CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

NCI Pediatric Early Phase Clinical Trials Network

A program funded by the National Cancer Institute of the National Institutes of Health

Pediatric Early Phase Clinical Trial Network (PEP-CTN) and Developmental Therapeutics (DVL) Chair
Brenda J. Weigel, M.D.
weige007@umn.edu

PEP-CTN and Developmental Therapeutics (DVL) Vice Chair
Elizabeth Fox, M.D.
foxe@email.chop.edu

PEP-CTN Operations Data & Statistics Center Director
Thalia Beeles, MPH
tbeeles@childrensoncologygroup.org

PEP-CTN Statistician
Charles G. Minard, Ph.D.
minard@bcm.edu

PEP-CTN and DVL Chair's Office
University of Minnesota/
Masonic Cancer Center
Masonic Children's Hospital
420 Delaware Street, SE
MMC 366
Minneapolis, MN 55455

P 612 626 5501
F 612 624 3913

Children's Oncology Group Group Chair
Peter C. Adamson, M.D.
adamson@email.chop.edu

Group Chair's Office
The Children's Hospital of Philadelphia
3501 Civic Center Blvd
CTRB 10060
Philadelphia, PA 19104

P 215 590 6359
F 215 590 7544

PEP-CTN Operations Data & Statistics Center
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

A National Cancer Institute supported member group of the National Clinical Trials Network

January 31, 2019

Martha Kruhm, M.S., RAC
Head, Protocol and Information Office (PIO)
National Institutes of Health/NCI/DCTD/CTEP/OIB/PIO
9609 Medical Center Drive, OIB MSC 9742, Room #5W246
Bethesda, MD 20892-9742

Dear Ms. Kruhm,

Enclosed please find Amendment #10 for **ADVL1211**, *A Phase 1 Study of XL184 (Cabozantinib) in Children and Adolescents with Recurrent or Refractory Solid Tumors, including CNS Tumors*.

The protocol has been amended in response to the Request for Amendment from Dr. Malcolm Smith, dated December 20, 2018, in which COGC transitions to PEP-CTN. Additional administrative and editorial changes were included for consistency.

Sincerely,

Patrice Navrude, MS, Protocol Coordinator for
Meredith Chuk, M.D., **ADVL1211 Study Chair**, and
Brenda Weigel, M.D., PI, PEP-CTN

SUMMARY OF CHANGES

The following specific revisions have been made to the protocol and informed consent document. Additions are in **boldfaced font** and deletions in ~~strikethrough font~~.

SUMMARY OF CHANGES PROTOCOL DOCUMENT:

#	Section	Comments
1.	General	The version date and amendment number have been updated throughout the protocol. COGC has been replaced with PEP-CTN. PEP-CTN logo has been added throughout the protocol.
2.	Title Page	PEP-CTN has replaced COGC as the lead organization. Supplemental COG sites have been removed.
3.	Study Committee	Study Committee members contact information has been updated **PEP-CTN Operations and Data/Statistics**
4.	Certificate of Confidentiality	"~~The Children's Oncology Group has received~~ **This trial is covered by** a Certificate of Confidentiality from the federal government…"
5.	13.3	~~CTEPAERS@childrensoncologygroup.org.~~ **PEPCTNAERS@childrensoncologygroup.org**
6.	14.4	Developmental therapeutics has been replaced with COG PEP-CTN to show that the study will be monitored in accordance with PEP-CTN polices for data and safety monitoring.
7.	Appx XVI	CTEP and CTSU registration procedures have been added.

SUMMARY OF CHANGES INFORMED CONSENT DOCUMENT:

#	Section	Comments
1.	General	The version date has been updated throughout. COGC and Phase I Consortium have been replaced with PEP-CTN. PEP-CTN logo has been added throughout.
2.	Certificate of Confidentiality	~~The Children's Oncology Group has received~~ This trial is covered by a Certificate of Confidentiality from the federal government…

Activated: October 15th, 2012
Closed: February 27, 2015

Version Date: 1/31/19
Amendment #: 10

CHILDREN'S ONCOLOGY GROUP

ADVL1211

A PHASE 1 STUDY OF XL184 (CABOZANTINIB) IN CHILDREN AND ADOLESCENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS, INCLUDING CNS TUMORS

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

STUDY CHAIR
Meredith Chuk, MD
Mark O Hatfield-Warren Grant Magnuson Clinic
Pediatric Oncology Branch, NCI, CCR
10 Center Dr., MSC 1101
Building 10, CRC, Room 1-5750
Bethesda, MD 20892-1928
Phone: (301) 796-5006
Email: meredith.chuk@fda.hhs.gov

For COG PEP-CTN Operations and Statistics & Data Center Contacts See:
http://members.childrensoncologygroup.org

TABLE OF CONTENTS

STUDY COMMITTEE

STUDY CHAIR
Meredith Chuk, MD
Mark O Hatfield-Warren Grant Magnuson Clinic
Pediatric Oncology Branch, NCI, CCR
10 Center Dr., MSC 1101
Building 10, CRC, Room 1-5750
Bethesda, MD 20892-1928
Phone: (301) 796-5006
Email: meredith.chuk@fda.hhs.gov

STUDY VICE CHAIR
Brigitte Widemann, MD
Mark O Hatfield-Warren Grant Magnuson Clinic
Pediatric Oncology Branch, NCI, CCR
10 Center Dr., MSC 1101
Building 10, CRC, Room 1-5750
Bethesda, MD 20892-1928
Phone: (301) 496-7387
Fax: (301) 480-8871
Email: widemanb@mail.nih.gov

SENIOR STATISTICIAN
Charles Minard, PhD
Baylor College of Medicine
One Baylor Plaza, BCM 122
Houston, TX 77030
Phone: (713) 798-2353
Fax: (713) 798-2816
Email: minard@bcm.edu

STATISTICIAN
Xiaowei Liu
Statistics
Children's Oncology Group - Operations Center
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1535
Fax: (626) 445-4334
Email: xwliu@childrensoncologygroup.org

STUDY PHARMACIST
Brooke Bernhardt, PharmD
Pharmacy
Baylor College of Medicine
6621 Fannin Street, MC 2-2510
Houston, TX 77030
Phone: (832) 824-5292
Fax: (832) 825-5261
Email: mbbernha@txch.org

STUDY COMMITTEE MEMBERS
Brenda J. Weigel, MD
Chair, Developmental Therapeutics
Hematology/Oncology
University of Minnesota Medical Center - Fairview
Department of Pediatrics
420 Delaware Street, SE MMC 366
Minneapolis, MN 55455
Phone: (612) 626-5501
Fax: (612) 624-3913
Email: weige007@umn.edu

Elizabeth Fox, MD
Vice Chair, Developmental Therapeutics
Children's Hospital of Philadelphia
Pediatrics/Division of Oncology
3501 Civic Center Blvd.
CTRB-4016
Philadelphia, PA 19104
Phone: (267) 425-3010
Fax: (267) 425-0113
Email: foxe@email.chop.edu

Yaël P. Mossé, MD
Division of Oncology
Children's Hospital of Philadelphia
CTRB Room 3056
3501 Civic Center Blvd.
Philadelphia, PA 19104
Phone: (215) 590-0965
Fax: (267) 426-0685
E-mail: mosse@chop.edu

Maya Beth Lodish, MD
Department of Pediatrics
Division of Pediatric Endocrinology, Mission Hall
550 16th Street
4th Floor, Box 0434
San Francisco, CA 94143
Phone: (415) 476-3310
Fax: (415) 476-5356
Email: Maya.lodish@ucsf.edu

AeRang Kim, MD
Children's National Medical Center
111 Michigan Avenue, N.W.
Washington, DC 20010
Phone: (202) 476-4744
Fax: (202) 476-5685
Email: aekim@childrensnational.org

STUDY COMMITTEE

PROTOCOL COORDINATOR
Patrice Navrude, MS
Children's Oncology Group – Operations Center
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1607
Fax: (626) 445-4334
E-mail: pnavrude@childrensoncologygroup.org

STUDY NURSE
Janet Gammon, RN, BSN
Hospital for Sick Children
Hematology/Oncology
555 University Ave.
Toronto, ON M5G 1X8
Phone: (416) 813-5861
Fax: (416) 813-5574
E-mail: janet.gammon@sickkids.ca

For PEP-CTN Operations and
Data/Statistics contacts see:
http:members.childrensoncologygroup.org

AGENT NSC# AND IND#'s
Cabozantinib (XL184, NSC# 761968)

Sponsor: CTEP

SEE SECTION 8.4.6 FOR SPECIMEN SHIPPING ADDRESS

This trial is covered by 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 mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

ABSTRACT

XL184 (cabozantinib) is an oral small molecule inhibitor of multiple tyrosine kinases including primarily MET, VEGFR2 and RET. Overexpression or dysregulation of these tyrosine kinases contribute to the pathogenesis of a number of pediatric and adult solid tumors. XL184 has been shown to inhibit these tyrosine kinases *in vivo* and has shown dose-dependent tumor suppression in a variety of xenograft models. Treatment with XL184 has also shown antitumor activity in clinical trials in adults assessing its activity in several tumor types. This is a limited dose-escalation study of XL184 in pediatric and adolescent patients with relapsed or refractory solid tumors including CNS tumors. We will evaluate the MTD or recommended phase 2 dose and toxicity of XL184 administered orally on a continuous dosing schedule in the pediatric population. We will also preliminarily define the antitumor effects of XL184 within the confines of a phase I study, with a particular focus on medullary thyroid cancer (MTC) given the activity of XL184 seen in adult patients with MTC. Pharmacokinetic and pharmacodynamic studies will be conducted to further define the properties of XL184 in pediatric and adolescent patients.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Time	**Agent**
Days 1-28	Oral XL184*

*Refer to dosing nomogram in Appendix II for dosing schedule.

Treatment will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. Therapy may otherwise continue provided that the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose of XL184 (cabozantinib) administered orally to children with refractory solid tumors including CNS tumors.

1.1.2 To define and describe the toxicities of XL184 (cabozantanib) administered on this schedule.

1.1.3 To characterize the pharmacokinetics of XL184 (cabozantanib) in children with refractory solid tumors.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of XL184 (cabozantanib) within the confines of a Phase 1 study.

1.2.2 To assess the biologic activity of XL184 (cabozantanib).

1.2.3 To assess the biomarker response (CEA and calcitonin) in patients with medullary thyroid cancer treated with XL184.

1.2.4 To evaluate overall survival from study entry through a five-year follow-up period.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Overexpression or dysregulation of certain receptor tyrosine kinases (RTKs) including VEGFR, MET and RET have been implicated in the pathogenesis of a variety of tumors. Molecularly targeted therapy against these receptors can interrupt this signaling leading to tumor shrinkage and in some cases prolonged survival as seen in colorectal and renal cancers.[1] These RTKs are overexpressed in a variety of pediatric cancers; VEGFR in pediatric sarcomas[2] and MET in osteosarcoma, glioma, and papillary thyroid cancer[3,4]. Activating RET mutations are the driving force for the development of medullary thyroid cancer (MTC) in patients with MEN2, where tumors can appear early in childhood, particularly in MEN2B.[5]

XL184 is a small molecule inhibitor of multiple tyrosine kinases including primarily MET, VEGFR2 and RET and to a lesser extent KIT and TIE-2. In vitro models also show that XL184 also inhibits AXL a RTK thought to be involved in gliomagenesis.[6]

Selective inhibition of VEGFR2 may lead to increased invasiveness and metastasis.[7] Preclinical models suggest that inhibition of VEGFR2 together with c-MET may not only decrease tumor size, but decrease invasiveness and metastases.[8,9]

2.2 Preclinical Studies

2.2.1 Antitumor Activity

After treatment with XL184 in *in vivo* models, immunohistochemical analysis showed significant and sustained inhibition of MET, RET and VEGFR2 in solid tumors expressing high levels of these RTKs and inhibition of VEGFR2 and TIE-2 in lung lysate.[6]

XL184 has shown dose-dependent inhibition of tumor growth in a variety of xenograft models including human breast, lung and MTC, transgenic RIP-Tag2 model of pancreatic cancer and rat glioma.[6] *In vivo* models showed that plasma exposures of XL184 were similar across the models tested and that peak concentrations between 2 and 27 mcM were required for target inhibition and anti-tumor activity. However, much lower trough concentrations (as low as 0.1mcM) were seen in these models suggesting that sustained elevated plasma levels of XL184 are not needed for efficacy.[6]

XL184 has also been shown to block both osteoblastic and osteolytic progression of murine xenograft prostate tumors that express both MET and the VEGF co-receptor NP-1. [7]

2.2.2 Animal Toxicology

Cardiovascular toxicology studies in beagle dogs showed no significant effects on systolic blood pressure, heart rate, left ventricular pressure or QT/QTc prolongation at doses of 150 mg/kg and 1000 mg/kg. There was a transient increase in diastolic blood pressure (22%) that led to a 12% increase in mean arterial pressure at the 1000 mg/kg dose.[6]

In chronic dosing toxicity studies, XL184 was well tolerated in rats and dogs with daily dosing for 26 weeks.[7]

2.2.3 Preclinical Pharmacokinetic Studies

Preclinical pharmacology showed that XL184 is metabolized by demethylation, oxidation and glucuronidation. It is an inhibitor of CYP2C8, CYP2C9*3 and CYP2C19 isoenzymes *in vitro* and is a substrate for CYP3A4 metabolism. CYP3A4 induction was seen *in vitro* in one of two studies with human hepatocytes but not with HEPG2 cell lines. XL184 is highly protein-bound (98%).[6]

2.3 Adult Studies

2.3.1 Phase 1 Studies

As of May 2011, there have been 1333 adult subjects treated with XL184 in a variety of clinical trials. In the initial phase I study in adults, 85 patients were treated at doses ranging from 0.08 to 11.52 mg/kg/day with subsequent cohorts receiving fixed doses of 175 mg, 250 mg and 265 mg daily. The MTD in this study was 175 mg po daily (salt form; equivalent to 140 mg freebase form). However, a significant percentage of patients receiving this dose required dose-reductions for toxicity and a dose of 125 mg (100 mg freebase form) was found to be better tolerated. Other studies with XL184 have also found that patients required significant dose-reductions with long-term treatment and based on tolerability and response data at doses of 40 mg per day[10], starting doses as low as 60 mg per day

are currently being studied in adults (personal communications Exelixis;[11,12]).

DLTs in adult phase I studies were grade 3 lipase elevation, palmar-plantar erythrodysesthesia (PPE), and AST/ALT elevation at 11.25 mg/kg, grade 3 PPE and elevation of AST at 250 mg qd, and grade 2 and 3 mucositis at 265 mg per day. Other common but non dose-limiting toxicities seen with XL184 were fatigue, diarrhea, anorexia, nausea, constipation, vomiting, rash, hypertension, hypopigmentation of hair, and mucositis. Side effects associated with inhibition of VEGF signaling have also been seen including thrombotic events, hypertension, hemorrhage, and rare cases of GI perforation and rectal/perirectal abscess.[6,11,12]

Thirty-seven patients with MTC were treated on the initial phase I study. 17/35 (49%) had tumor shrinkage > 30% on at least one evaluation, 10 patients (29%) had a confirmed partial response and 15/37 (41%) had stable disease ≥ 6 months. Responses were seen in patients treated at doses between 75 and 175mg and in patients with and without RET mutations. Patients with other tumor types experienced stable disease for at least 3 months including colorectal carcinoma (n=3), sarcoma (n=2), melanoma (n=2), carcinoid (n=2), and adenocyctic, follicular thyroid, papillary thyroid, parotid, appendiceal carcinoma, papillary renal cell carcinoma and mesothelioma.[6,11-13]

2.3.2 Phase 2 and 3 Studies

In a phase II study in patients with relapsed glioblastoma multiforme (GBM), patients were treated with either 125 or 175 mg of XL184 on a daily schedule. Interim results from 124 patients revealed progression free survival at 6 months (PFS6) in the 175 mg cohort was 21% for all patients. Overall response rate (ORR) in patients without prior antiangiogenic therapy (n=34) was 21% and 8% in patients who had previously received antiangiogenic drugs. Median duration of response was 5.9 months (range 1.9-12.8). In the 125 mg cohort, ORR in patients who had not received prior antiangiogenic therapy (n=25) was 32% and mediation duration of response had not been met. The most frequent grade 3 /4 AEs were fatigue, diarrhea, transaminitis, headache, and PPE. Patients in the 125 mg cohort had fewer dose reductions and lower rates of drug discontinuation with similar signs of activity.[14]

In a phase 2 randomized discontinuation study in patients with advanced solid tumors 531 patients have been enrolled as of August 2011. Forty patients (8%) have had a confirmed PR, 17 ovarian, 7 prostate, 6 NSCLC, 4 melanoma, 3 HCC, 2 breast and 1 SCLC. Fifty four percent of patients experienced disease control (PR + SD) at week 12.[6,15]

Data from an ongoing phase III study in adults with medullary thyroid carcinoma (MTC) showed an increase in progression free survival in the XL184 arm compared to placebo. In this study 330 patients (median age 55 yrs (67% male) with RET mutation status: pos 48%; negative 12%; unknown 39%) with unresectable, locally advanced or metastatic MTC were randomized 2:1 to receive either XL184 or placebo in a double-blind randomized fashion. Statistically significant PFS prolongation of 7.2 months was observed; median PFS for XL184 was 11.2 mo vs. 4.9 months with placebo ($p<0.0001$). The ORR was 28% for XL184 and 0% for placebo ($p<0.0001$).[16]

Ongoing studies with XL184 in adults include phase II studies for various solid

tumors including prostate cancer, neuroendocrine tumors, breast cancer and phase III studies in adults with MTC, and adults with prostate cancer.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Pharmacokinetic studies in adults show dose-proportional increases in maximal concentration (C_{max}) and drug exposure (AUC) from 0.08 to 11.52 mg/kg. Steady-state (Day 19) C_{max} in the initial phase I study at the MTD of 175mg capsule daily (n=19) was 2,310 ng/ml and AUC was 41,600 ng·h/ml. Steady-state C_{max} for patients with GBM treated with single agent XL184 at a dose of 175mg/d was 1950 ± 1050 ng/ml (n=27) and 1350 ± 589 ng/ml for patients treated with 125mg/d (n=78). Half-life is reported to be between 58 and 136 hours.[6,11,13]

Effect of Food on the Bioavailability of cabozantinib in Healthy Adult Subjects (Study XL184-004). Study XL184-004 is a Phase 1, open-label, randomized, single-dose, two-treatment, two way crossover study to assess the effect of food on the bioavailability of cabozantinib in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned treatment of Test (175 mg cabozantinib, dosed as one 100 mg capsule and three 25 mg capsules 30 minutes after administration of a high fat breakfast) or Reference (175 mg cabozantinib, dosed as one 100 mg capsule and three 25 mg capsules under fasting conditions). Blood samples were collected up to 504 hours post dose for each subject after each treatment to assess plasma cabozantinib pharmacokinetics.

Based on the preliminary PK data from 46 subjects who completed both treatments, a high fat meal did not appear to alter the terminal t1/2, z of cabozantinib [mean t1/2, z : 131 hours (fed) vs. 128 hours (fasted)]. The high fat meal significantly increased the median tmax to 6 hours from 4 hours (fasted). The high fat meal also significantly increased both the cabozantinib Cmax and AUC values by 39% and 56%, respectively. The geometric mean ratio of Cmax fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of AUC0-last fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

Preliminary results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib (e.g., chronic use of modafinil) should be avoided because of its potential to reduce cabozantinib exposure. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. In addition, caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Pharmacodynamic evaluation showed significantly increased PGF, VEGF-A, soluble MET and EPO and decreased sVEGFR2 in patient plasma after initiation of treatment with XL184.[11] Preliminary analyses showed that baseline levels of Ang2, EPO and OPN significantly correlated with tumor response in a variety of tumor types (MTC, melanoma, colorectal carcinoma and others).[6] Analysis of hair samples as surrogate markers revealed significant decreases in phosphorylated MET and downstream targets AKT and ERK (25-54%, 20-59% and 29-49% decrease from baseline, respectively).[6]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There is no prior experience with XL184 in the pediatric population.

2.5 Overview of Proposed Pediatric Study

This is a phase 1 limited dose-escalation study of XL184 (cabozantinib) in pediatric and adolescent patients with recurrent or refractory solid tumors including CNS tumors. The primary objectives of this study are to identify a maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D), characterize the toxicity profile and describe the pharmacokinetics of XL184 in pediatric and adolescent patients with solid tumors.

Patients ages 2 to 18, inclusive, with refractory or recurrent solid tumors including CNS tumors will be eligible. Dosing will be based on body surface area (BSA) and rounded to nearest tablet to achieve the most accurate weekly doses. Doses on some days of the week may differ. Refer to dosing nomogram in Appendix II for details. XL184 will be administered orally at a starting dose of 30 mg/m^2/day, which is roughly equivalent to the well tolerated 60 mg daily dose currently being evaluated in several adult studies. Doses will then be escalated to 40 mg/m^2 and 55 mg/m^2 in subsequent cohorts. One cycle will be 28 days in length and dosing will be continuous. The dose will be escalated using a rolling six design.

The maximum tolerated dose (MTD) will be determined from toxicities seen during the first cycle of therapy. The MTD will be the dose level immediately below the level in which ≥ 2 out of 2 to 6 patients experience a DLT. To be eligible for the toxicity endpoint, patients must have received $\geq 85\%$ of the prescribed study medication or have experienced a DLT during cycle 1.

Doses will not be escalated beyond 55 mg/m^2. If an MTD is not identified, a recommended dose will be established based on tolerability, pharmacokinetic parameters and response, if applicable. After the MTD or recommended phase 2 dose is determined in Part A, an additional 6 patients may be enrolled in an expansion phase and treated at this dose to gain additional PK and toxicity data in the pediatric population. Every attempt will be made to treat a minimum of 6 patients < 12 years of age and 6 patients ≥ 12 years of age at the MTD or recommended phase 2 dose. Given the activity seen in patients with medullary thyroid carcinoma (MTC), an additional cohort for MTC patients (Part B) will be open for enrollment if slots are filled for Part A, with the goal of enrolling at least four patients with MTC.

Intra-patient dose-escalation will be allowed for patients with medullary thyroid carcinoma (MTC) remaining on study once an MTD or recommended dose is determined to allow patients who may be on study for extended periods of time, i.e. patients with MTC, the opportunity to receive the recommended dose.

Pharmacokinetic sampling will be performed before drug administration, day 21-cycle 1 for steady state parameters, pre C3, if possible at any time a patient experiences a DLT, pre C4 and with each disease evaluation for patients enrolled after Amendment #5A. Pharmacokinetic parameters including maximum concentration (C_{max}) with the first dose and at steady state, area under the concentration time curve (AUC), apparent clearance and trough concentration will be measured or calculated.

Given the antiangiogenic targeting of XL184 and concern for possible impact on growth in children, linear growth will be monitored and a baseline tibial x-ray for all patients, then prior to C2 and C5 and then 6 months later for patients with open growth plates remaining on study. MRIs will be obtained for patients with abnormal radiograph findings of the growth plate.

Disease evaluations will be conducted after every other cycle starting after the end of cycle 1 and then every third cycle if the patient has stable disease or better for 2 sets of restaging.

Pharmacodynamic studies looking at markers of angiogenesis and components of the cMET pathway will be conducted. VEGF-A, soluble VEGFR2 (sVEGFR2), hepatocyte growth factor (HGF) and soluble MET (sMET) will be measured prior to and following XL184 dosing and expression of c-MET in archival tumor samples will be measured.

2.6 Amendment to Open PK Expansion (January 2014)

As of January 2014, a total of 29 patients have been enrolled on ADVL1211: 6 patients at Dose Level 1, 11 patients at Dose Level 2 and 12 patients at Dose Level 3. During the dose escalation phase (Part A) during Cycle 1, dose-limiting toxicities (DLTs) occurred in 0/6 patients at 30 and 40 mg/m^2 and 1/6 patients at 55 mg/m^2 (Grade 3 fatigue and headache). Other Cycle 1 DLTs in expansion cohorts included Grade 2 palmar plantar erythrodysesthesia (PPE) and oral mucositis in 1 patient at 40 mg/m^2, Grade 3 proteinuria and Grade 2 hypertension (HTN) in 1 patient at 55 mg/m^2, and Grade 3 HTN and reversible posterior leukoencephalopathy syndrome in 1 patient at 55mg/m^2. Later cycle DLTs occurred in 10 patients at all dose levels and included Grade 3 weight loss (n=2), Grade 3 PPE (n=2), Grade 3 and 4 lipase increase (n=1 each), Grade 4 neutropenia (n=1), Grade 2 fatigue (n=1), Grade 2 arthralgia (n=1) and Grade 3 anorexia, dyspnea, skin ulcer (n=1).

Pharmacokinetic studies conducted in 18 patients during the dose-escalation phase showed

that cabozantinib exposure was not dose proportional. The mean ± SD steady state AUC_{0-24h} at 30 mg/m^2 (n=6), 40 mg/m^2 (n=6) and 55 mg/m^2 (n=6) was 31.9 ± 7.8, 33.3 ± 11.3 and 33.7 ± 15 µg•h/mL, respectively. Given the toxicities seen at Dose Level 3 and in later cycles and comparable exposure of cabozantinib, the recommended Phase 2 dose for further evaluation in pediatric patients with solid tumors is 40 mg/m^2 (Dose Level 2) and enrollment will be expanded at this dose level to gain additional pharmacokinetic and safety information in at least 6 patients under the age of 12 and 6 patients between 12 and 18 years of age. *We will also collect trough levels with each disease evaluation in all patients enrolled after Amendment #5A to gain additional information about steady state pharmacokinetics*.-**COMPLETE**

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the page CTSU OPEN (Oncology Patient Enrollment Network) to ensure that a reservation for the study is available. To access the Slot Availability page:

1. Log in to https://open.ctsu.org/open/
2. From the home page, select **Create New Registration**. *The ENROLL Create New page appears.*
3. Select the Protocol Number and Click the **Slot Availability link**. *The Slot Availability window will open.*

3.2 IRB Approval

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

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

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

3.3 **Patient Registration**

Prior to enrollment on study, 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 following the steps in Section 3.1 above 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) the COG screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 **Eligibility Checklist**

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be 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. 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 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 ≥ 2 and ≤ 18 years of age at the time of study enrollment.

4.1.2 Body Surface Area (BSA): Patients must have a body surface area ≥ 0.44 m^2 when enrolling on dose level -1. Patients must have a body surface area ≥ 0.35 m^2 when enrolling on dose levels 1, 2, or 3.

4.1.3 Diagnosis:

Part A: Patients with relapsed or refractory solid tumors (excluding medullary thyroid cancer) including CNS tumors and malignant melanoma are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.

Part B: Patients with medullary thyroid cancer (MTC), with or without bone marrow involvement, will be eligible for Part B. These patients will be enrolled at Dose Level 2, the recommended Phase 2 Dose determined in the dose escalation part of the study.

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

4.1.5 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.

4.1.6 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. 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.

4.1.7 Prior Therapy

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

a. Myelosuppressive chemotherapy:
At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).

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. Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody. (See table on DVL homepage listing monoclonal antibody half-lives.)

f. XRT: At least 14 days after local palliative XRT (small port); 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.

g. Stem Cell Infusion without TBI: No evidence of active graft vs. host disease and at least 56 days must have elapsed after transplant or stem cell infusion.

4.1.8 Organ Function Requirements

4.1.8.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors 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 4.1.8.1.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. At least 5 of every cohort of 6 patients with a solid tumor must be evaluable for hematologic toxicity in the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

4.1.8.2 Adequate Renal Function Defined as:
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
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.

- Urine protein: ≤ 30 mg/dl in urinalysis or ≤ 1+ on dipstick, unless quantitative protein is < 1000 mg in a 24 h urine sample.

4.1.8.3 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 ≥ 2.8 g/dL.

4.1.8.4 Adequate coagulation status Defined As:
- PT and INR ≤ 1.5x ULN

4.1.8.5 Adequate Pancreatic Function Defined As:
- Serum amylase ≤ 1.5 x ULN and
- Serum lipase ≤ 1.5 x ULN

4.1.8.6 Adequate Blood Pressure Control defined as:
A blood pressure (BP) ≤ the 95th percentile for age, height, and gender (Appendix VIII) measured as described in Section 6.4, and not receiving medication for treatment of hypertension. Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP (See Section 6.4).

4.1.8.7 Central Nervous System Function Defined as:
Patients with seizure disorder may be enrolled if receiving non-enzyme inducing anticonvulsants and well controlled. See Appendix XIII for a list of recommended non-enzyme inducing anticonvulsants.

4.1.8.8 Adequate Cardiac Function Defined As:
- No history of congenital prolonged QTc syndrome, NYHA Class III or IV congestive heart failure (CHF)
- No clinically significant cardiac arrhythmias, stroke or myocardial infarction within 6 months prior to enrollment
- QTc ≤ 480 msec. Note: 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). See Appendix XV for a list of drugs that prolong QTc.

4.1.9 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.

4.1.10 Archival tumor tissue slides from either initial diagnosis or relapse must be sent per Section 8.5.1.2 and Appendix XI. 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 due to risks of fetal and teratogenic adverse events as seen in animal/human studies. 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 two methods of birth control- a medically accepted barrier method of contraceptive method (e.g., male or female condom) and a second effective method of birth control- during protocol therapy and for at least 4 months after the last dose of XL184. Abstinence is an acceptable method of birth control.

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.

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 active agents: Patients must not be receiving any of the following potent CYP3A4 inducers or inhibitors: erythromycin, clarithromycin, ketoconazole, azithromycin, itraconazole, grapefruit juice or St. John's wort. A list of other known CYP3A4 inducers and inhibitors that should be discontinued prior to initiation of protocol therapy and should be avoided during study therapy if reasonable alternatives exist is included in Appendix IX.

4.2.2.6 Patients who are receiving systemic treatment anticoagulation are not eligible. Patients receiving prophylactic systemic anticoagulation will be allowed as long as eligibility PT/INR requirements are met (See Section 4.1.8.4).

4.2.2.7 Enzyme-inducing Anticonvulsants: Patients must not have received enzyme–inducing anticonvulsants within 14 days prior to enrollment (See Appendix XIII for a list of unacceptable enzyme inducing anticonvulsants).

4.2.2.8 QTc Agents: Patients who are receiving drugs that prolong QTc are not eligible (See Appendix XV for a list of agents).

4.2.3 Patients must be able to swallow intact tablets. Patients who cannot swallow intact tablets are not eligible.

4.2.4 Patients with active bleeding are not eligible. Specifically, no clinically significant GI bleeding, GI perforation, intra-abdominal abcess or fistula for 6 months prior to enrollment, no hemoptysis or other signs of pulmonary hemorrhage for 3 months prior to enrollment.

4.2.5 Patients with evidence of an acute intracranial or intratumoral hemorrhage on CT or MRI are not eligible (patients with evidence of resolving hemorrhage will be eligible).

4.2.6 Surgery: Patients who have had or are planning to have the following invasive procedures are not eligible:

- Major surgical procedure, laparoscopic procedure, open biopsy or significant traumatic injury within 28 days prior to enrollment.
- Central line placement or subcutaneous port placement is not considered major surgery but must be placed at least 3 days prior to enrollment for external lines (e.g. Hickman or Broviac) and at least 7 days prior to enrollment for subcutaneous port.
- Core biopsy within 7 days prior to enrollment.
- Fine needle aspirate within 7 days prior to enrollment.

- Surgical or other wounds must be adequately healed prior to enrollment

4.2.7 Patients on antihypertensive therapy for control of blood pressure at the time of enrollment are not eligible.

4.2.8 Patients with any medical or surgical conditions that would interfere with gastrointestinal absorption of this oral agent are not eligible.

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

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

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Time	**Agent**
Days 1-28	Oral XL184*

*Refer to dosing nomogram in Appendix II for dosing schedule.

XL184 will be administered orally at approximately the same time as prescribed. XL184 should be taken on an empty stomach; patients should fast 2 hours before and 1 hour after taking the drug. Tablets should not be crushed or chewed; tablets should be swallowed whole. See also Section 9.1.6 for medications and foods to be avoided.

A cycle of therapy is considered to be 28 days.

Drug doses should be adjusted based on the BSA calculated from height and actual body weight measured within 7 days prior to the beginning of each cycle, and according to the dosing nomogram (see Appendix II). Sites will fill out the number of prescribed tablets per day in the patient diary (see Appendix III). Patients must complete the patient diary with the date, time and number of XL184 tablets taken each day. The patient diary should be reviewed after completion of each treatment cycle.

If a patient vomits after the dose of XL184 is administered, the dose should not be repeated.

If a dose of XL184 is missed and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. If more than 6 hours have passed since the scheduled dosing time, the patient should not take the missed dose but should wait and take the next regularly scheduled dose.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease, has again met laboratory parameters as defined in the eligibility sections 4.1.8.1- 4.1.8.3 and 4.1.8.5, and has not experienced study-drug related adverse events warranting permanent discontinuation.

Patients who have a delay in starting subsequent cycles for resolution of toxicity should also have the required observations in Section 8.1 until the start of the next cycle.

5.3 Dose Escalation Schema

5.3.1 *Inter-Patient Escalation- (Part A)* COMPLETE

The starting dose will be 30 mg/m^2 (Dose Level 1) with dose levels for subsequent groups of patients as follows.

Dose Level	*XL184 Dose (mg/m^2 po daily)*
-1	*23*
1*	***30***
2	*40*
3	*55*

** Starting Dose Level*

There will be no escalations beyond dose level 3 (55 mg/m^2).

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 23 mg/m^2 (Dose Level -1).

With Amendment #5A, patients enrolled onto Part A of the study will be treated at the recommended Phase 2 dose, which has been determined to be Dose Level 2 (40 mg/m^2).

5.3.2 *Part B: Patients with medullary thyroid cancer (MTC) can be accrued to a separate stratum if there are no available slots on Part A. These patients will be enrolled at one dose level below the dose level at which patients on Part A are actively enrolling, or at the starting dose level (Dose Level 1) if dose escalation has not yet occurred.* COMPLETE

With Amendment #5A, patients enrolled onto Part B of the study will be treated at the recommended Phase 2 dose, which has been determined to be Dose Level 2 (40 mg/m^2).

5.3.3 *Intra-Patient Escalation (Patients with MTC only)*

Intra-patient dose escalation will be allowed for patients with MTC remaining on study in cycles of therapy subsequent to Cycle 1, once an MTD or recommended Phase 2 dose is identified, if the patient has not experienced dose-limiting toxicity at the dose at which they began therapy. Patients who are one dose level below the MTD can escalate to the MTD. Patients who are more than one dose level below the MTD can escalate one dose level per cycle until they reach the MTD as long as they do not experience a DLT when escalating. Sites have to confirm with the Study Chair and the COG Phase 1 Operations office that their patient may proceed with an intra-patient dose escalation following the completion of Cycle 1 or subsequent cycles. COMPLETE

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 XL184. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy. Any drug-related toxicity that requires a dose reduction in Cycle 1 will also be considered a DLT.

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

5.5.1 Non-Hematological Dose-Limiting Toxicity

5.5.1.1 Any Grade 3 or Grade 4 non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting of < 3 days duration
- Grade 3 diarrhea ≤ 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT/bilirubin, that return to levels that meet initial eligibility criteria or baseline within 7 days of study drug interruption and that does not recur upon re-challenge with XL184. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L. See section 6.6 for dose modifications for liver toxicity.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation
- Grade 3 asymptomatic amylase or lipase elevation that resolves to ≤ Grade 1 within 7 days of study drug interruption and that does not recur upon re-challenge with XL184. See section 6.7 for dose modifications for pancreatic toxicity.
- Grade 3 proteinuria (urine protein/creatinine (P/C) ratio > 1.9) unless it is confirmed with a second measurement within 72 hours.

5.5.1.2 Dose-limiting hypertension

- Any Grade 4 hypertension
- A blood pressure >25 mmHg above the 95th percentile for age, height, and gender (Appendix VIII) confirmed by repeated measurement is dose limiting.
- In patients who begin antihypertensive therapy a blood pressure > 10 mmHg but ≤ 25 mmHg above the 95th percentile for age, height, and gender (Appendix VIII) for > 14 days is dose limiting.

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

5.5.1.4 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.

5.5.1.5 Any toxicity requiring interruption of study drug during a cycle of therapy

for ≥ 7 days or which recurs upon drug challenge.

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

5.5.2 Hematological dose limiting toxicity

5.5.2.1 Hematological dose limiting toxicity is defined as:

- In patients evaluable for hematological toxicity (see Section 4.1.8.1), Grade 4 thrombocytopenia (platelet count < 25,000/mm^3) or Grade 4 neutropenia (see Section 6.1), not due to malignant infiltration.
- Myelosuppression that causes a delay of > 14 days between treatment cycles.
- In patients with CNS tumors, requirement of platelet transfusion(s) for platelets ≤ 50,000/mm^3 on more than one occasion during a cycle will be considered a DLT. *I.e.* If a patient with a CNS tumor requires more than one platelet transfusion to achieve a count > 50,000/mm^3 (poor initial response, etc.) on one occasion this is not a DLT, but if it occurs again during the cycle, it will be dose limiting.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor. If a patient's dose is reduced due to toxicity, any future XL184 total weekly dose should not exceed a previously un-tolerated dose.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 If a patient experiences dose-limiting Grade 4 neutropenia or thrombocytopenia, the treatment will be withheld. Counts should be checked every 3 - 4 days for thrombocytopenia and every other day for neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level (See Appendix IIB). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.1.2 If dose-limiting toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.1.3 Two dose reductions will be allowed for toxicity. If a patient experiences a dose-limiting toxicity after two dose reductions, they must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.5.1, the treatment will be withheld. If the toxicity resolves to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level (See Appendix IIB). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.2.2 If dose-limiting toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.2.2.1 The exception to this is Grade 3 weight loss as it is unlikely that the patient would return to baseline within 14 days. Patients who experience Grade 3 weight loss may resume study medication after 14 days with a dose-reduction (see Appendix II-B) if the patient is deriving benefit from therapy, the weight loss has stabilized and the treating physician feels it is in the best interest of the patient. Patients should be removed from protocol therapy if their weight loss is ≥ 20% from baseline and persists for ≥ 28 days after the introduction of supplemental NG/G tube feeding or TPN.

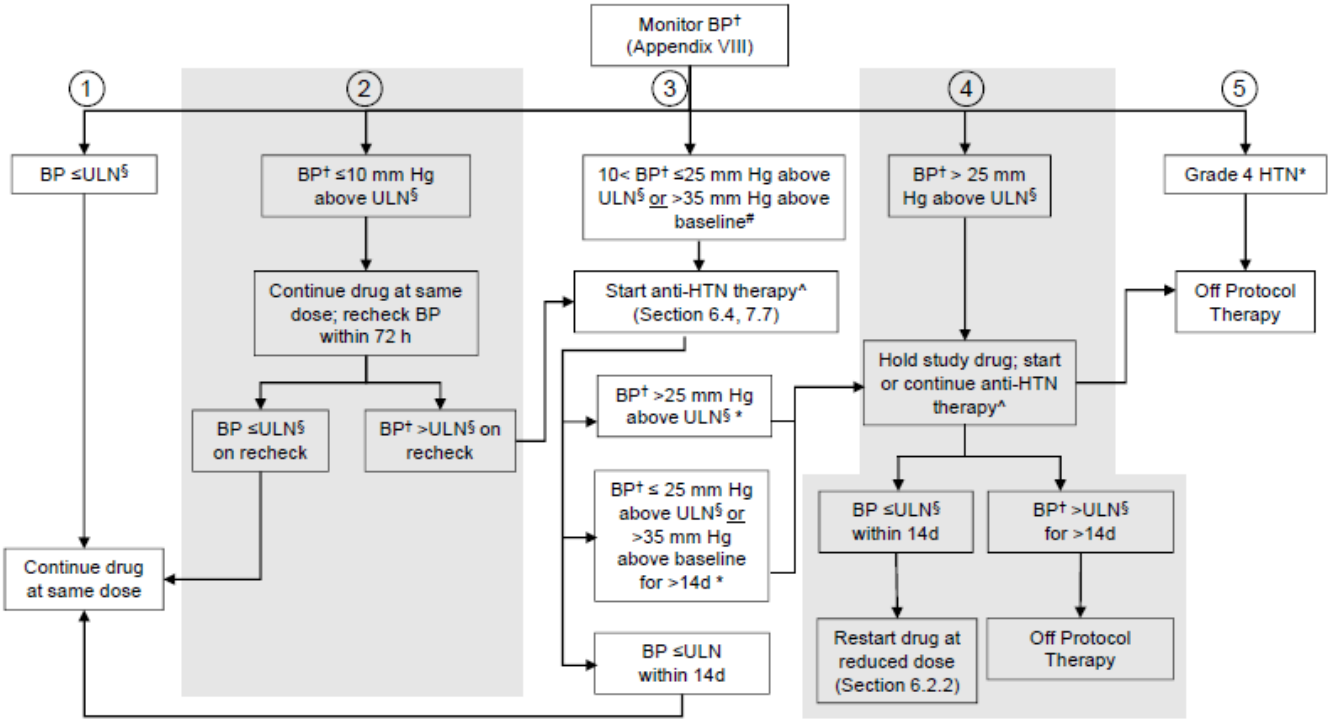
6.2.3 Two dose reductions will be allowed for toxicity. If a patient experiences a dose-limiting toxicity after two dose reductions, they must be removed from protocol therapy.

6.3 Dose Modifications for Proteinuria

- If urinalysis shows ≥ trace protein then obtain UPC.
- If the urine protein/creatinine (P/C) ratio ≤ 1.9 continue XL184. If patient has Grade 3 proteinuria (urine protein/creatinine (P/C) ratio > 1.9), a second measurement should be obtained within 72 hours. A second confirmation of Grade 3 proteinuria will be considered a DLT.
- If the second measurement confirms Grade 3 proteinuria (urine protein/creatinine (P/C) ratio > 1.9), then interrupt XL184 treatment and re-assess weekly.
- If XL184 is held for ≥ 14 days then remove from protocol therapy. If the urine protein/creatinine (P/C) ratio decreases to ≤ 1.9 in < 14 days then resume XL184 at a lower dose as outlined in Section 6.2.1.
- Monitor the UPC weekly for 2 consecutive weeks once protocol therapy resumes.

6.4 Dose Modifications for Hypertension

- **Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows: 1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position at rest with an appropriately sized cuff that are separated by at least 5 minutes. Avoid using the lower extremity if possible. 2) Average the systolic blood pressure from the 2nd and 3rd measurements. 3) Average the diastolic blood pressure from the 2nd and 3rd measurements. 4) The baseline BP is the average of the systolic over the average of the diastolic measurements.
- **Elevation** in either the systolic or diastolic blood pressure should be considered when following the algorithm below.
- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. See Appendix VIII.
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. If confirmed, patients with elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage XL184- related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.
§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix VIII)
* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.
^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.
# Baseline BP is defined in Section 6.4.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95% for age, height, and gender, continue XL184 at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN for age, height, and gender, continue XL184 at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue XL184 at the same dose.
  - If the BP remains above the ULN on recheck, then start antihypertensive therapy (Section 7.7) and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the 95% for age, height, and gender on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy (see Section 7.7), continue XL184 at the same dose, and monitor BP at least twice weekly.
  - If the BP returns to ≤ ULN within 14 days, continue XL184 at the same dose and continue anti-hypertensive therapy.

- If the BP remains elevated ≤ 25 mm Hg above the 95% or > 35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy, **hold** XL184, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that XL184 is held. The antihypertensive therapy should be continued until the BP is less than the ULN.
  - If the BP returns to ≤ ULN within 14 days, restart XL184 at a reduced dose (Section 6.1.1).
  - If the BP remains > ULN for more than 14 days, patient is Off Protocol Therapy.
- If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, **hold** XL184, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that XL184 is held.
  - If the BP is ≤ ULN within 14 days, XL184 may be restarted at a reduced dose (Section 6.2.2).
  - If the BP is > ULN for > 14 days, the patient is Off Protocol Therapy (Section 10.1).

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the 95% for age, height, and gender **hold** XL184, monitor BP and administer anti-hypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, XL184 may be restarted at a reduced dose (Section 6.2.2).
  - If the BP is > ULN for >14 days, the patient is Off Protocol Therapy (Section 10.1).

Arm 5 of algorithm:

- If the participant develops Grade 4 hypertension, **discontinue** XL184, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 10.1).

6.5 Dose Modifications for DVT

If a patient develops a DVT while on study, XL184 should be held until adequate anticoagulation is established. Full dose anticoagulation with warfarin is not permitted. Heparins should be used for anticoagulation. The drug may be resumed with a dose reduction if the DVT is dose-limiting (i.e. ≥ grade 3) and if the patient is deriving clinical benefit.

6.6 Dose Modifications for Liver Toxicity

XL184 should be held for grade 3 elevation of ALT, AST or bilirubin. Note: For the purposes of this trial the ULN for ALT is defined as 45 U/L. XL184 may be re-administered at the same dose if levels of ALT, AST and bilirubin meet eligibility criteria or baseline within 7 days of drug discontinuation. Elevated laboratory parameters should be checked at least twice weekly until eligibility criteria is met.

If lab values do not resolve to initial eligibility criteria or baseline within 7 days of interruption or if toxicity recurs with re-challenge, then this will be considered dose-limiting per section 5.5.1. XL184 will then be dose-reduced according to Section 6.2.1 when eligibility criteria is met.

6.7 Dose Modifications for Pancreatic Toxicity

XL184 should be held if patient experiences Grade 3 asymptomatic amylase or lipase elevation. Elevated laboratory parameters should be checked at least twice weekly until ≤ Grade 1.

If lab values do not resolve to ≤ 1 Grade within 7 days of interruption or if toxicity recurs with re-challenge, then this will be considered dose-limiting per section 5.5.1. XL184 will then be dose-reduced according to Section 6.2.1 when eligibility criteria is met.

6.8 Dose Modifications for Diarrhea

See Appendix XIV for specific guidelines for supportive care measures for patients who develop therapy-associated diarrhea.

- If dose-limiting Grade 3 (> 3 days) or Grade 4 therapy-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications, the dose of XL184 should be reduced per Appendix IIB.

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 XL184.

Diarrhea is a common side effect of XL184. Loperamide should be used at the first sign of significant diarrhea (See Appendix XIV).

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome) is a common side effect of XL184. Careful attention should be paid to skin exams and supportive care instituted early if any swelling or erythematous skin changes or symptoms of pain or burning/tingling are noted. Patients should be instructed to apply moisturizing creams, avoid any trauma, harsh chemicals and limit hot water exposure. Topical steroid creams may be used and consider early dermatology referral.

7.4 Growth Factors

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

7.5 Concomitant Medications

Proton pump inhibitors (PPIs) and H_2-antagonists should be avoided if possible (See Section 9.1.6).

Medications that are strong inhibitors or inducers of CYP3A4 should be avoided (see

Appendix IX). Corticosteroids may induce CYP3A4 and are therefore not routinely recommended on study unless deemed absolutely necessary or when used in stable or decreasing doses from the time of study enrollment.

The use of enzyme inducing anticonvulsants is not permitted. See Appendix XIII for a list of unacceptable enzyme inducing and recommended non-enzyme inducing anticonvulsants.

XL184 has been associated with prolonged QTc, so medications that prolong QTc are prohibited and medications that may prolong QTc should be avoided when possible (see Appendix XV).

7.6 Surgery

Patients should not have elective surgical procedures while on therapy. For patients who require emergent or urgent procedures, therapy may not be restarted until 28 days after major procedures and 7 days after minor procedures such as line replacement (3 days for external lines [e.g. Hickman or Broviac]), as detailed in section 4.2.6.

7.7 Concurrent Anti-Hypertensive Therapy

The algorithm in Section 6.4 will be used to grade and manage XL184 related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine, which are permissible without discussion with the study chair) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 6.4.

7.8 Management of Hypothyroidism

Patients with Grade 2 hypothyroidism adequately managed with thyroid hormone replacement may continue on protocol therapy. Patients with Grade 3 or greater hypothyroidism will be considered to have had a dose-limiting toxicity. These patients should be managed according to Section 6.2 and should also be evaluated by an endocrinologist for further management. Patients who enter the study on thyroid replacement should have their medication adjusted to maintain TSH in the normal range.

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 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	During Cycles 2 & 3	Prior to Subsequent Cycles^	30 days, 6 months, and annually up to 60 months ^^
History	X	Weekly		X[15]	X
Physical Exam with vital signs	X	Weekly		X[15]	X
Blood pressure[1]	X	Weekly	Every other week (Cycle 2)	X[15]	
Height, weight, BSA	X			X[15]	X
Performance Status	X				
Pregnancy Test[2]	X			X[15]	
CBC, differential, platelets	X	Weekly[3,4]	Every other week	X[3,4,15]	
Urinalysis [5]	X	Weekly		X[15]	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	Every other week	X[15]	
Creatinine, ALT, bilirubin	X	Weekly	Every other week	X[15]	
Albumin	X			X[15]	
Amylase, lipase	X	Weekly	Every other week	X[15]	
PT and INR	X				
TSH [6]	X	Once mid-cycle (days 15-22)		X[15]	
RET mutation status (germline and tumor) for patients with MTC (if available)	X				
CEA and calcitonin for patients with MTC[7]	X	End of Cycle 1		Every other cycle x 2 then q 3 cycles	

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	During Cycles 2 & 3	Prior to Subsequent Cycles^	30 days, 6 months, and annually up to 60 months ^^
Tumor Disease Evaluation[8, 14]	X	End of Cycle 1		Every other cycle x 2 then q 3 cycles[8, 14]	
EKG (including QTc interval) [13]	X	End of Cycle 1	End of Cycle 2	Every other cycle x 2 then q 3 cycles[13]	
Plain radiograph tibial growth plate[9]	X			X[9]	
Patient Diary[10]		Weekly		X	
Pharmacokinetics[11] ***COMPLETE***	*X*	*X*	*X*	*X*	
Pharmacodynamics[12]	X	X			
Tissue Studies[12]	X				

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

^^ Required observations beginning 30 days, 6 months (± 14 days), and annually (± 30 days) following the last dose of investigational agent until patient is off study (see Section 10.2).

1 Blood pressure will be measured with an appropriate sized cuff at rest. Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP (See Section 6.4). Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (> 95th percentile for age, height, and gender). If both BP measurements are > 95th percentile for age, height, and gender, follow the guidelines in Section 6.4. Patients with confirmed elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the 95th percentile for age, height, and gender (See Appendix VIII).

2 Males or females of reproductive potential may not participate unless they have agreed to use both a medically accepted barrier method of contraceptive method (e.g., male or female condom) and a second effective method of birth control during protocol therapy and for at least 4 months after the last dose of XL184. Abstinence is an acceptable method of birth control.

3 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day (see Section 6.1).

4 If patients develop Grade 4 thrombocytopenia then CBCs should be checked every 3 to 4 days (see Section 6.1).

5 See Appendix VII for UPC rationale and calculation and Section 6.3 for dose modifications if UPC > 1.9. If patient is being followed for prior proteinuria and UPC is obtained, urinalysis is not required. If 24 hour urine for protein is obtained, both urinalysis and UPC are not required. If patient has Grade 3 proteinuria (urine protein/creatinine (P/C) ratio >1.9), a second measurement should be obtained within 72 hours.

6 Patients found to have an abnormal TSH level should have a free T4 level measured.

7 Calcitonin measurements should be obtained in the fasting state.

8 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.

9 Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.1.

[10] Patient diary (see Appendix III) should be reviewed and uploaded into RAVE weekly during Cycle 1, and then after completion of each treatment cycle.

[11] *See Section 8.4 and Appendix V for timing of PK studies.* ***COMPLETE***

[12] See Section 8.5 for timing of Pharmacodynamic/Biomarker studies and details regarding tumor tissue submission. Archival tumor tissue should be submitted for all patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

[13] Patients with prolonged QTc should have correctable causes of prolonged QTc addressed if possible, including medications (See Appx. XV) and correction of electrolyte abnormalities (incl. Ca^{++} and Mg^{++}). If there is no evidence of QTc prolongation after completion of 6 cycles of therapy, further EKGs are not required.

[14] Patients currently enrolled on Part B of the study should be evaluated every 6 months.

[15] Patients currently enrolled on Part B of the study should be evaluated/have this test performed every other cycle.

8.2 Monitoring for Specific Toxicities

8.2.1 Growth Plate Toxicity

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

a. If patients are found to have a closed tibial growth plate, no further radiographs will be required.
b. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained prior to cycles 2, 5 and then every 6 months until off protocol therapy.
   - Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physeal pathology and undergo more frequent x-ray follow up. MRI should be performed without contrast.
   - Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of XL184 should be made after discussion with the Study Chair or Study Vice-Chair and DVL Leadership, taking into account the presence of any symptoms referable to the knee as well as the patient's response to XL184. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue XL184 or not.

8.2.2 Thyroid Toxicity

Patients will have a TSH level measured prior to initial treatment, once mid-cycle of Cycle 1 (Day 15-22), and prior to subsequent cycles. Patients found to have an abnormal TSH level should have a free T4 level measured. Thyroid toxicity will be handled like any other non-hematological toxicity. Guidance on the management of patients who develop hypothyroidism is included in Section 7.8.

8.3 Radiology Studies

8.3.1 Bone Age/ Knee MRI

All tibial radiographs and knee MRIs (if obtained) should be submitted for Central Review.

8.3.2 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 grid.

COG institutions that are not connected to the grid can send the images on hard copy film, CD ROM, or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1211) and date and shipped to Syed Aamer at the address below:

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

8.4 *Pharmacology COMPLETE*

8.4.1 *Description of Studies and Assay*

Plasma samples will be collected for the purpose of determining XL184 concentrations for pharmacokinetic analysis of XL184 and/or metabolite concentrations.

8.4.2 *Sampling Schedule (See Appendix IV and V)*

Blood samples will be obtained at the following time points:

- ***Required from all patients:***
  - *Cycle 1 Day 1 (pre, 4 hours after the first dose)*
  - *Cycle 1 Day 21 (± 2) (pre, 2, 4, 8 and 24 hours after dose)*
  - *Cycle 3 Day 1 (pre) for patients remaining on study*

- ***Required from patients enrolled after Amendment #5A:***
  - *Cycle 4 Day 1 (pre) for patients remaining on study*
  - *With each disease evaluation (beyond Cycle 4; pre-Day 1 dose) for patients remaining on study*

- ***Recommended from all patients:***
  - *If possible any time a patient experiences a DLT.*

8.4.3 *Sample Collection and Handling Instructions*

Blood samples (3 ml) will be collected in 3-mL K_2-EDTA Vacutainer tubes (lavender top) tubes for pharmacokinetic evaluation. ***Record the exact time and***

date the sample is drawn. During Cycle 1, record the exact time the drug is administered. Record the actual date and time the last dose of drug was administered prior to the collection of trough samples (pre-Cycle 3, pre-Cycle 4 and pre-Day 1 dose with each disease evaluation).

8.4.4 *Sample Processing Instructions*

Tubes should be chilled on wet ice or in a refrigerator prior to collection. Immediately after blood collection, blood tubes should be inverted several times and then kept on wet ice until centrifuged. Within 30 minutes of blood collection, samples should be separated by centrifugation for 10 minutes (1000 - 1200 g) at approximately 4°C. The resultant plasma should be withdrawn in approximately equal volumes into two (2) appropriately labeled polypropylene tubes for PK assay and stored (within 1 hour of the blood sampling time) at -70°C or lower until shipment. The analyst should attempt to transfer the maximum amount of plasma without disturbing the barrier between the red blood cells (bottom layer) and the plasma (top layer). One tube is the primary sample; the other tube is the back-up sample. Refer to PK Manual provided by Exelixis for additional sample processing instructions.

8.4.5 *Sample Labeling*

Each tube must be labeled with the patient's I.D. and accession number, the study I.D. (ADVL1211), and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

8.4.6 *Sample Shipping Instructions*

The primary samples collected for each subject should be shipped to Alturas Inc, on sufficient dry ice in an insulated container. Samples should be shipped between Monday and Wednesday for overnight delivery to ensure delivery to Alturas Analytics, Inc, before Friday. The back-up samples should be shipped to Alturas, Inc after confirmation of receipt of the primary samples.

Samples should be shipped to the following address:
Jennifer Zimmer, Ph.D.
Senior Scientist
Alturas Analytics, Inc.
1324 Alturas Dr.
Moscow, ID 83843
Phone: (208) 883-3400
Fax: (208) 882-9246

Refer to PK Manual provided by Exelixis for additional sample shipping instructions.

8.5 Correlative Studies

8.5.1 Description of Studies

8.5.1.1 Pharmacodynamic Biomarkers

Blood samples will be collected for all subjects for potential analyses of cabozantinib mechanism of action based biomarkers (*e.g.* VEGF-A, PlGF, sVEGFR2, sKIT) and/or other disease specific markers such as circulating

tumor cells. Markers of bone homeostasis (eg serum bone-specific ALP, NTx, and CTx) may be monitored to assess the effects of cabozantinib on bone metabolism. Additional exploratory studies may be performed to characterize disease subtypes and potential biomarkers of response or resistance. Analyses may include but are not limited to quantification and genotyping of circulating plasma DNA, evaluation of micro RNAs, and analyses of additional soluble markers.

8.5.1.2 Tumor Tissue Banking

Archival tumor tissue slides should be submitted. **If a patient does not have tissue available, the study chair must be notified prior to enrollment.** Tumor analyses may involve evaluation of the signaling pathways related to cabozantinib targets (eg, VEGFR, MET, KIT, RET) and include methods such as genotyping, fluorescence in situ hybridization (FISH) and/or immunohistochemistry (IHC). Broader genome-wide copy number and mutation profiling may also be conducted. See Appendix XI for details.

8.5.2 Sampling Schedule (See Appendix IV and X)

Blood samples will be collected as outlined in Appendix X.

8.5.3 Sample Collection and Handling Instructions

Refer to Appendix XII and Pharmacodynamic Lab Manual provided by Exelixis for detailed instructions regarding collection and storage of these specimens.

8.5.4 Sample Processing and Shipping Instructions

Refer to Appendix XII and Pharmacodynamic Lab Manual provided by Exelixis for detailed instructions regarding processing and shipment of these specimens.

8.5.5 Sample Labeling

Each tube must be labeled with the patient's I.D. and accession number, the study I.D. (ADVL1211), and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form (Appendix X), which must accompany the sample(s).

9.0 AGENT INFORMATION

9.1 Cabozantinib

(XL-184, Cabozantinib s-malate, EXEL-7184, EXEL-02977184) NSC# 761968

9.1.1 Structure and molecular weight

The chemical name of cabozantinib is *N*-(4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate. The molecular formula is $C_{28}H_{24}FN_3O_5C_4H_6O_5$ and the molecular weight is 635.6.

9.1.2 Supplied by:

Cabozantinib is supplied by Exelixis and distributed by the DCTD, NCI.

9.1.3 Formulation

Cabozantinib is available in 20 mg and 60 mg tablets. The yellow, film-coated tablets contain cabozantinib malate equivalent to 20 mg or 60 mg of cabozantinib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape. In active ingredients include the following: microcrystalline cellulose (Avicel PH-102), lactose anhydrous (60M), hydroxypropyl cellulose (EXF), croscarmellose sodium (Ac-Di-Sol), colloidal silicon dioxide, and magnesium stearate. Inactive components of the yellow film coating include HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow.

9.1.4 Storage

Store intact bottles at controlled room temperature, 20° to 25°C.

9.1.5 Stability

Stability testing of the intact bottles is on-going. Cabozantinib (XL184) should be dispensed in its original container. Cabozantinib (XL184) tablets are stable up to 24 hours when dispensed in an open container, such as in a pill cup, and are stable for up to 7 days when dispensed in a closed container, such as a pharmacy dispensing bottle (i.e., one other than the original container).

9.1.6 Administration

Take cabozantinib on an empty stomach; patients should fast 2 hours before and 1 hour after taking the drug. Do not crush or chew the tablets; tablets should be swallowed whole.

Cabozantinib is a substrate of CYP3A4. Coadministration of cabozantinib with medications that are strong inhibitors/inducers of CYP3A4 should be avoided. Examples of strong CYP3A4 inducers are rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, Phenobarbital, and St. John's Wort. Strong CYP3A4 inhibitors are ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Refer to Section 7.5 regarding use of corticosteroids. Use alternative medications. **Avoid grapefruit/ grapefruit juice, star fruit and Seville oranges while participating in this trial.** Refer to Appendix IX for additional details.

Cabozantinib is highly protein bound (99.9%). Use caution when coadministering cabozantinib with medications that are highly protein-bound (e.g., diazepam,

furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with cabozantinib as warfarin is highly protein-bound and has a very narrow therapeutic index.

Avoid concomitant use of cabozantinib with proton pump inhibitors (PPIs) and H_2 -antagonists if possible. The PPIs and H_2 –antagonists may decrease cabozantinib plasma exposure levels and its effectiveness in humans. Examples of PPIs are omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole; examples of H_2 –antagonists are ranitidine, famotidine, and nizatidine. Cimetidine is a moderate CYP3A4 inhibitor. Avoid using cimetidine with cabozantinib. If needed, antacids are recommended for the initial treatment of dyspepsia or indigestion. If antacids are not adequate, the use of H2 blockers (other than cimetidine) is preferred over PPIs. If antacids, H_2 blockers, or PPIs are needed, take them at least 2 hours (preferably 4 hours) after taking cabozantinib but at least 14 hours before the next dose of cabozantinib if possible.

9.1.7 Comprehensive Adverse Events and Potential Risks list (CAEPR)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below).
Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2438 patients.*
Below is the CAEPR for XL184 (Cabozantinib s-malate).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, October 4, 2016[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Musculoskeletal and connective tissue disorders - Other (muscle spasms)		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspnea		
		Pneumothorax[6]	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
Voice alteration			***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (hair color changes)		***Skin and subcutaneous tissue disorders - Other (hair color changes) (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6]Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.

[7]Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[8]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[9]Thromboembolic event includes pulmonary embolism which may be life-threatening.

Adverse events reported on XL184 (Cabozantinib s-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib s-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Hemorrhoids; Ileus; Pancreatitis; Rectal pain; Rectal ulcer
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (implant site inflammation); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatitis toxic); Portal vein thrombosis
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (D-dimer); Investigations - Other (eosinophil count increased); Investigations - Other (glucose urine present); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (muscle hemorrhage); Musculoskeletal and connective tissue disorders - Other (osteonecrosis); Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis); Myalgia; Neck pain; Osteoporosis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory

impairment; Nervous system disorders - Other (cerebral hematoma); Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Renal and urinary disorders - Other (azotemia); Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hypoxia; Laryngeal edema; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (splinter hemorrhages); Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2 Agent Ordering and Agent Accountability

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

9.3 Clinical Drug Request

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

9.4 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.4.1 Useful Links and Contacts

- CTEP Forms, Templates, Documents:
  http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration:
  PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines:
  http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:
  https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account:
  https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help:
  ctepreghelp@ctep.nci.nih.gov
- PMB email:
  PMBAfterHours@mail.nih.gov
- PMB phone and hours of service:
  (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

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).
b) Adverse Events requiring removal from protocol therapy (See Section 6).
c) Refusal of further protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Physician determines it is not in the patient's best interest.
f) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of XL184 (See Section 8.1).
g) Study is terminated by Sponsor.
h) 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.

Patients who are off protocol therapy are to be followed beginning 30 days, 6 months, and annually (± 30 days) following the last dose of investigational agent until they meet the criteria for Off Study (see Section 10.2). Ongoing adverse events, or adverse events attributed to protocol therapy that emerge during the follow up period after the patient is removed from protocol therapy 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) Death.
b) Lost to follow-up.
c) Withdrawal of consent for any further required observations or data submission.
d) The fifth anniversary of study entry.

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Parts of the Study:
Part A: Patients with relapsed or refractory solid tumors including CNS tumors and excluding patients with medullary thyroid cancer
Part B: Patients with medullary thyroid cancer (MTC)

A minimum of 2 evaluable patients will be entered at each dose level for determination of MTD or recommended Phase 2 dose (RP2D) in Part A. Once the MTD or RP2D has been defined, up to 6 additional patients with relapsed/refractory solid tumors 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 enrollment and determination of the MTD or RP2D within 15-29 months if all dose levels are studied with six evaluable patients. A maximum of 51 patients is anticipated in Part A, which accounts for potential expansion to 12 patients at each dose level (see Section 11.2.2) and an inevaluability rate of 20%. **COMPLETE**

Patients with medullary thyroid cancer may enroll to Part B of the study if there are no available slots on Part A. Part B will enroll concurrently at one dose level below that of solid tumor patients enrolled in Part A. If dose escalation has not yet occurred in Part A, patients in Part B will enroll at the initial dose level 1. Up to 6 patients may be enrolled onto each lagging dose level, for a maximum total of 18 evaluable patients in Part B. **COMPLETE**

Once the MTD or RP2D is identified, intra-patient dose escalation will be allowed for patients with medullary thyroid cancer (MTC) remaining on study in cycles of therapy subsequent to cycle 1, provided that the patient did not experience dose-limiting toxicity (DLT) at the dose at which they began therapy. Patients who are one dose level below the MTD or RP2D can escalate to the MTD or RP2D. Patients who are more than one dose level below the MTD or RP2D can escalate one dose level per cycle until they reach the MTD or RP2D as long as they do not experience a DLT when escalating. **COMPLETE**

The recommended Phase 2 dose (RP2D) in patients with solid tumors was determined to be 40 mg/m^2 (see details in Section 2.6). In order to acquire additional PK data at this dose level, an additional 6 evaluable patients will be enrolled for a total of 12 evaluable patients at this dose level (6 < 12 years of age and 6 ≥ 12 years of age). If at any time cycle 1 DLT occurs in ≥ 33% of evaluable patients in Part A at 40 mg/m^2, the maximum tolerated dose will have been exceeded and the cohort will be closed to further enrollment. Part B will remain open with Part A at 40 mg/m^2 (the RP2D) to patients with MTC and may enroll a maximum of 6 evaluable patients (4 more in addition to the 2 already enrolled). Part B will close to enrollment when the PK cohort in Part A at 40 mg/m^2 has completed enrollment, or if 2 or more out of 6 evaluable patients in the Part B cohort experience cycle 1 DLT. Up to 12 additional patients will be enrolled for a maximum total of 41 patients in the study, which accounts for a 20% inevaluability rate. It should take an additional 3-6 months for completion of enrollment.

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 will be replaced.

11.2.2 *Maximum Tolerated Dose (Part A):* COMPLETE

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

- *One of the DLTs does not appear to be 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*

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

11.3 *Dose Escalation and Determination of MTD:-* COMPLETE

The rolling six phase 1 trial design will be used for the conduct of this study. [17] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

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

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

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

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

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

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 XL184 will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of XL184 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. Overall survival from study entry will also be assessed and summarized using the Kaplan-Meier method at the 6 month, 12 month, and 5 year timepoints.

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 21-28 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.

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 12.8 from a sequence of overall response assessments.

12.3 Biomarker Response Criteria for Patients with MTC

Patients with MTC will use the response criteria outlined above in Section 12.2 to evaluate response and progression. Additional biomarker response data will be collected in patients with tumor markers (CEA and/or calcitonin) 2x ULN at baseline.

Complete Response (CR): Normalization (≤ ULN) of CEA or calcitonin (CTN) level following treatment, confirmed with a repeat CEA/CTN level at least 4 weeks apart.

Partial Response (PR): A ≥ 50% decrease in the CEA or CTN level relative to the baseline level, confirmed with a repeat CEA/CTN level at least 4 weeks apart.

Progressive Disease (PD):	A ≥ 50% increase in the CEA or CTN relative to the prior value on 2 consecutive measurements at least 4 weeks apart (e.g., if the last prior CTN value was 1,000 pg/ml, consecutive values of 1,500 pg/ml and then 2,250 pg/ml at least 4 weeks later would represent progression). The patient must have been taking XL184 for 4 weeks prior to the first measurements and must have continued to take the drug through the time that the second measurement was drawn.
Stable Disease (SD):	<50% increase or decrease in CTN or CEA level relative to the baseline level.

12.4 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.4.1 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.

12.4.2 Complete Response

Disappearance of all evaluable disease.

12.4.3 Partial response

Partial responses cannot be determined in patients with evaluable disease

12.4.4 Stable Disease (SD)

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

12.4.5 Progressive Disease

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

12.4.6 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.8 from a sequence of overall response assessments.

12.5 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.5.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

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

Complete response: 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

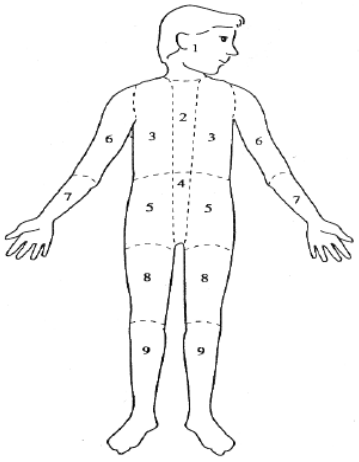
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale[14] as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.3.1 for details on transferring images to the Imaging Research Center.

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.

12.5.4 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 12.8.

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.6.1 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.

12.6.2 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 12.8.

12.7 Response Criteria for Patients with CNS Tumors

12.7.1 Measurable Disease

Any lesion that is at minimum 10 mm in one dimension on standard MRI or CT, for CNS tumors.

12.7.2 Evaluable Disease

Evaluable disease is defined as 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, CSF cytology, or other reliable measures.

12.7.3 Selection of Target and Non-Target Lesions

For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

12.7.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial response (PR):** ≥50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.
- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD.

- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

12.7.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.
- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.
- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

12.7.6 Response criteria for tumor markers (if available):
Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

12.7.7 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 12.8 from a sequence of overall response assessments.

12.8 Best Response

12.8.1 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

12.8.2 **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 data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) 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 (NCI) **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 in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

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.

Effective Date: May 5, 2011

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

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or

birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

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

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

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.
- Myelosuppression, including Grade 4 lymphopenia, does not require expedited reporting unless it is associated with hospitalization.
- Grade 1 and 2 adverse events listed in the table below do **not** require expedited reporting via CTEP-AERS:

Category	Adverse Events
INFECTIONS AND INFESTATIONS	Infection
METABOLISM AND NUTRITION DISORDERS	Dehydration
METABOLISM AND NUTRITION DISORDERS	Hypocalcemia
METABOLISM AND NUTRITION DISORDERS	Hypomagnesemia
METABOLISM AND NUTRITION DISORDERS	Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Pain in extremity
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Musculoskeletal and connective tissue disorders - Other (muscle spasms)
NERVOUS SYSTEM DISORDERS	Dizziness
NERVOUS SYSTEM DISORDERS	Headache
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Alopecia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.7 of the protocol.

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/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf (telephone CTEP at: **(301) 897-7497** 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 (Adverse Event Reporting System), accessed via the CTEP home page http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.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 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org.

Fax supporting documentation to the NCI (fax # 301-230-0159) and send by email to the ADVL1211 COG Study Assigned Research Coordinator. **ALWAYS include the ticket number on all faxed and 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 data form packet (See Section 14.1).

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

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

13.6 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) 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 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.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE 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 faxed along with any additional medical information to (301) 230-0159 (Appendix VI). Copies of all documents faxed to the NCI must also be emailed to the ADVL1211 COG Study Assigned Research Coordinator. 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 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.

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.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are faxed, with the corresponding shuttle sheet to the Statistics & Data Center at (626) 447-2204.

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 the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RAVE screens) provided in the data form packet.

See separate Data Form Packet, which includes submission schedule.

14.2 CDUS

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

14.3 CRADA/CTA/CSA

Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative

agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations

must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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 PEP-CTN 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 PEP-CTN 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 COG PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

REFERENCES

1. Gschwind A, Fischer OM, Ullrich A: The discovery of receptor tyrosine kinases: targets for cancer therapy. Nat Rev Cancer 4:361-70, 2004
2. DuBois S, Demetri G: Markers of angiogenesis and clinical features in patients with sarcoma. Cancer 109:813-9, 2007
3. Ramirez R, Hsu D, Patel A, et al: Over-expression of hepatocyte growth factor/scatter factor (HGF/SF) and the HGF/SF receptor (cMET) are associated with a high risk of metastasis and recurrence for children and young adults with papillary thyroid carcinoma. Clin Endocrinol (Oxf) 53:635-44, 2000
4. Kong DS, Song SY, Kim DH, et al: Prognostic significance of c-Met expression in glioblastomas. Cancer 115:140-8, 2009
5. Traugott AL, Moley JF: The RET Protooncogene. Cancer Treat Res 153:303-19, 2009
6. Investigator's Brochure XL184. July 2010. Exelixis. San Francisco, CA 94083, 2010
7. Paez-Ribes M, Allen E, Hudock J, et al: Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 15:220-31, 2009
8. Sennino B NR, Tabruyn SP, Weon-Kyoo Y, Aftab DT, McDonald DM: Reduction of tumor invasiveness and metastasis and prolongation of survival of RIP-Tag2 mice after inhibition of VEFGR plus c-MET by XL-184. Abstract A13: AACR-NCI-EORTC International Conference, November 2009, 2009
9. Yakes FM, Chen J, Tan J, et al: Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther, 2011
10. Lee RJ, Michaelson MD, Saylor PJ, et al: Investigator-sponsored trial of efficacy and tolerability of cabozantinib (cabo) at lower dose: A dose-finding study in men with castration-resistant prostate cancer (CRPC) and bone metastases. ASCO Meeting Abstracts 30:4566
11. Kurzrock R CE, Sherman SI, Pfister DG, Cohen RB, Ball D, Hong DS, Ng CS, Salgia R, Ratain MJ Long-term results on a cohort of medullary thyroid carncer (MTC) patients (pts) in a phase I study of XL184 (BMS 907351), and oral inhibitor of MET, VEGFR2, and RET. Clin Oncol 28:7s, 2010 (suppl; abstr 5502), 2010
12. Kurzrock R, Sherman SI, Ball DW, et al: Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol 29:2660-6, 2011
13. Salgia R SS, Hong DS, Ng CS, Frye J, Janisch L, Ratain MJ, Kurzrock R: A phase I study of XL184, a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including patients with medullary thyroid carcinoma (MTC). J Clin Oncol 26:2008 (May 20 suppl; abst 3522), 2008
14. Wen PY PM, Schiff D, et al. : Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients (pts) with progressive glioblastoma (GBM). J Clin Oncol 28:7s, 2010 (suppl; abstr 2006), 2010
15. Gordon MS VN, Schoffsky P, et al.: Cabozantinib (XL184) has activity in both soft tissue and bone: results of a phase 2 randomized discontinuation trial (RDT) in patients with advanced solid tumors. ASCO 2011 abstract, 2011
16. Exelixis: Exelixis' Cabozantinib Meets Primary Endpoint in Phase 3 Clinical Trial for Medullary Thyroid Cancer, Exelixis Press Release, 2011
17. Skolnik JM, Barrett JS, Jayaraman B, et al: Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 26:190-5, 2008
18. Xin G, Wang M, Jiao LL, et al: Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria. Clin Chim Acta 350(1-2):35-9, 2004

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 IIA: XL184 DOSING NOMOGRAM

Patients must have a body surface area ≥ 1.04 m^2 when enrolling on dose level -1, a BSA ≥ 0.96 m^2 to enroll on dose level 1, a BSA ≥ 0.72 m^2 to enroll on dose level 2, and a BSA ≥ 0.65 m^2 to enroll on dose level 3. If dose reduction is required due to toxicity, patients will decrease their administered dose per the tables below each respective dose level.

Patients enrolled after Amendment #1 should follow the dosing nomogram in Appendix IIB. Patients enrolled on study **prior to Amendment #1** must not change their dosing schedule and should continue to use the same dosing nomogram below.

Dose Level -1

Dose Level **23 mg/m^2 (DOSE LEVEL -1)**

BSA (m^2)	Dose (mg)	Total Weekly Dose (mg)
1.04 – 1.55	40 mg po q M, W, Th, Sat, Sun	200 mg
1.56- ≥ 2.00	40 mg once daily	280 mg

Dosing **if Dose Reduction** for Toxicity at **23 mg/m^2 Dose Level**

BSA (m^2)	Dose (mg)	Total Weekly Dose
1.04 – 1.55	20 mg once daily	140 mg
1.56 - ≥ 2.00	40 mg po q M, W, Th, Sat, Sun	200 mg

Dose Level 1

XL184 Dose Assignment: **30 mg/m^2 (DOSE LEVEL 1)**

BSA (m^2)	Administered dose (mg)	Total Weekly Dose (mg)
0.96 – 1.14	40 mg po q M, T, W, Fri, Sat, Sun	240 mg
1.15 – 1.42	40 mg po once daily	280 mg
1.43 – 1.67	60 mg po q M, T, W, Fri, Sat, Sun	360 mg
1.68 – ≥ 2.0	60 mg po once daily	420 mg

Dosing **if Dose Reduction** for Toxicity at **30 mg/m^2 Dose Level**

BSA (m^2)	Administered dose (mg)	Total Weekly Dose (mg)
0.96 – 1.14	60 mg po q M, W, Fri	180 mg
1.15 – 1.42	40 mg po q M, W, Th, Sat, Sun	200 mg
1.43 – 1.67	40 mg po once daily	280 mg
1.68 – ≥ 2.0	60 mg po q M, W, Th, Sat, Sun	300 mg

APPENDIX IIB: XL184 DOSING NOMOGRAM (AMENDMENT #5A)

Patients enrolled on any amendment should follow the dosing nomogram below. Patients enrolled on study **prior to Amendment #1** must not change their dosing schedule and should continue to use the same dosing nomogram (see Appendix IIA). **If a patient's dose is reduced due to toxicity, any future XL184 total weekly dose should not exceed a previously un-tolerated dose.**

Dose Level -1 **23 mg/m²**	**Dose Level 1** **30 mg/m²**	**Dose Level 2** **40 mg/m²**	**Dose Level 3** **55 mg/m²**			
BSA (m²)	**BSA (m²)**	**BSA (m²)**	**BSA (m²)**	**Weekly Dose/ Schedule for Initial Dosing**	**Weekly Dose/Schedule for 1st Dose Reduction due to Toxicity**	**Weekly Dose/Schedule for 2nd Dose Reduction due to Toxicity**
0.44 – 0.55	0.35 – 0.42			80 mg = 20 mg M, W, F, Sun	60 mg = 20 mg M, W, F	Off therapy
0.56 – 0.68	0.43 – 0.52	0.35 – 0.39		100 mg = 20 mg M, W, Th, Sat, Sun	60 mg = 20 mg M, W, F	Off therapy
0.69 – 0.79	0.53 – 0.60	0.40 – 0.45		120 mg =20 mg M, T, W, F, Sat, Sun	80 mg = 20 mg M, W, F, Sun	60 mg = 20 mg M, W, F
0.80 – 0.96	0.61 – 0.73	0.46 – 0.55	0.35 – 0.40	140 mg =20 mg Daily	100 mg = 20 mg M, W, Th, Sat, Sun	60 mg = 20 mg M, W, F
0.97 – 1.11	0.74 – 0.85	0.56 – 0.64	0.41 – 0.46	160 mg = 40 mg M, W, F, Sun	120 mg = 20 mg M, T, W, F, Sat, Sun	80 mg = 20 mg M, W, F, Sun
1.12 – 1.36	0.86 – 1.04	0.65 – 0.78	0.47 – 0.57	200 mg = 40 mg M, W, Th, Sat, Sun	140 mg = 20 mg Daily	100 mg = 20 mg M, W, Th, Sat, Sun
1.37 – 1.58	1.05 – 1.21	0.79 – 0.90	0.58 – 0.66	240 mg = 40 mg M, T, W, F, Sat, Sun	160 mg = 40 mg M, W, F, Sun	120 mg = 20 mg M, T, W, F, Sat, Sun
1.59 – 1.86	1.22 – 1.46	0.91 – 1.09	0.67 – 0.80	280 mg = 40 mg Daily	200 mg = 40 mg M, W, Th, Sat, Sun	140 mg = 20 mg Daily
1.87 – 2.04	1.47 – 1.57	1.10 – 1.17	0.81 – 0.85	300 mg = 60 mg M, W, Th, Sat, Sun	200 mg = 40 mg M, W, Th, Sat, Sun	140 mg = 20 mg Daily
≥ 2.05	1.58 – 1.85	1.18 – 1.36	0.86 – 0.99	360 mg = 60 mg M, T, W, F, Sat, Sun	240 mg = 40 mg M, T, W, F, Sat, Sun	160 mg = 40 mg M, W, F, Sun
	1.86 – 2.14	1.37 – 1.65	1.00 – 1.16	420 mg = 60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun	200 mg = 40 mg M, W, Th, Sat, Sun
	≥ 2.15	1.66 – 1.85	1.17 – 1.35	480 mg = 80 mg M, T, W, F, Sat, Sun	360 mg = 60 mg M, T, W, F, Sat, Sun	240 mg = 40 mg M, T, W, F, Sat, Sun

Dose Level -1 **23 mg/m^2**	**Dose Level 1** **30 mg/m^2**	**Dose Level 2** **40 mg/m^2**	**Dose Level 3** **55 mg/m^2**			
BSA (m^2)	**BSA (m^2)**	**BSA (m^2)**	**BSA (m^2)**	**Weekly Dose/ Schedule for Initial Dosing**	**Weekly Dose/Schedule for 1st Dose Reduction due to Toxicity**	**Weekly Dose/Schedule for 2nd Dose Reduction due to Toxicity**
		1.86 – 2.07	1.36 – 1.5	560 mg = 80 mg Daily	420 mg = 60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun
		≥ 2.08	1.51 – 1.68	600 mg = 100 mg M, T, W, F, Sat, Sun	420 mg = 60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun
			1.69 – 2.00	700 mg =100 mg Daily	480 mg = 80 mg M, T, W, F, Sat, Sun	360 mg = 60 mg M, T, W, F, Sat, Sun
			≥ 2.01	840 mg = 120 mg Daily	600 mg = 100 mg M, T, W, F, Sat, Sun	420 mg = 60 mg Daily

APPENDIX III: XL184 PATIENT DIARY

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

Complete each day with the date, time and number of XL184 tablets taken. Make note of other drugs and supplements taken. Your doctor will tell you what foods you should avoid. If a dose of XL184 is missed and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. If more than 6 hours have passed since the scheduled dosing time, you should not take the missed dose but should wait and take the next regularly scheduled dose. If you vomit after the dose of XL184 is administered, that dose should NOT be repeated. Wait until the next regularly scheduled dose to take the drug again. Return the completed diary to your institution weekly during Cycle 1, and then after each treatment cycle. Your institution will upload this document into RAVE weekly during Cycle 1, and then after each treatment cycle.

Sites will fill out the day of the week and number of prescribed tablets per day according to the dosing nomogram in Appendix II.

EXAMPLE				***Number of Tablets taken***		***Comments***
WEEK 1	***Date***	***Time***		***20 mg***	***60 mg***	*He felt nauseated an hour after taking the drug but did not vomit.*
Day 1: Monday	*1/15/12*	*8:30*	*AM*	*# prescribed: 3 # taken: 3*	*# prescribed: 0 # taken: 0*	

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|
BSA: _____ Dose: _____mg/m² Weekly Cumulative Dose per Nomogram: _____ mg

WEEK 1	**Date**	**Time**		**20 mg**	**60 mg**	**Comments**
Day 1: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 2: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 3: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 4: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 5: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 6: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 7: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

WEEK 2	Date	Time		20 mg	60 mg	Comments
Day 8: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 9: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 10: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 11: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 12: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 13: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 14: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

WEEK 3	Date	Time		20 mg	60 mg	Comments
Day 15: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 16: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 17: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 18: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 19: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 20: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

Day 21: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

WEEK 4	Date	Time		20 mg	60 mg	Comments
Day 22: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 23: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 24: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 25: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 26: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 27: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 28: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

Comments:

APPENDIX IV: CORRELATIVE STUDIES GUIDE

Correlative Study	Appx.	Tube Type	Blood Volume per Sample	Total Volume Cycle 1	Total Volume	Cycle 1								Cycle 3+**
						Day 1		Day 21(± 2 days)				Day 22	Day 28(± 2 days)	Day 1
						Pre-Dose	4 hr	Pre- Dose	2 hr	4 hr	8 hr	24±2hr	Pre- Dose	Pre- Dose
Pharmacokinetic COMPLETE	*V*	*Refer to Sample Kit*	*3 mL*	***21 mL***	***24 mL****	*X*	*X*	*X*	*X*	*X*	*X*	*X*		*X*
Pharmacodynamics	X, XII	Refer to Sample Kit	5 mL	**20 mL**	**20 mL**	X*		X					X	
Tissue Studies	XI, XII													
Total Volume for All Studies				**41 mL**	**44 mL****									

**Two pre-treatment samples will be collected: at baseline and prior to dose on Day 1 of Cycle 1*

*** For patients enrolled after Amendment #5A trough (pre) dose PK should be obtained with each disease evaluation within 72 hours before Day 1 dose of subsequent cycle. An additional 3 mL of blood will be collected with each disease evaluation.* **COMPLETE**

APPENDIX V: PHARMACOKINETIC STUDY FORM COMPLETE

COG Pt ID # _____ ***ACC #*** _____ ***Institution*** _____ ***Dose Level:*** _____ ***mg/m²***
Please do not write patient names on this form or on samples.

Total Weekly Dose per Nomogram: _____ ***mg*** ***Cycle 1, Day 1 Date:*** |__/__|__/__|__/__| ***Body Surface Area:*** _____ ***m²***

Blood samples (3 mL each) will be obtained on Cycle 1, Day 1 (pre-dose and 4 hours post dose), Cycle 1 Day 21 (± 2 days) (pre-dose, 2, 4, 8 and 24 hours post dose), Cycle 3 Day 1 (pre-dose). A sample on Cycle 4 Day 1 (pre-dose) and on Day 1 (pre-dose) with each disease evaluation should be obtained for patients enrolled after Amendment #5A. If possible, a sample should be collected at the time of DLT. Record the exact date and time each sample is drawn and the XL184 dose is administered.

Blood Sample No.	***Barcode # (from Sample Label)***	***Time Point***	***Scheduled Collection Time***	***Scheduled Dose***	***Last Dose Given; Record Actual Date and Time (24-hr clock)***	***Actual Date Sample Collected or Dose Given***	***Actual Time Sample Collected or Dose Given (24-hr clock)***
1		***Cycle 1, Day 1***	*Prior to first dose^*			___/___/___	|__|__| : |__|__|
				Cycle 1, Day 1 Dose		___/___/___	|__|__| : |__|__|
2		***Cycle 1, Day 1***	*4 hours after first dose*			___/___/___	|__|__| : |__|__|
3		***Cycle 1, Day 21 (± 2)***	*Prior to dose on Day 21 (± 2)^*			___/___/___	|__|__| : |__|__|
				Cycle 1, Day 21 Dose		___/___/___	|__|__| : |__|__|
4		***Cycle 1, Day 21***	*2 hrs after Day 21 dose*			___/___/___	|__|__| : |__|__|
5		***Cycle 1, Day 21***	*4 hrs after Day 21 dose*			___/___/___	|__|__| : |__|__|
6		***Cycle 1, Day 21***	*8 hrs after Day 21 dose*			___/___/___	|__|__| : |__|__|
7		***Cycle 1, Day 22***	*24 (±2) hrs after Day 21 dose**			___/___/___	|__|__| : |__|__|
8@		***Cycle 3, Day 1***	*Prior to Cycle 3, Day 1 dose*		___/___/___ |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
For patients enrolled after Amendment #5A:							
9@		***Cycle 4, Day 1***	*Prior to Cycle 4, Day 1 dose*		___/___/___ |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
With Each Disease Evaluation (For patients enrolled after Amendment #5A):							
10@		***Cycle #___, Day 1***	*Prior to Cycle , Day 1 dose*		/ / |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
11@		***Cycle #___, Day 1***	*Prior to Cycle , Day 1 dose*		/ / |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
12@		***Cycle #___, Day 1***	*Prior to Cycle ___, Day 1 dose*		___/___/___ |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
13@		***Cycle #___, Day 1***	*Prior to Cycle , Day 1 dose*		/ / |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
14@		***Cycle #___, Day 1***	*Prior to Cycle ___, Day 1 dose*		___/___/___ |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
15@		***Cycle #___, Day 1***	*Prior to Cycle , Day 1 dose*		___/___/___ |__|__| : |__|__|	___/___/___	|__|__| : |__|__|

Blood Sample No.	***Barcode # (from Sample Label)***	***Time Point***	***Scheduled Collection Time***	***Scheduled Dose***	***Last Dose Given; Record Actual Date and Time (24-hr clock)***	***Actual Date Sample Collected or Dose Given***	***Actual Time Sample Collected or Dose Given (24-hr clock)***
16@		***Cycle #___, Day 1***	*Prior to Cycle , Day 1 dose*		___/___/___ | | | : | | |	___/___/___	|__|__| : |__|__|
17@		***Cycle #___, Day 1***	*Prior to Cycle , Day 1 dose*		/ / | | | : | | |	___/___/___	|__|__| : |__|__|
18@		***Cycle #___, Day 1***	*Prior to Cycle ___, Day 1 dose*		___/___/___ | | | : | | |	___/___/___	|__|__| : |__|__|
19@		***Cycle #___, Day 1***	*Prior to Cycle ___, Day 1 dose*		___/___/___ |__|__| : |__|__|	___/___/___	|__|__| : |__|__|
For patients enrolled on any Amendment:							
		At time of 1st DLT	*unscheduled*		/ / | | | : | | |	___/___/___	|__|__| : |__|__|
		At time of 2nd DLT	*unscheduled*		___/___/___ |__|__| : |__|__|	___/___/___	|__|__| : |__|__|

^ Blood samples should be drawn within 15 minutes prior to dose.
**** Drug should be held on Cycle 1, Day 22 until PK sample is drawn.***
@ The pre-dose sample can be collected within 72 hours prior to the start of the subsequent cycle.

Sample Processing/ Shipping Procedures: *Samples should be processed according to Section 8.4.4 and then batched and shipped as described in the PK Lab Manual. Please indicate on the sample label whether the shipped sample is the primary sample or the back-up sample.*

One copy of this Pharmacokinetic Study Form should be should be uploaded into RAVE. A second copy should be sent with the samples to the lab at the address listed in the PK Lab Manual provided by Exelixis. Refer to PK Lab Manual for detailed guidelines for packaging and shipping PK samples.

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:* _____

APPENDIX VI: PREGNANCY INFORMATION FORM

Attach to CTEP-AERS 5-Day Report

PREGNANCY INFORMATION FAX
FACSIMILE TRANSMISSION
Ticket Number:_____

Study #:
SAF 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 initial reporting, fax both the Pregnancy CTEP-AERS Report and this additional Pregnancy Information Form. For follow-up reporting, fax only this Pregnancy Information Form (See Section 13.7). Copies of all documents that are faxed to the NCI during initial and follow-up reporting must also be sent via email to the ADVL1211 COG Study Assigned Research Coordinator.

APPENDIX VII: URINE PROTEIN TO CREATININE (UPC) RATIO

Clinical Meaning of UPC

There is a good correlation between the ratio of urine protein to creatinine concentrations (UPC) in a random urine sample and the amount of protein excreted in a 24-hour urine collection period.[18] Thus, the UPC allows for an estimation of the 24-hour urine protein excretion from a random sample. The creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate:

- Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day
- Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day
- Normal protein excretion is <100 mg to 150 mg per 24 hours.
- The UPC ratio is roughly equal to the 24 hour urine protein excretion in g/day

Calculating UPC Ratio

UPC ratio = (Urine protein [mg/dL]) / (urine creatinine [mg/dL]) = numerically equivalent to grams (g) protein excreted in urine over 24 hours.

Example: If a subject has a urine protein of 90 mg/dL and urine creatinine of 30 mg/dL,
then UPC ratio = $\frac{90\ (mg/dL)}{30\ (mg/dL)} = 3$
Result UPC is 3 correlating to roughly 3g of protein excretion in a 24-hour period.

Units for UPC ratio

UPC is a calculated ratio. The guidelines in the protocol are based on having urine protein and urine creatinine measured in the same units (e.g., mg/dL). The SI units for urine protein and urine creatinine are not the same, so these must be converted to mg/dL before calculating the ratio. For reference, the conversion factors for commonly used units for protein and creatinine are provided below.

Starting units	Conversion to mg/dL
Protein (g/L)	Multiply by 100
Creatinine (µmol/L)	Divide by 88.4
Creatinine (mmol/L)	Multiply by 11.3

APPENDIX VIII: BLOOD PRESSURE LEVELS FOR CHILDREN BY AGE AND HEIGHT PERCENTILE

Blood pressure (BP) levels for BOYS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.5.1 for definition of dose limiting hypertension, Section 6.4 for management and grading of hypertension, and Section 7.7 for medical treatment of XL184 related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.5.1 for definition of dose limiting hypertension, Section 6.4 for management and grading of hypertension, and Section 7.7 for medical treatment of XL184 related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

APPENDIX IX: CYP3A4 INDUCERS AND INHIBITORS

The use of the following medications should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list; please refer to other resources such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx for additional information.

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors	Other Inhibitors	Inducers
Clarithromycin	Aprepitant	Cimetidine	Amiodarone	Barbiturates
Indinavir	Diltiazem		Bocepravir	Carbamazepine
Itraconazole	Erythromycin		Chloramphenicol	Efavirenz
Ketoconazole	Fluconazole		Ciprofloxacin	Glucocorticoids*
Nefazodone	Grapefruit		Delaviridine	Modanfinil
Nelfinavir	Grapefruit juice		Fluvoxamine	Nevirapine
Posaconazole	Verapamil		Imatinib	Oxcarbazepine
Ritonavir			Mifepristone	Phenobarbital
Saquinavir			Norfloxacin	Phenytoin
Telithromycin			Norfluoxetine (fluoxetine)	Pioglitazone
			Star fruit	Rifabutin
			Telaprevir	Rifampin
			Voriconazole	St. John's wort

* Refer to Section 7.5 regarding use of corticosteroids.

APPENDIX X: PHARMACODYNAMIC/BIOMARKER STUDY FORM

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

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

Dose Level: _____mg/m^2 Total Weekly Dose per Nomogram: _____mg

NOTE: To be accessioned for Exelixis.

Blood samples (5 mL each) will be obtained at baseline and prior to dose on Day 1, Day 21 (± 2 days) and Day 28 (± 2 days) of Cycle 1. Record the exact date and time each sample is drawn.

Blood Sample No.	Barcode # (from Sample Label)	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
1		**Baseline/Pre-Study**	Prior to first dose on Day 1	___/___/___	|__|__| : |__|__|
2		**Cycle 1, Day 1**	Prior to first dose on Day 1*	___/___/___	|__|__| : |__|__|
3		**Cycle 1, Day 21 (± 2)**	Prior to dose on Day 21 (± 2)*	___/___/___	|__|__| : |__|__|
4		**Cycle 1, Day 28 (± 2)**	Prior to dose on Day 28 (± 2)*	___/___/___	|__|__| : |__|__|

*** Blood samples should be drawn within 1 hour prior to dose.**

Sample Processing Procedures- Refer to PD Lab Manual for additional details

1. Draw 5 mL of whole blood into a pre-labeled 6-mL Vacutainer tube (refer to PD Kit provided by Exelixis).
2. Invert the collection tube gently at least 5 times.
3. Within 30 minutes of collection, separate the plasma fraction by centrifugation (1200 × g for 10 minutes). A refrigerated centrifuge is preferred, and if available, should be set to 4°C.
4. Transfer the plasma to a 15 mL polypropylene tube and mix gently and thoroughly with a pipette. Be sure to avoid aspiration of cellular material near the buffy coat. Aliquot 0.5 mL into each of the 4 pre-labeled 1.2-mL cryovials. Distribute any extra plasma evenly between the vials.
5. Freeze plasma samples immediately (-70°C or colder). The samples must be stored on dry ice if a freezer is not immediately available.

Sample Shipping Procedures- Refer to Appendix XII for sample shipping guidelines.

One copy of this Biomarker Study Form should be should be uploaded into RAVE. A second copy should be sent with the samples to the lab at the address listed in Appendix XII. Refer to Pharmacodynamic Lab Manual provided by Exelixis for additional details.

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: _____

APPENDIX XI: TISSUE STUDY FORM

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

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

NOTE: To be accessioned for Exelixis.

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

Protocol number: **ADVL1211**
Institution: _____
Patient ID #: _____
Accession #: _____
Sample Date: _____
Site of Acquired Tissue: _____
Number of Slides: _____
Barcode # : _____
(from Sample Label provided by Exelixis)

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

Tumor Tissue:
Archival tumor tissue slides (10-15 unstained slides approximately 5 micron thickness on positively charged glass slides) from a formalin-fixed, paraffin-embedded tumor block will be shipped at room temperature .

Fill two to three 5-place slide containers with the slides and label each container with a Pharmacodynamics Sample Label (provided by Exelixis). Please indicate above the date of the sample, site of tissue acquisition and whether it was obtained at diagnosis or relapse. One copy of this form should be uploaded into RAVE.

Shipping Procedures- Refer to Appendix XII for sample shipping guidelines.

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: PACKAGING AND SHIPPING INSTRUCTIONS FOR PHARMACODYNAMIC AND ARCHIVAL TISSUE SAMPLES

Packaging Instructions:

1. Shipments should be scheduled after all samples have been collected from at least one subject. Samples may be batched for shipment after the end of cycle.
2. Once the pharmacodynamic and tissue samples are collected, the Pharmacodynamic Biomarker and Tumor Tissue CRFs and corresponding Study Forms (Appx X-XI) should be completed and uploaded into RAVE. An email notification must then be sent to the Study Research Coordinator. **The Study Research Coordinator will notify each site when the shipment may proceed.**
3. Shipment of Plasma Samples
    a. Place the tubes into a sealable plastic bag (one subject per bag) surrounded by absorbent material.
    b. Place the plastic bags into a suitable Styrofoam shipping container (e.g., ThermoSafe) and fill with enough dry ice for 2 days in transit (e.g., 8 pounds).
4. Shipment of Archival Tumor samples
    a. Make sure the microscope slide holders are properly labeled and taped closed. Surround the slide holders with packing material such as bubble wrap and pack into a shipping box such that the samples cannot move.
5. The shipping address is:
    Covance Biorepository Services
    Attn: Juan Rivera – Biorepository/LTS Building 210
    671 South Meridian Road
    Greenfield, Indiana, 46140
    (317) 467-7585

    Include a copy of Pharmacodynamic/Biomarker Study Form (Appendix X) and Tissue Study Form (Appendix XI) along with the sample shipment.

Please **DO NOT** ship samples on a Thursday or Friday, or within 2 days of holiday.

APPENDIX XIII: UNACCEPTABLE ENZYME INDUCING AND RECOMMENDED NON-ENZYME INDUCING ANTICONVULSANTS

Recommended Non-enzyme inducing anticonvulsants	
Generic Name	*Trade Name*
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Tigabine	Gabitril
Topiramate	Topamax
Valproic Acid	Depakote, Depakene
Zonisamide	Zonegran
Unacceptable Enzyme inducing anticonvulsants	
Generic Name	*Trade Name*
Carbamazepine	Tegretol
Felbamate	Felbatol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxcarbazepine	Trileptal

APPENDIX XIV: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

Each family will be instructed to have antidiarrheal medication available and begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given **loperamide** based on body weight. The doses and schedules for loperamide included here are higher than the standard but consistent with COG protocols D9802, P9761, ARST0121, and ADVL0918.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any notable increase in the number of bowel movements over what is normal for him/her, begin taking loperamide (Imodium).

Please follow these directions carefully, using dosing guidelines below:

- Take _____ at the first sign of diarrhea.
- Continue taking _____ every 2 hours until the diarrhea slows or the normal pattern of bowel movements returns. Repeat the same doses and frequency if the diarrhea returns.
- Do not exceed _____ in a 24 hour period.
- Please call your doctor if you have any questions about taking loperamide, if your child's diarrhea is not under control after two days, or if he/she is feeling extremely weak, lightheaded, or dizzy.
- Make an extra effort to give your child lots of fluids (several glasses of pedialyte, fruit juices, soda, soup, etc.) while your child is participating in this study.
- Side effects may include tiredness, drowsiness or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child's physician.
- Do not give your child any laxatives without consulting with his/her physician.

LOPERAMIDE DOSING RECOMMENDATIONS (NOTE: maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg per day.
≥ 13 kg to < 20 kg	Take 1 mg (1 teaspoonful of the 1 mg/5 mL oral solution or one-half capsule or tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 1 mg (one teaspoonful of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 6 mg per day.
≥ 20 kg to < 30 kg	Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half capsule or tablet) every 3 hours. During the night, the patient may take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 caplet) every 4 hours. Do not exceed 8 mg per day.
≥ 30 kg to < 43 kg	Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half capsule or tablet) every 2 hours. During the night, the patient may take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 4 hours. Do not exceed 12 mg per day.
Over 43 kg	Take 4 mg (4 teaspoonfuls of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 2 hours. During the night, the patient may take 4 mg (4 teaspoonfuls of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg per day.

APPENDIX XV: MEDICATIONS ASSOCIATED WITH PROLONGED QTC

For the most current list of medications, please refer to the following website: www.torsades.org.

1. Medications that prolong QTc

Generic name	Brand name
Amiodarone	Cordarone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®
Flecainide	Tambocor®
Halofantrine	Halfan®

Generic name	Brand name
Haloperidol	Haldol®
Ibutilide	Corvert®
Mesoridazine	Serentil®
Methadone	Dolophine®
Moxifloxacin	Avelox®
Pentamidine	Pentam®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Procan®
Quinidine	Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

2. Medications that may prolong QTc

Generic name	Trade name
Alfuzosin	Uroxatral®
Amantadine	Symmetrel®
Atazanavir	Reyataz®
Chloral hydrate	Noctec®
Clozapine	Clozaril®
Dolasetron	Anzemet®
Dronedarone	Multaq®
Eribulin	Halaven®
Escitalopram	Cipralex®
Escitalopram	Lexapro®
Famotidine	Pepcid®
Felbamate	Felbatrol®
Fingolimod	Gilenya®
Foscarnet	Foscavir®
Fosphenytoin	Cerebyx®
Gemifloxacin	Factive®
Granisetron	Kytril®
Iloperidone	Fanapt®
Indapamide	Lozol®
Isradipine	Dynacirc®
Lapatinib	Tykerb®
Levofloxacin	Levaquin®
Lithium	Lithobid®

Generic name	Trade name
Moexipril/HCTZ	Uniretic®
Nicardipine	Cardene®
Nilotinib	Tasigna®
Octreotide	Sandostatin®
Ofloxacin	Floxin®
Ondansetron	Zofran®
Oxytocin	Pitocin®
Paliperidone	Invega®
Quetiapine	Seroquel®
Ranolazine	Ranexa®
Risperidone	Risperdal®
Roxithromycin	Rulide®
Sertindole	Serdolect®
Sertindole	Serlect®
Sunitinib	Sutent®
Tacrolimus	Prograf®
Tamoxifen	Nolvadex®
Telithromycin	Ketek®
Tizanidine	Zanaflex®
Vardenafil	Levitra®
Venlafaxine	Effexor®
Voriconazole	VFend®
Ziprasidone	Geodon®

APPENDIX XVI: CTEP AND CTSU REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Requirements for ADVL1211 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory

Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.