsules in the original bottle and store at room temperature. Close the bottle tightly after taking a dose. Keep out of the reach of children.

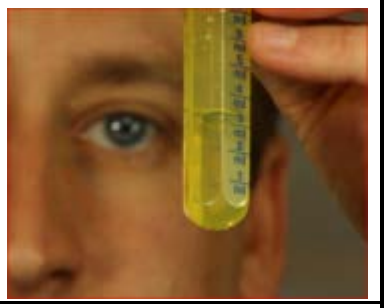
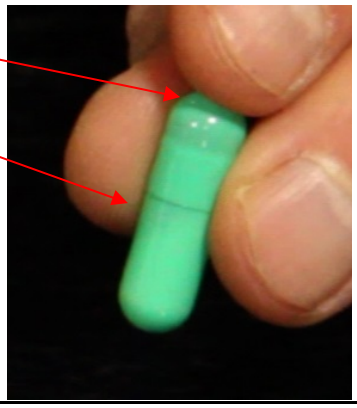
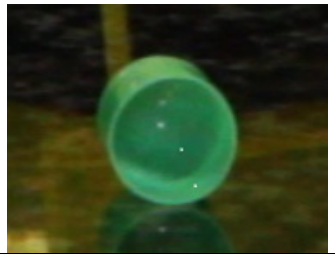
PATIENT DIARY INSTRUCTIONS (Appendix V-C)**:** Please record the date and time each dose is taken. Record any missed or extra doses as well as vomiting after a dose in the comments section. Remember to also include the date when these events happened.

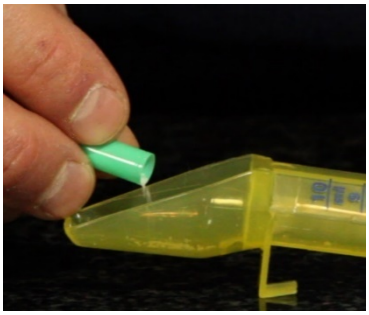
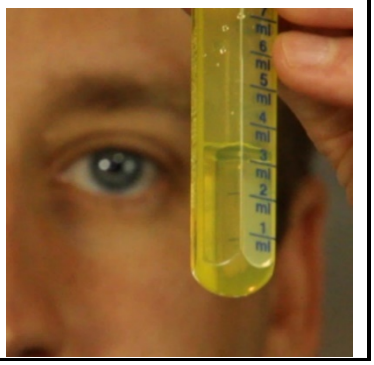
If you have any questions regarding how to take your study medication, please contact the study clinic at the telephone number provided above.

HOW TO TAKE THE MICROSPHERES USING THE DOSING SPOON PROVIDED SUPPLIES



1	**If your dose is less than 200 mg**, add 3 mL to 4 mL of cold or room temperature water to the supplied dosing spoon by running the water down the spoon into the barrel. Do not dry the spoon head after adding water. The amount of water does not need to be exact. **If your dose is 200 mg or more**, add 5 mL to 7 mL of cold or room temperature water to the supplied dosing spoon by running the water down the spoon into the barrel. Do not dry the spoon head after adding water. The amount of water does not need to be exact.	

2	Hold the dosing spoon upright to check that you have the correct amount of water as described in step 1. Place the dosing spoon with water in it onto a clean flat surface close by. The built-in spoon rest allows the water to stay in the barrel. (Example picture is of the 3 to 4 mL water amount) 
3	Remove the capsule(s) needed for the total dose from the bottle(s) provided.
4	Hold the capsule so that the cap of the capsule is up. Gently tap the capsule body (smaller portion) on a clean surface to move the microspheres to the body of the capsule. 
6	Hold the capsule over the center of the spoon head. Using both hands, gently grasp both ends of the capsule shell and turn the capsule cap and body in opposite directions to separate the two ends. 
7	Look in the capsule cap to ensure that it is empty. If there are microspheres in the capsule cap, empty them onto the center of the spoon head by gently tapping the capsule cap while over the spoon head. 

8	Carefully pour the microspheres from the capsule body onto the center of the spoon head. Gently tap the capsule body with finger over the spoon head as needed to get the microspheres onto the spoon. 
9	Look in the capsule body to see that it is empty. If there are still microspheres in the capsule body, empty them onto the center of the spoon head by gently tapping. Repeat steps 4 through 9 for each capsule needed for the dose.
10	Throw away the empty capsule shells after the microspheres have been put onto the spoon head and you have verified the dose.
11	Pick up the spoon and keep it level so the water stays in the barrel and the microspheres stay on the spoon head. In one pouring movement, pour the microspheres and water into the patient's mouth. If needed for younger patients secure the patient's head and gently pinch cheeks to pucker the mouth. 
12	Inspect the spoon head and dosing barrel for residual microspheres.
13	Add cold or room temperature water to the dosing spoon again (same amount as step 1) to rinse any remaining microspheres on the spoon head into the barrel.
14	Hold the dosing spoon upright (spoon head facing up) and ensure that the correct amount of water has been added. The amount does not need to be exact. (Example picture is of the 3 to 4 mL water amount) 

15	With the spoon still upright, gently swirl the water to get any remaining microspheres into the water in the barrel.
16	In one pouring movement, pour the rinse water and remaining microspheres into the patient's mouth. If needed for younger patients secure the patient's head and gently pinch cheeks to pucker the mouth. 
17	Look at the spoon head and dosing cylinder for remaining microspheres. If microspheres are still seen on the spoon head or barrel, perform steps 13 through 16 again. 
18	Dosing is now complete. Wash the spoon and save for future Crizotinib dosing use.
19	Clean the counter area where dosing was completed with water.

APPENDIX III-C: CRIZOTINIB MICROSPHERE PATIENT EDUCATION SHEET

Crizotinib Miscrosphere Capsules

Please read this information before preparing and taking your drug.

Please ask your doctor, nurse, or pharmacist if you have any questions.

WHAT DO I NEED?

- ***Crizotinib***

20 mg #_____capsule(s)

40 mg #_____capsule(s)

120 mg #_____capsule (s)

- ***Diluents (Liquids)***

purified water _____mL

- ***Supplies****:*
  - Crizotinib dosing spoon provided with the drug by your pharmacy
  - Disposable pad or paper towels
  - Disposable gloves and mask
  - Oral syringe, medicine cup, or measuring spoon
  - A container to collect waste (zip-top plastic bag or medical waste bag or container)

HOW DO I PREPARE THE DRUG?

If you are pregnant, could become pregnant, or are breast-feeding, we recommend that you wear appropriate safety equipment such as mask and gloves.

1. First, choose a quiet working space away from food, windows, fans or heat ducts.
2. Clean the working space with damp paper towels.
3. Place a pad or paper towel on the clean working space.
4. Next, place all needed items and drug on the pad or paper towel.
5. Then, wash your hands with soap and water.
6. Last, put on gloves (we recommend that you use gloves; women of childbearing should also use a mask)
7. Finally, start making or mixing the drug as per instructions provided (*protocol Appendix III-b)*.

HOW DO I STORE MY MEDICATION? WHEN WILL MY MEDICATION EXPIRE?

- Keep medication in its original container and stored according to the labeled conditions.
- Store away from food and out of the reach of children or pets
- When you are finished, place all dirty gloves, cup, or other tools used to mix the drug, as well as the spoon if you are no longer planning to use it, in a plastic Ziploc bag or a special bag or container provided by your nurse or pharmacist.

HOW DO I TAKE THE MEDICATION?

- My dose is: _____
- Take each dose by mouth twice a day for 21 days in a row.
- During each administration, the dose should be taken with water. After the dose has been taken, drink a small glass of water to ensure that the microspheres are rinsed from the mouth and to prevent residual taste. Avoid grapefruit or grapefruit juice.
- Cycle 1 Day 1: Crizotinib should be given in the evening ONLY with water.
- **On scheduled pharmacokinetic study days during Cycle 1 (Day 2 and between Days 15 and 21) the crizotinib morning dose should be administered in the clinic.**
- On Days 1-5 of each cycle, crizotinib should be taken at least one (1) hour before chemotherapy (except on Day 1 of Cycle 1 when crizotinib is given in the evening regardless of when other chemotherapy drugs are given).
- If a dose is missed or forgotten at the due time, it can be taken up to (but not greater than) 6 hours later to help prevent missed doses.
- If you inadvertently take 1 extra dose during a day, do not take the next dose of crizotinib.
- If you vomit after a dose of crizotinib, that dose will not be repeated; wait until the next scheduled time to administer a dose.
- When you are finished, place the dirty gloves, cup, and other tools used to prepare the drug, as well as the spoon if you are no longer planning to use it, in a plastic zip top bag or the waste container that was provided to you by your doctor, nurse, or pharmacist.
- Complete the patient diary by recording the date and time the dose of crizotinib is given as well as the number of capsules taken for each dose.

WHAT SHOULD I DO WITH THE LEFT-OVER CAPSULES?

Throw away the leftover drug in the plastic Ziploc. Close the plastic bag. (Site: check all apply or insert your local policies)

- ❑ *Return the closed bag to the clinic at the next visit; or*
- ❑ _____

*W*HAT DO I DO WITH EXPIRED OR NOT USED DRUG (LIKE MY CAPSULES/ TABLETS)?

Return unused and/or expired study drug to the clinic or hospital at your next study visit.

WHAT PRECAUTION/SAFETY DO I NEED?

If crizotinib gets into eyes, flush with large amount of water while holding eyelids open for at least 15 minutes. Call your study doctor or nurse immediately at _____ and/or contact the Poison Center at 1-800-222-1222.

If you spilled the study drug on your skin, remove contaminated clothing. Wash area with soap and large amount of water. Call your study doctor or nurse about spill.

APPENDIX IV-B: CRIZOTINIB NOMOGRAM FOR PATIENTS RECEIVING FORMULATED CAPSULES

Note: Patients enrolled on Part C (pre-Amendment #4) must continue to receive the formulated capsules (FC) per below dosing nomogram. For patients receiving the crizotinib microsphere formulation (cMS) refer to Appendix IV-C.

Crizotinib Dose Assignment: 130 mg/m^2/ dose BID
(Dose Level -1)

BSA (m^2)	Total Daily Crizotinib Dose (mg/day)	Crizotinib (mg PO BID)	
		AM Dose	PM Dose
1.07-1.34	300	150	150
1.35-1.73	400	200	200
1.74-2.11	500	250	250
2.12- ≥ 2.30	600	300	300

Crizotinib Dose Assignment: 165 mg/m^2/ dose BID
(Dose Level 1)

BSA (m^2)	Total Daily Crizotinib Dose (mg/day)	Crizotinib (mg PO BID)	
		AM Dose	PM Dose
1.07-1.36	400	200	200
1.37-1.66	500	250	250
1.67-1.96	600	300	300
1.97-2.27	700	350	350
2.28- ≥ 2.30	800	400	400

Crizotinib Dose Assignment: 215 mg/m^2/ dose BID
(Dose Level 2)

BSA (m^2)	Total Daily Crizotinib Dose (mg/day)	Crizotinib (mg PO BID)	
		AM Dose	PM Dose
1.07-1.27	500	250	250
1.28-1.51	600	300	300
1.52-1.74	700	350	350
1.75-1.97	800	400	400
1.98-2.20	900	450	450
2.21- ≥ 2.30	1000	500	500

Crizotinib Dose Assignment: 280 mg/m^2/ dose BID
(Dose Level 3)

BSA (m^2)	Total Daily Crizotinib Dose (mg/day)	Crizotinib (mg PO BID)	
		AM Dose	PM Dose
1.07-1.16	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
1.88-2.05	1100	550	550
2.06-2.23	1200	600	600
2.24- ≥ 2.30	1300	650	650

APPENDIX IV-C: CRIZOTINIB NOMOGRAM FOR PATIENTS RECEIVING MICROSPHERES

Crizotinib Dose Assignment: 130 mg/m^2/ dose
(Dose Level -2)

BSA (m^2)	Crizotinib Dose Cycle 1: Day 1 ONLY
	PM Dose (Total Dose)
0.43-0.53	60
0.54-0.69	80
0.70-0.84	100
0.85-1.00	120
1.01-1.15	140
1.16-1.30	160
1.31-1.46	180
1.47-1.61	200
1.62-1.76	220
1.77-1.92	240
1.93-2.07	260
2.08-2.23	280
>2.23	300

BSA (m^2)	Crizotinib Dose#	
	AM Dose	PM Dose
0.43-0.53	60	60
0.54-0.69	80	80
0.70-0.84	100	100
0.85-1.00	120	120
1.01-1.15	140	140
1.16-1.30	160	160
1.31-1.46	180	180
1.47-1.61	200	200
1.62-1.76	220	220
1.77-1.92	240	240
1.93-2.07	260	260
2.08-2.23	280	280
>2.23	300	300

 # BID on Days 2-21 of Cycle 1 and Days 1-21 of Subsequent Cycles

Crizotinib Dose Assignment: 165 mg/m^2/ dose
(Dose Level -1)

BSA (m^2)	Crizotinib Dose Cycle 1: Day 1 ONLY
	PM Dose (Total Dose)
0.43-0.54	80
0.55-0.66	100
0.67-0.78	120
0.79-0.90	140
0.91-1.03	160
1.04-1.15	180
1.16-1.27	200
1.28-1.39	220
1.40-1.51	240
1.52-1.63	260
1.64-1.75	280
1.76-1.87	300
1.88-2.00	320
2.01-2.12	340
2.13-2.24	360
≥2.25	380

BSA (m^2)	Crizotinib Dose#	
	AM Dose	PM Dose
0.43-0.54	80	80
0.55-0.66	100	100
0.67-0.78	120	120
0.79-0.90	140	140
0.91-1.03	160	160
1.04-1.15	180	180
1.16-1.27	200	200
1.28-1.39	220	220
1.40-1.51	240	240
1.52-1.63	260	260
1.64-1.75	280	280
1.76-1.87	300	300
1.88-2.00	320	320
2.01-2.12	340	340
2.13-2.24	360	360
≥2.25	380	380

 # BID on Days 2-21 of Cycle 1 and Days 1-21 of Subsequent Cycles

Crizotinib Dose Assignment: 215 mg/m^2/dose
(Dose Level 1)

BSA (m^2)	Crizotinib Dose Cycle 1: Day 1 ONLY
	PM Dose (Total Dose)
0.43-0.51	100
0.52-0.60	120
0.61-0.69	140
0.70-0.79	160
0.80-0.88	180
0.89-0.97	200
0.98-1.06	220
1.07-1.16	240
1.17-1.25	260
1.26-1.34	280
1.35-1.44	300
1.45-1.53	320
1.54-1.62	340
1.63-1.72	360
1.73-1.81	380
1.82-1.90	400
1.91-2.00	420
2.01-2.09	440
2.10-2.18	460
2.19-2.27	480
≥2.28	500

BSA (m^2)	Crizotinib Dose#	
	AM Dose	PM Dose
0.43-0.51	100	100
0.52-0.60	120	120
0.61-0.69	140	140
0.70-0.79	160	160
0.80-0.88	180	180
0.89-0.97	200	200
0.98-1.06	220	220
1.07-1.16	240	240
1.17-1.25	260	260
1.26-1.34	280	280
1.35-1.44	300	300
1.45-1.53	320	320
1.54-1.62	340	340
1.63-1.72	360	360
1.73-1.81	380	380
1.82-1.90	400	400
1.91-2.00	420	420
2.01-2.09	440	440
2.10-2.18	460	460
2.19-2.27	480	480
≥2.28	500	500

 # BID on Days 2-21 of Cycle 1 and Days 1-21 of Subsequent Cycles

APPENDIX V-B: CRIZOTINIB PATIENT DIARY (FORMULATED CAPSULES)

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2
Please do not write patient names on this form.

Instructions: Complete the diary below by recording the date and time the dose of crizotinib is given as well as the number of capsules taken for each dose. **Make note of other drugs and supplements taken in the Comments section of the diary.**

Crizotinib should be given twice a day, approximately 12 hours apart. On Days 1-5, crizotinib should be taken at least 1 hour before chemotherapy. The crizotinib capsules should be swallowed whole. Do **not** open, crush, or chew the capsules before swallowing. If the capsule is broken and the powder gets on the skin, wash the area thoroughly with water. Inform your study doctor or nurse immediately.

If you vomit after taking crizotinib, do not take another dose. Record this event in the diary and continue on the normal dosing schedule. If you miss a crizotinib dose and less than 6 hours have passed since the scheduled dosing time, that dose should be taken immediately. If you miss a crizotinib dose and more than 6 hours have passed since the scheduled dosing time, skip that dose and continue on the normal dosing schedule. If you accidently take 1 extra dose during a day, skip the next scheduled dose of crizotinib.

Return the completed diary and all study medication bottles to the study clinic at each visit (weekly during Cycle 1 and then after each treatment cycle). The study clinic will submit this diary into an electronic system to record the information.

EXAMPLE

WEEK 1	*Date*	*Time*		*# of crizotinib capsules prescribed to take*			*Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)*
				150 mg	*200 mg*	*250 mg*	
				AM#___ PM#___	*AM#_2__ PM#_2__*	*AM#___ PM#___*	
				# of crizotinib capsules taken			
				150 mg	*200 mg*	*250 mg*	
Day 1	*1/7/14*	*8.30*	*AM*		*2*		*He felt nauseated an hour after taking the drug but did not vomit.*
		8.30	*PM*		*2*		

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__| **Dose Level: _____mg/m^2/dose** **Part of Study:____**

WEEK 1	**Date**	**Time**		**# of crizotinib capsules prescribed to take**			**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				150 mg	**200 mg**	**250 mg**	
				AM#___ PM#___	**AM#___ PM#___**	**AM#___ PM#___**	
				# of crizotinib capsules taken			
				150 mg	**200 mg**	**250 mg**	
Day 1			**AM**				
			PM				
Day 2			**AM**				
			PM				
Day 3			**AM**				
			PM				
Day 4			**AM**				
			PM				
Day 5			**AM**				
			PM				

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2
Please do not write patient names on this form.

WEEK 1	Date	Time		# of crizotinib capsules prescribed to take 150 mg AM#___ PM#___ 200 mg AM#___ PM#___ 250 mg AM#___ PM#___ # of crizotinib capsules taken 150 mg	200 mg	250 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 6			AM				
			PM				
Day 7			AM				
			PM				
WEEK 2	**Date**	**Time**		**# of crizotinib capsules taken** **150 mg**	**200 mg**	**250 mg**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
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**		**# of crizotinib capsules taken** **150 mg**	**200 mg**	**250 mg**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
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				

APPENDIX V-C1: CRIZOTINIB PATIENT DIARY (MICROSPHERES)-CYCLE 1 ONLY

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2
Please do not write patient names on this form.

NOTE: For Cycle 2+ use the Patient Diary in Appendix V-C2.

Instructions: Complete the diary below by recording the date and time the dose of crizotinib is given. **Make note of other drugs and supplements taken in the Comments section of the diary.**

Crizotinib should be given approximately 12 hours apart. **On Day 1 of Cycle 1 crizotinib should be given once in the evening; on Days 2-21 of Cycle 1 crizotinib should be given twice daily. On scheduled study visits (including pharmacokinetic study days on Day 2 and between Days 15-21) patients should take their crizotinib morning dose in the clinic.** On Days 2-5, the crizotinib morning dose should be taken at least 1 hour before chemotherapy, except on Day 1 only chemotherapy will be given in the morning at the clinic. If crizotinib powder gets on the skin, wash the area thoroughly with water. Inform your study doctor or nurse immediately. See Appendix III-B for crizotinib handling and administration guidelines.

Do not swallow capsules whole. Empty capsule contents and take as directed per Crizotinib Microsphere Administration Instructions (Appendix III-B) and Crizotinib Microsphere Patient Education Sheet (Appendix III-C).

If you vomit after taking crizotinib, do not take another dose. Record this event in the diary and continue on the normal dosing schedule. If you miss a crizotinib dose and less than 6 hours have passed since the scheduled dosing time, that dose should be taken immediately. If you miss a crizotinib dose and more than 6 hours have passed since the scheduled dosing time, skip that dose and continue on the normal dosing schedule. If you accidently take 1 extra dose during a day, skip the next scheduled dose of crizotinib.

Return the completed diary and all study medication bottles to the study clinic at each visit (weekly during Cycle 1). The study clinic will submit this diary into an electronic system to record the information.

EXAMPLE							
WEEK 1	*Date*	*Time*		*# of crizotinib microsphere capsules prescribed to take* *20 mg* / *40 mg* / *120 mg* *AM#___ PM#___* / *AM# 2 PM# 2* / *AM# 1 PM# 1* *# of crizotinib microsphere capsules taken* *20 mg* / *40 mg* / *120 mg*			*Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)*
Day 1	*9/14/15*		*AM*	*AM dose **should not** be taken on Day 1 of Cycle 1. ONLY take the Day 1 evening dose.*			
		8.30	*PM*		*2*	*1*	*He felt nauseated an hour after taking the drug but did not vomit.*
Day 2	*9/15/15*	*8.30*	*AM*		*2*	*1*	
		8.30	*PM*		*2*	*1*	

Patient Diary for Cycle 1 is continued on the next couple of pages.

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2 Cycle #: 1

Please do not write patient names on this form.

Cycle #: 1 **Start Date**: |__/__|__/__|__/__| **Dose Level: _____mg/m^2/dose**
End Date: |__/__|__/__|__/__|

WEEK 1	Date	Time		# of crizotinib microsphere capsules prescribed to take 20 mg AM#___ PM#___ 40 mg AM#___ PM#___ 120 mg AM#___ PM#___ # of crizotinib microsphere capsules taken 20 mg	40 mg	120 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 1			AM	AM dose **should not** be taken on Day 1 of Cycle 1. ONLY take the Day 1 *evening* dose.			
			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		# of crizotinib microsphere capsules prescribed to take 20 mg AM#___ PM#___ 40 mg AM#___ PM#___ 120 mg AM#___ PM#___ # of crizotinib microsphere capsules taken 20 mg	40 mg	120 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
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				

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2 Cycle #: 1
Please do not write patient names on this form.

WEEK 3	Date	Time		# of crizotinib microsphere capsules prescribed to take 20 mg AM#___ PM#___ 40 mg AM#___ PM#___ 120 mg AM#___ PM#___ # of crizotinib microsphere capsules taken 20 mg	40 mg	120 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
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				

APPENDIX V-C2: CRIZOTINIB PATIENT DIARY (MICROSPHERES)-CYCLE 2+ ONLY

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m²

Please do not write patient names on this form.

Instructions: Complete the diary below by recording the date and time the dose of crizotinib is given. **Make note of other drugs and supplements taken in the Comments section of the diary.**

Crizotinib should be given twice a day, approximately 12 hours apart. On Days 1-5, crizotinib should be taken at least 1 hour before chemotherapy. **On scheduled study visits patients should take their crizotinib morning dose in the clinic.** See Appendix III-B for crizotinib handling and administration guidelines. If crizotinib powder gets on the skin, wash the area thoroughly with water. Inform your study doctor or nurse immediately.

Do not swallow capsules whole. Empty capsule contents and take as directed per Crizotinib Microsphere Administration Instructions (Appendix III-B) and Crizotinib Microsphere Patient Education Sheet (Appendix III-C).

If you vomit after taking crizotinib, do not take another dose. Record this event in the diary and continue on the normal dosing schedule. If you miss a crizotinib dose and less than 6 hours have passed since the scheduled dosing time, that dose should be taken immediately. If you miss a crizotinib dose and more than 6 hours have passed since the scheduled dosing time, skip that dose and continue on the normal dosing schedule. If you accidently take 1 extra dose during a day, skip the next scheduled dose of crizotinib.

Return the completed diary and all study medication bottles to the study clinic at each visit (after each treatment cycle). The study clinic will submit this diary into an electronic system to record the information.

EXAMPLE

WEEK 1	*Date*	*Time*		*# of crizotinib microsphere capsules prescribed to take*			*Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)*
				20 mg	*40 mg*	*120 mg*	
				AM#___ PM#___	*AM#_2__ PM#_2__*	*AM#_1__ PM#_1_*	
				# of crizotinib microsphere capsules taken			
				20 mg	*40 mg*	*120 mg*	
Day 1	*9/14/15*	*8.30*	*AM*		*2*	*1*	*He felt nauseated an hour after taking the drug but did not vomit.*
		8.30	*PM*		*2*	*1*	

Cycle #: _____ Start Date: |__/__|__/__|__/__| **Dose Level: _____mg/m²/dose**
End Date: |__/__|__/__|__/__|

WEEK 1	**Date**	**Time**		**# of crizotinib microsphere capsules prescribed to take**			**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				20 mg	**40 mg**	**120 mg**	
				AM#___ PM#___	**AM#___ PM#___**	**AM#___ PM#___**	
				# of crizotinib microsphere capsules taken			
				20 mg	**40 mg**	**120 mg**	
Day 1			**AM**				
			PM				
Day 2			**AM**				
			PM				
Day 3			**AM**				
			PM				
Day 4			**AM**				
			PM				
Day 5			**AM**				
			PM				

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2 Cycle #:___ ***Please do not write patient names on this form.***

WEEK 1	Date	Time		# of crizotinib microsphere capsules prescribed to take 20 mg AM#___ PM#___ 40 mg AM#___ PM#___ 120 mg AM#___ PM#___ # of crizotinib microsphere capsules taken 20 mg	40 mg	120 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 6			AM				
			PM				
Day 7			AM				
			PM				
WEEK 2	**Date**	**Time**		**# of crizotinib microsphere capsules taken** **20 mg**	**40 mg**	**120 mg**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
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**		**# of crizotinib microsphere capsules taken** **20 mg**	**40 mg**	**120 mg**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
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				

APPENDIX VI: 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]	X1 and X-A (Parts A to C)	2 ml	12 ml	2 ml	12 ml	K+ EDTA
	X2 and X-A (Part D)	2 ml	14 ml	2 ml	14 ml	K+ EDTA
Pharmacogenomics	VIII	3 ml	3 ml	3 ml	3 ml	K+ EDTA
Bone Marrow[b]	XI	3-5 ml	3-5 ml	5 ml	5 ml	Preservative free heparin tubes
Bone Marrow[c]	XII	3-5 ml	3-5 ml	5 ml	5 ml	K+ EDTA
Peripheral Blood[c]	XII	10 ml	20 ml	15 ml	30 ml	K+ EDTA
Tumor Tissue	IX					
Total Blood Volume in Cycle 1			**35-37 ml**		**45-47 ml**	
Total Bone Marrow Volume			**6-10 ml**		**10 ml**	

[a] Required for all Patients
[b] Additional Studies for Patients with Neuroblastoma
[c] Additional Required Studies for Patients with ALCL

APPENDIX VII: CORRELATIVE BIOLOGY STUDIES

1. **COMPREHENSIVE DNA RESEQUENCING OF ALK FOR NEUROBLASTOMA**
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 crizotinib 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 FOR NEUROBLASTOMA**
We will define whole genome DNA copy number status as well as *ALK* allelic using the Illumina HH550K Single Nucleotide Polymorphism (SNP) array.[13,28,29] 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 FOR NEUROBLASTOMA*****
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 IN NEUROBLASTOMA**
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.[30] We will then screen for transformation *in vitro* using standard assays.

5. **DETERMINE THE BIOCHEMICAL CONSEQUENCES OF *ALK* ACTIVATION IN NEUROBLASTOMA 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 CRIZOTINIB AT TIME OF DISEASE PROGRESSION ON THIS STUDY**
We will collect bone marrow samples before and during treatment with crizotinib, 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.

7. **DEFINE c-Met EXPRESSION IN ALL NON-ALCL, NON-NEUROBLASTOMA TUMORS**. We will perform immunohistochemistry studies on all non-neuroblastoma solid tumors to determine c-Met expression.

APPENDIX VIII: PHARMACOGENOMIC STUDY FORM

COG Pt ID # _____ ACC # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Institution: _____

Body Surface Area: ____ m^2 Dose Level: _____mg/m^2

Total Dose (combined am and pm dose): _____mg/day

- One peripheral blood sample (3 mL) will be obtained at baseline prior to the first dose of crizotinib 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 dose is administered.

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

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. (ADVL1212), and the date and time the sample was drawn; please label as "**pharmacogenomic sample**".
3. Gently mix the blood with the anticoagulant by gently inverting the tube (15 times).
4. Record the date and time of sample collection on this form.
5. After mixing the blood with the anticoagulant, place the blood collection tube inside a cryovial storage box **and store the blood at -70° 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 uploaded into RAVE. A second copy should be sent with the sample to the Mayo Clinic laboratory (see address below).

Sample Shipping

1. Ship the sample on dry ice. Shipments should be sent **Monday through Wednesday only** for priority overnight delivery. Do not ship on Thursday or Friday.
2. Please notify Renee McGovern of a pending shipment along with the FedEx tracking number by phone at (507) 284-4303 or by e-mail (mcgovern.renee@mayo.edu).
3. Ship samples to:

Mayo Clinic
Gonda 19-151
200 First Street SW
Rochester, MN 55905

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

COG Pt ID # _____ ACC # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Institution: _____

Body Surface Area: ____ m^2 Dose Level: _____mg/m^2

Total Dose (combined am and pm dose): _____mg/day

Tumor Sample Labeling:
Samples should be labeled with the following information:

Protocol number: **ADVL1212**
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 uploaded into RAVE.
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-1: PHARMACOKINETIC STUDY FORM (PARTS A-C)

COG Pt ID # _____ ACC # _____ Cycle 1, Day 1 Date: _____

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

Institution: _____ Crizotinib Formulation (tick one): □ OS □ FC

Body Surface Area: ____ m^2 Dose Level: _____mg/m^2 Total Dose: _____mg/day

Cycle 1, Date of Steady State Sampling: _____

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 21 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 crizotinib dose is administered before the pharmacokinetic sample is drawn. Sample handling and processing instructions are described below and in Section 8.3.

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. (ADVL1212), 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 crizotinib.
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 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 a cryovial storage box and store the plasma at -20 °C to -70 °C** within 1 hour of collection until shipment.

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to Covance at the address listed in Appendix X-A. See Appendix X-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 X-2: PHARMACOKINETIC STUDY FORM FOR MICROSPHERES (PART D ONLY)

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

BSA: ____ m^2 Dose Level: _____mg/m^2 Cycle 1, Day 1 Date: _____

Total Crizotinib Dose: Day 1_____mg/day Days 2-21 _____mg/day

Blood samples (2 mL per timepoint) will be obtained in K_2EDTA tubes during Cycle 1. Record the exact date and time each sample is drawn and the last crizotinib dose is administered before the pharmacokinetic sample is drawn. Sample handling and processing instructions are described below and in Section 8.3.

Blood Sample No.	Time Point Cycle 1	Scheduled Collection Time	Actual Crizotinib Dose Given	Actual Date Sample Collected or Dose Given	Actual Time Collected or Dose Given (24-hr clock)
1	**Day 1**	Pre-Day 1 dose		___/____/___	____ : ____
		Day 1 Dose	_____mg PM	___/____/___	____ : ____
2	**Day 2**	12 hrs after 1st dose (Pre-Day 2 dose)		___/____/___	____ : ____
		Day 2 Dose*	_____ mg AM	___/____/___	____ : ____
		Last dose before Pre-Dose at Steady State# Obtained	_____mg AM _____mg PM	___/____/___	____ : ____ ____ : ____
3	**Pre-Dose at Steady State#**	12 hrs after the last dose recorded above		___/____/___	____ : ____
		Steady State Dose*#	_____mg AM	___/____/___	____ : ____
4	**Steady State#**	1 hr post-steady-state dose		___/____/___	____ : ____
5		2 hrs post-steady-state dose		___/____/___	____ : ____
6		4 hrs post-steady-state dose		___/____/___	____ : ____
7		6-8 hrs a post-steady-state dose		___/____/___	____ : ____

*To be administered in the clinic.
Steady State is defined as being between Days 15 and 21 of BID dosing in Cycle 1.

Sample Processing Procedures

1. **Label** the cryovial tube with the patient's study registration number, the study I.D. (ADVL1212), 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 crizotinib.
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 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 a cryovial storage box and store the plasma at -20 ºC to -70 ºC** within 1 hour of collection until shipment.

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to Covance at the address listed in Appendix X-A. See Appendix X-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 X-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

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.

PACKAGING

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 X-1 or Appendix X-2 of the ADVL1212 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.

****

SHIPPING

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.

****

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

COG Pt ID # _____ ACC # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Institution: _____

Body Surface Area: ____ m^2 Dose Level: _____mg/m^2

Total Dose (combined am and pm dose): _____mg/day

- 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 every other cycle at times of disease evaluation (See Section 8.1 and Section 8.6.2).

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 (ADVL1212), 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 XII: BONE MARROW AND PHERIPHERAL BLOOD STUDIES FORM (FOR PATIENTS WITH ALCL ONLY)

COG Pt ID # _____ ACC # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Institution: _____

Body Surface Area: ____ m^2 Dose Level: _____mg/m^2

Total Dose (combined am and pm dose): _____mg/day

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

- Bone marrow samples (5 mL if > 10 kg and 3-5 mL in children ≤ 10 kg) will be obtained prior to starting Cycle 1 and repeated until negative in patients with ALCL.
- 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 (ADVL1212), the type of sample (bone marrow or peripheral blood), 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:

[redacted]

- Email [redacted] when the sample is being shipped.
- 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 XIII: PREGNANCY INFORMATION FORM

Attach to CTEP-AERS 5-Day Report

PREGNANCY INFORMATION FAX
FACSIMILE TRANSMISSION
Ticket Number:_____

Study #:
SAE FAX NO: (301) 230-0159
ALTERNATE FAX NO: (301) 897-7404

Initial Report Date: ___ - ___ - ___ (DD - MMM - YY)	Follow-up Report Date: ___ - ___ - ___ (DD - MMM - YY)
Principal Investigator:	Reporter:
Reporter Telephone #:	Reporter FAX #:

Investigator Number ☐☐☐☐☐ Subject Number ☐☐☐☐☐

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials ☐☐☐

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male

Subject's Weight: _____ kg

Subject's Date of Birth: ___ - ___ - ___ (DD - MMM - YYYY)

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug:	Study Drug Start Date: ___ - ___ - ___ (DD - MMM - YY) Study Drug Stop Date: ___ - ___ - ___ (DD - MMM - YY) OR ☐ Study Drug Continuing		
Dose:	Route:	Frequency:	Kit #:

First Day of Last Menstrual Period: ___ - ___ - ___ (DD - MMM - YY) Estimated Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)

Method of Contraception (check all that apply):
☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide
☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown
☐ CVS Results: ☐ Normal ☐ Abnormal
☐ Amniocentesis Results: ☐ Normal ☐ Abnormal
☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome
Was pregnancy interrupted? ☐ Yes ☐ No
If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic
Date of Termination: ___ - ___ - ___ (DD - MMM - YY)
If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)
☐ Vaginal Birth: ☐ Premature ☐ Term OR ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)
Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

NOTE: For an initial reporting email both the Pregnancy CTEP-AERS Report and this additional Pregnancy Information Form. For follow-up reporting, email only this Pregnancy Information Form. See Section 13. 7.

APPENDIX XIV: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with crizotinib and/or chemotherapy. Study patients 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 the diet.

Crizotinib

Drugs that may interact with 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 crizotinib
• **Echinacea** • **St. John's Wort** • **Grapefruit, grapefruit juice, 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.*

Cyclophosphamide:

Drugs that may interact with cyclophosphamide	
• **Allopurinol** • **Chloramphenicol** • **Cyclosporine** • **Digoxin** • **Etanercept** • **Hydrochlorothiazide** • **Indomethacin** • **Nevirapine**	• **Ondansetron** • **Pentostatin** • **Tamoxifen** • **Trastuzumab** • **Warfarin**
Food and supplements* that may interact with cyclophosphamide	
• **St John's Wort** • **Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"**	

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

Topotecan

Drugs that may interact with topotecan

• **Antibiotics and antifungals**
  • **Clarithromycin, erythromycin, itraconazole, ketoconazole**
• **Arthritis medications**
  • **Leflunomide, tofacitinib**
• **Anti-rejection medications**
  • **Cyclosporine, tacrolimus**
• **Antiretrovirals and antivirals**
  • **Darunavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir**
• **Heart medications**
  • **Amiodarone, amlodipine, carvedilol, dronedenarone, nicardipine, propranolol, verapamil**
• **Some chemotherapy (be sure to talk to your doctor about this)**
• **Many other drugs, including the following:**
  • **Atorvastatin, clozapine, dipyridamole, ivacaftor, lomitapide, natalizumab**

Food and supplements* that may interact with topotecan
• **Echinacea** • **Grapefruit, grapefruit juice**

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

APPENDIX XV: MEDICATIONS ASSOCIATED WITH PROLONGED QTC

The use of the following medications should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references. For the most current list of medications, please refer to the following reference:
Woosley, RL and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date March 1st, 2016, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

1. Medications that prolong QTc:

Generic name	Brand name
Amiodarone	Cordarone®
Anagrelide	Agrylin®
Arsenic trioxide	Trisenox®
Azithromycin	Zithromax®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Ciprofloxacin	Cipro®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Dronedarone	Multaq®
Erythromycin	Erythrocin®
Escitalopram	Lexapro®

Generic name	Brand name
Flecainide	Tambocor®
Fluconazole	Diflucan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Methadone	Dolophine®
Moxifloxacin	Avelox®
Ondansetron	Zofran®
Pentamidine	Pentam®
Pimozide	Orap®
Procainamide	Procan®
Propofol	Diprivan®
Quinidine	Quinaglute®
Sevoflurane	Ulane®
Sotalol	Betapace®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

2. Medications that may prolong QTc:

Generic name	Trade name
Aripiprazole	Abilify®
Bortezomib	Velcade®
Bosutinib	Bosulif®
Ceritinib	Zykadia®
Clomipramine	Anafranil®
Crizotinib	Xalkori®
Dabrafenib	Tafinlar®
Dasatinib	Sprycel®
Degarelix	Firmagon®
Desipramine	Norpramine®
Dolasetron	Anzemet®
Eribulin mesylate	Halaven®
Famotidine	Pepcid®
Foscarnet	Foscavir®
Gemifloxacin	Factive®
Granisetron	Kytril®
Isradipine	Dynacirc®

Generic name	Trade name
Lapatinib	Tykerb®
Lenvatinib	Lenvima®
Leuprolide	Leupron Depot®
Mirtazapine	Remeron®
Nicardipine	Cardene®
Nilotinib	Tasigna®
Olanzapine	Zyprexa®
Osimertinib	Tagrisso®
Pazopanib	Votrient®
Promethazine	Phenergan®
Risperidone	Risperdal®
Sorafenib	Nexavar®
Sunitinib	Sutent®
Tacrolimus	Prograf®
Vemurafenib	Zelboraf®
Venlafaxine	Effexor®
Vorinostat	Zolinza®

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 must be justified in writing by the investigator and approved by the IRB.

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

ADVL1212, *A Phase 1 Study of Crizotinib (IND# 105573) in Combination with Conventional Chemotherapy for Relapsed or Refractory Solid Tumors or Anaplastic Large Cell Lymphoma*

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

This study is a clinical trial (a protocol, or research study involving patients) 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 1 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. The Phase 1 Consortium is the group within COG that consists of 21 hospitals based in the United States and Canada, and participation in this study will be limited to these hospitals.

This is a Phase 1 study of a drug called crizotinib in combination with chemotherapy. Crizotinib has been FDA approved for use in adults with non-small cell lung cancer (NSCLC) that has spread to other parts of the body and is caused by a defect in a gene called ALK (anaplastic lymphoma kinase). The combination of crizotinib with chemotherapy is considered experimental because it has not been proven to work in a situation like yours. We are using crizotinib because it seems to work against cancer in test tubes and animals. Crizotinib has been successfully used in adults and children. This is called a Phase 1 study because the goal is to find the highest dose of crizotinib in combination with chemotherapy (topotecan and cyclophosphamide) that we can give safely to children. With Amendment #4, the recommended dose was determined to be Dose Level 2 from the dose escalation part of the study (Part C).

Why is this study being done?

We are testing new experimental drugs such as crizotinib in the hopes of finding a drug that may be effective against tumors or lymphoma that have come back or that have not responded to standard therapy.

The goals of this study are:

- **To find the highest safe dose of crizotinib that can be given in combination with standard chemotherapy drugs without causing severe side effects;**
- **To learn what kind of side effects crizotinib in combination with standard chemotherapy drugs can cause;**
- **To learn more about the pharmacology (how your body handles the drug) of crizotinib in combination with standard chemotherapy drugs;**
- **To learn more about the biology of crizotinib in combination with standard chemotherapy drugs;**
- **To determine whether crizotinib in combination with standard chemotherapy drugs is a beneficial treatment for your tumor.**

How many people will take part in the study?

There will be about 18-64 patients participating in this study overall. 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
- Bone marrow tests (if required)
- Spinal tap (if you have lymphoma)
- Pregnancy test (if you are a woman who could have children)
- Electrocardiogram (EKG) a test that monitors the function of your heart
- X-rays, CT scans, or other tests that 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, crizotinib will be given for 21 days. This entire period is called a cycle. You may continue to receive crizotinib for up to 35 cycles (up to 24 months) unless you develop serious side effects or your tumor worsens.

The crizotinib will be given by mouth, followed by a small glass of water. Since we do not have information on how well the medicine is absorbed, if you vomit, the crizotinib should not be taken again. If you are taking the crizotinib capsules (Part C), you should not crush, open or chew the capsules; the capsules must be swallowed whole. If you enrolled on Part D, you will be given the crizotinib microsphere capsules; the microsphere capsules should be taken as instructed and should not be swallowed whole.

In addition to crizotinib you also will receive topotecan and cyclophosphamide on Days 1 through 5. Topotecan and cyclophosphamide are both given directly into the vein through either a needle or small tubing inserted each treatment day or through a long-term catheter called a central line.* Approximately 24 to 48 hours later, you will receive myeloid growth factor.

**Your physician may recommend that you have a special kind of IV called a "central line." This is a special kind of IV placed into a big vein in your chest that can stay in for a long time. If you get a central line, you will have a separate consent form for it. Potential risks of central line placement include accumulation of air inside the chest; bleeding; infection; blood clot development in the line; and risks from the anesthesia. After placement, the central line may become infected which may require hospitalization, antibiotics and possibly removal and replacement of the central line.*

Part D - Cycle 1 Only

Cycle Day							
1	2	3	4	5	6	7-21	21
CRIZ (Once in the evening)	CRIZ (Twice a day) →						Evaluation
CPM	CPM	CPM	CPM	CPM			
TOPO	TOPO	TOPO	TOPO	TOPO			
					MGF		

Part C[#] and Part D*

Cycle Day							
1	2	3	4	5	6	7-21	21
CRIZ (Twice a day) →							Evaluation
CPM	CPM	CPM	CPM	CPM			
TOPO	TOPO	TOPO	TOPO	TOPO			
					MGF		

CRIZ: Crizotinib
CPM: Cyclophosphamide
TOPO: Topotecan
MGF: Myeloid Growth Factor (filgrastim (G-CSF) or pegfilgrastim)
All cycles
*Cycle 2+ for Part D

Parts C and D: If you enroll with Amendment #4, you will be treated at Dose Level 2, the recommended dose determined from the dose-escalation part of the study. If you have bad side effects, your dose may be decreased.

During the study you will have tests and procedures to check for side effects and see how your tumor is doing. These tests are part of regular cancer care, but you may have them more often because you are on the study:

* A medical history
* Physical exam
* Vital signs (blood pressure, pulse, temperature)
* Eye exam
* Blood tests
* Bone marrow tests (if required)
* Spinal tap (if you have lymphoma)
* Urine tests (if you have neuroblastoma)
* MRIs, X-rays, CT scans, or other tests that are needed to check your tumor

Copies of the scans used to diagnose your cancer and some of the tissue already taken may be sent to a central review center. COG does this to double check the hospitals' results.

You will be given a Patient Diary at the beginning of each cycle of crizotinib. Use the diary to record the date and time you take the drug, side effects you experience, and any other medications and supplements you are taking. This diary should be returned to the clinic along with the medication bottle (even if it is empty) weekly during Cycle 1 and then after each treatment cycle. This will help us to know how much of the drug you take and how it made you feel.

Capsule Questionnaire (Part C Patients Only)
If you are receiving the crizotinib capsules for this study, 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 well the drug can be swallowed. The questionnaire should be filled out within 10 minutes of taking the crizotinib capsules. It will take you about 5 minutes to fill out the questionnaire each time. 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.

Microsphere Capsule Questionnaire (Part D Patients Only)
If you are receiving the crizotinib microsphere capsules for this study, we would like to ask you to fill out a short questionnaire at the time of the first dose, and then once per week during Cycle 1, and then at every visit thereafter so we can learn more about how the drug tastes. The questionnaire should be filled out within 10 minutes of taking the crizotinib microsphere capsule powder. It will take you about 5 minutes to fill out the questionnaire each time. 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.

Research Tests

We would also like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about crizotinib 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 given to you. Some of these tests are required but others are optional (you can decide whether you want to do them or not).

Pharmacokinetic Studies (Required)
During the study blood samples will be collected to determine how much crizotinib is in your blood. About 2 mL (approximately ½ teaspoon) of blood will be drawn for each sample. If you enroll on Part C, 6 blood samples will be obtained over 2 separate days (Day 1 and on a day between Days 15 and 21). If you enroll on Part D, 7 blood samples will be obtained over 3 separate days (Day 1, Day 2 and on a day between Days 15 and 21). These 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. *These blood samples are required from all participants in this study.*

If you enrolled on Part C, a total of 12 mL (about two and a half teaspoons total) will be taken for the pharmacokinetic tests in this study. If you enrolled on Part D, a total of 14 mL (about 3 teaspoons total) will be taken for the pharmacokinetic tests in this study. *This amount of blood is safe even for small children.*

You may be reimbursed up to $100 for inconveniences you experience as a result of your participation in these pharmacokinetic studies. Your doctor will explain to you what qualifies for reimbursement (e.g. costs of parking).

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 crizotinib 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
As part of your regular care, your doctor may have removed some tumor tissue 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. The ALK gene testing may help us learn more about how crizotinib works in the tissues in your body. The tissue will be sent directly to the lab for testing.

The information learned from this research will not change the way you are treated and the results of these tests will not be returned to you. The research done with your tissue may help us learn more about crizotinib in combination with standard chemotherapy drugs and may help children who receive these drugs in the future.

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

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

Additional Studies to Consider for Patients with Neuroblastoma Only

For patients with neuroblastoma, we would like to test your bone marrow to see how much a gene called ALK can be found. 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, crizotinib, works in your body. These samples would be drawn at the same time when bone marrow is obtained prior to treatment with crizotinib and then every other cycle at the time of your disease evaluations. *These bone marrow samples are required from all patients with neuroblastoma.*

Additional Studies to Consider for Patients with Anaplastic Large Cell Lymphoma Only
For patients with lymphoma, 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 crizotinib. 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 crizotinib, on Day 15 of Cycle 1, and once in each additional cycle. These samples would be drawn at the same time as routine blood tests. *These blood and bone marrow samples are required from all patients with lymphoma.*

How long will I be in the study?

You may be in the study for up to 24 months or 35 cycles of therapy. Your doctor may decide to take you off study if any of the following occur:

- Your tumor gets worse
- The side effects of crizotinib in combination with standard chemotherapy drugs are too harmful for you
- You need a treatment that is not allowed on this study
- 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
- If you become pregnant

After you are finished taking crizotinib in combination with standard chemotherapy drugs, 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 crizotinib in combination with standard chemotherapy drugs can be evaluated by your doctor. Also, your doctor can discuss what follow-up care and testing could be most helpful for you.

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

If you choose to take part in this study, there is a risk that:

- **You may lose time at school or home and spend more time in the hospital or doctor's office than usual**
- **You may be asked sensitive or private questions which you normally do not discuss**

The crizotinib used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Risks and side effects related to crizotinib include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Crizotinib, more than 20 may have:
• **Vision Changes***
• **Discomfort in the eyes from light**
• **Constipation, diarrhea, nausea, vomiting**
• **Swelling of the body**
• **Tiredness, weakness**
• **Swelling and redness of the eyelids**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Crizotinib, from 4 to 20 may have:
• **Anemia which may cause tiredness, or may require blood transfusions**
• **Heartburn**
• **Sores in the throat or mouth which may cause difficulty swallowing**
• **Abnormal heartbeat or change in the heart rhythm or abnormal heartbeat which may cause fainting and may be life-threatening**
• **Headache**
• **Rash**
• **Weakness**
• **Muscle spasms**
• **Belly pain**
• **Infection, especially when white blood cell count is low**
• **Loss of appetite**
• **Dizziness**
• **Changes in taste**
• **Damage to nerves that may interfere with walking or organ function which may cause numbness, tingling, weakness or pain in muscles**

RARE, AND SERIOUS In 100 people receiving Crizotinib, 3 or fewer may have:
• **Swelling or damage of 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** • **Blood clot which may cause swelling, pain, shortness of breath** • **Change in the heart rhythm**

*Vision changes may include blurred vision, double vision, impaired vision, seeing spots before the eyes (floaters), flashing lights, brightness, rings, shadows, and/or streaking.

Risks and side effects related to <u>cyclophosphamide, topotecan</u> include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, Topotecan Hydrochloride, more than 20 and up to 100 may have:
• **Hair loss** • **Nausea, vomiting, loss of appetite** • **Sores in mouth which may cause difficulty breathing** • **Infection, especially when white blood cell count is low** • **Absence of menstrual period which may decrease the ability to have children** • **Blood in urine** • **Anemia which may require a blood transfusion** • **Constipation, diarrhea** • **Flu-like symptoms including fever, chills, body aches, muscle pain** • **Pain** • **Bruising, bleeding** • **Tiredness** • **Shortness of breath**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, Topotecan Hydrochloride, from 4 to 20 may have:
• **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions** • **Loss or absence of sperm which may lead to an inability to father children** • **Stuffy nose** • **Fluid around the heart** • **Headache** • **Cough** • **Rash**

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, Topotecan Hydrochloride, 3 or fewer may have:
• **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body** • **Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness** • **A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy** • **Swelling of the body including the brain which may cause dizziness, confusion** • **Scarring of the lungs**

Risks and side effects related to <u>myeloid growth factors (filgrastim (G-CSF) or pegfilgrastim)</u> include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving filgrastim or pegfilgrastim, more than 20 may have:
• **Nausea, vomiting[1]** • **Pain in bone**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving filgrastim or pegfilgrastim, from 4 to 20 may have:
• **Anemia which may cause tiredness, or may require transfusion** • **Damage to the lungs which may cause shortness of breath** • **Internal bleeding which may cause coughing up blood[1]** • **Swelling or tenderness of vessels[1]** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat[2]**

RARE, AND SERIOUS In 100 people receiving filgrastim or pegfilgrastim, 3 or fewer may have:
• **Rupture of the spleen leading to bleeding in the belly**

[1] Reported with filgrastim
[2] Reported with pegfilgrastim

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 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 an effective birth control method during the treatment and for 3 months after stopping the treatment. If a female caregiver is pregnant or suspects she is pregnant, she should not handle crizotinib. Check with your study doctor about what kind of birth control methods to use. Some methods might not be approved for use in this study. **If you think you/your partner might be pregnant, tell the study doctors right away. The NCI requires us to report the outcome of the pregnancy if you/your partner get pregnant while on this study. If your partner gets pregnant we will ask her permission to report the information.**

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.

Bone Marrow Examination (if required): You may be required to take bone marrow tests for diagnostic purposes. If this is the case, you will be informed of the risks associated with the procedure and your study doctor will obtain a separate consent form.

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 crizotinib in combination with standard chemotherapy 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. It is extremely unlikely that this treatment will cure your cancer. Because there is not much information about the effect of crizotinib in combination with standard chemotherapy 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**
- **Focusing on comfort care and quality of life instead of drugs to treat the tumor**

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**
- **Health Canada***
- **The Institutional Review Board (IRB) of this hospital**
- **The drug company partner (the company that makes crizotinib) and its staff**

* 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 crizotinib at no cost to you while you take part in the study. However, you or your health plan may need to pay for costs of the supplies and personnel who give you crizotinib and the other standard chemotherapy drugs. If, during the study, crizotinib becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide crizotinib for some reason. If this would occur, other possible options are:

- You might be able to get the crizotinib from the manufacturer or pharmacy but you or your insurance company may have to pay for it.

- If there is no crizotinib available at all, no one will be able to get more and the study would then close.

If a problem with getting crizotinib occurs, your study doctor will talk to you about these options.

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 will not be paid for taking part in this study. However, you may be reimbursed up to $100 (maximum) for inconveniences you experience as a result of your participation in the required pharmacokinetic studies as previously described above.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at **http://www.cancer.gov/clinicaltrials/learningabout.**

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. There are no plans for the study to pay for medical treatment for injuries. However, signing this form does not mean that you are giving up any legal rights to try to get compensation for injury.

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 regular 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.

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 http://www.childrensoncologygroup.org/index.php/family-handbook.

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 __ 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 _____

Physician or Responsible Investigator_____

Signature of Physician or Responsible Investigator_____

Date _____

Study Chart

You will receive crizotinib for 21 days. This 21-day period of time is called a cycle. The chart below shows what will happen to you during Cycle 1 and subsequent cycles. You will also receive standard chemotherapy drugs (topotecan and cyclophosphamide) on Days 1 to 5 of each cycle.

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 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 pregnancy test (for women of childbearing potential) • 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 a Patient Diary • Get a blood test for pharmacokinetic (PK) studies before taking crizotinib (All Parts) • Part C Only: Begin taking crizotinib twice a day. Keep taking crizotinib for 21 days, unless you are told to stop by your doctor. • Part D Only: Get crizotinib to take once in the evening on Day 1. • You will get chemotherapy on Day 1 through Day 5	**Day 1**	**Come into the clinic and do the following:** • Get a new Patient Diary • Get a physical exam by your doctor • All Parts: Keep taking crizotinib twice a day for 21 days if you do not have bad side effects and cancer is not getting worse. Call the doctor at _____ [insert phone number] if you do not know what to do. • Continue getting chemotherapy on Day 1 through Day 5.
Day 2	**Come into the clinic and do the following (Part D Only):** • Get a blood test for PK studies before taking the crizotinib morning dose. • Begin taking crizotinib twice a day. Keep taking crizotinib until Day 21, unless you are told to stop by your doctor.		
Days 2-20	**Come into the clinic and do the following:** • Get routine blood tests twice weekly • Return the Patient Diary at the end of each week • Get a physical exam by your doctor once weekly	**Day 2-20**	**Come into the clinic and do the following:** • Get routine blood tests once weekly
Days 15-21	**Come into the clinic and do the following (All Parts):** • Come into the clinic between Day 15 and day 21 to get blood tests done for PK studies		
Day 21	**Come into the clinic and do the following:** • Get routine blood tests • Get a physical exam by your doctor • Get an eye exam by your doctor • Get imaging scans (if required) • Get a test of bone marrow (if required) • Get a test of spinal fluid (if required) • Return the Patient Diary • Get a disease evaluation. 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 crizotinib. If you continue, please follow the schedule listed in the column under "Subsequent Cycles".	**Day 21**	**Come into the clinic and do the following:** • Get routine blood tests • Get urine tests (if you have neuroblastoma) • Get an eye exam (end of cycle 3 and then every 3 cycles) • Return the Patient Diary • Get imaging scans (if required) (every other cycle x 2, then every 3 cycles) • Get a bone marrow test (if required) (every other cycle x 2, then every 3 cycles) • Get a disease evaluation (every other cycle x 2, then every 3 cycles). 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".