CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Group Chair
Peter C. Adamson, M.D.
adamson@email.chop.edu

Group Statistician
Todd Alonzo, Ph.D.
talonzo@childrensoncology group.org

Group Vice Chair
Susan Blaney, M.D.
smblaney@txch.org

Chief Operating Officer
Elizabeth O'Connor, M.P.H.
econnor@childrensoncology group.org

Executive Director of Administration
Deborah L. Crabtree, M.S.
crabtreed@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

Group Operations Center
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

Statistics & Data Center Headquarters
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

Gainesville Office
6011 NW 1st Place
Gainesville, FL 32607

P 352 273 0556
F 352 392 8162

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

April 16, 2019

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Please find attached Amendment #3 to **ADVL1622**, *A Phase 2 Trial of XL184 (Cabozantinib) an Oral Small-Molecule Inhibitor of Multiple Kinases, in Children and Young Adults with Refractory Sarcomas, Wilms Tumor, and Other Rare Tumors*.

The protocol and ICD have been amended in response to an RRA received from Dr. John J. Wright due to the release of new XL184 toxicity information.

Please contact us if you have any further questions.

Sincerely,

Alina Stout, Protocol Coordinator for
Srivandana Akshintala MBBS, MPH, **ADVL1622** Study Chair, and
Brenda Weigel, MD, PI, PEP-CTN

SUMMARY OF CHANGES

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

I. PROTOCOL CHANGES:

#	Section	Comments
1.	Title Page	The version date has been updated. The amendment number has been updated.
2.	6.1	The XL184 CAEPR has been updated per the guidelines in the RRA.

II. ICD CHANGES:

#	Section	Comments
3.	General	The version date has been updated.
4.	"What side effects…?"	The XL184 risk language has been updated per the guidelines in the RRA. The XL184 toxicity list has been updated per the guidelines in the RRA.

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Activated:	05/08/17	Version Date:	04/16/19
Closed:		Amendment #:	3

CHILDREN'S ONCOLOGY GROUP

ADVL1622

Phase 2 Trial of XL184 (Cabozantinib) an Oral Small-Molecule Inhibitor of Multiple Kinases, in Children and Young Adults with Refractory Sarcomas, Wilms Tumor, and Other Rare Tumors

An Intergroup NCTN Phase 2 Study

NCI Supplied Agent: XL184 (cabozantinib, NSC# 761968)

IND Sponsor for XL184: DCTD, NCI

THIS PROTOCOL IS FOR RESEARCH PURPOSES ONLY, AND SHOULD NOT BE COPIED, REDISTRIBUTED OR USED FOR ANY OTHER PURPOSE. MEDICAL AND SCIENTIFIC INFORMATION CONTAINED WITHIN THIS PROTOCOL IS NOT INCLUDED TO AUTHORIZE OR FACILITATE THE PRACTICE OF MEDICINE BY ANY PERSON OR ENTITY. *RESEARCH* MEANS A SYSTEMATIC INVESTIGATION, INCLUDING RESEARCH DEVELOPMENT, TESTING AND EVALUATION, DESIGNED TO DEVELOP OR CONTRIBUTE TO GENERALIZABLE KNOWLEDGE. THIS PROTOCOL IS THE RESEARCH PLAN DEVELOPED BY THE CHILDREN'S ONCOLOGY GROUP TO INVESTIGATE A PARTICULAR STUDY QUESTION OR SET OF STUDY QUESTIONS AND SHOULD NOT BE USED TO DIRECT THE PRACTICE OF MEDICINE BY ANY PERSON OR TO PROVIDE INDIVIDUALIZED MEDICAL CARE, TREATMENT, OR ADVICE TO ANY PATIENT OR STUDY SUBJECT. THE PROCEDURES IN THIS PROTOCOL ARE INTENDED ONLY FOR USE BY CLINICAL ONCOLOGISTS IN CAREFULLY STRUCTURED SETTINGS, AND MAY NOT PROVE TO BE MORE EFFECTIVE THAN STANDARD TREATMENT. *ANY PERSON WHO REQUIRES MEDICAL CARE IS URGED TO CONSULT WITH HIS OR HER PERSONAL PHYSICIAN OR TREATING PHYSICIAN OR VISIT THE NEAREST LOCAL HOSPITAL OR HEALTHCARE INSTITUTION.*

STUDY CHAIR

Srivandana Akshintala MBBS, MPH
The Stephen D. Hassenfeld Children's Center for Cancer and Blood Disorders
160 East 32nd Street, 2nd Floor
New York, NY 10016
Phone: (212) 263-0188
Fax: (212) 263-8410
E-mail: srivandana.akshintala@nyumc.org

For Statistics and Data Center Contact Person see: http://members.childrensoncologygroup.org

Participating Organizations

COG / Children's Oncology Group

ALLIANCE / Alliance for Clinical Trials in Oncology

ECOG-ACRIN / ECOG-ACRIN Cancer Research Group

NRG / NRG Oncology

SWOG / SWOG

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
The CTSU Website is located at https://www.ctsu.org.

TABLE OF CONTENTS

STUDY COMMITTEE

STUDY CHAIR
Srivandana Akshintala MBBS, MPH
Hematology/Oncology
The Stephen D. Hassenfeld Children's Center
160 East 32nd Street, 2nd Floor
New York, NY 10016
Phone: (212) 263-0188
Fax: (212) 263-8410
E-mail: srivandana.akshintala@nyumc.org

STUDY VICE CHAIR
Brigitte C. Widemann, M.D.
Hematology Oncology
National Institutes of Health Clinical Center
10 Center Dr. 10-CRC, Rm 1-5750 MSC 1101
Bethesda, MD 20892
Phone: (301) 496-7387
Fax: (301) 480-8871
E-mail: widemanb@mail.nih.gov

STUDY STATISTICIAN
Donald A. Barkauskas, Ph.D.
Biostatistics
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1540
Fax: (626) 445-4334
E-mail: dbarkauskas@childrensoncologygroup.org

STUDY COMMITTEE MEMBERS
Brenda J. Weigel, M.D.
Hematology/Oncology
University of Minnesota /Masonic Cancer Center
420 Delaware Street, SE MMC 366
Minneapolis, MN 55455
Phone: (612) 626-5501
Fax: (612) 624-3913
E-mail: weige007@umn.edu

Elizabeth Fox, M.D.
Hematology/Oncology
Children's Hospital of Philadelphia
3501 Civic Center Blvd., CTRB-4016
Philadelphia, PA 19104
Phone: (267) 425-3010
Fax: (267) 425-0113
E-mail: foxe@email.chop.edu

AeRang Kim, M.D.
Hematology/Oncology
Children's National Medical Center
111 Michigan Avenue, N.W.
Washington, DC 20010
Phone: (202) 476-4744
Fax: (202) 476-5685
E-mail: aekim@childrensnational.org

Emily Dunn Stern, R.N., BSN, CPON, CCRP
Nursing
Children's National Medical Center
111 Michigan Avenue, N.W.
Washington, DC 20010
Phone: (202) 476-2802
Fax: (202) 476-2021
E-mail: estern@childrensnational.org

Gina Martin, BSN
Clinical Research Associate
Washington University School of Medicine
1 Children's Place, 9 South
St. Louis, MO 63110
Phone: (314) 454-6018
Fax: (314) 454-2780
E-mail: martin_g@kids.wustl.edu

Joel Reid, Ph.D.
Pharmacology
Mayo Clinic
17-42C Guggenheim Building
200 First Street SW
Rochester, MN 55905
Phone: (507) 284-0822
Fax: (507) 284-3906
E-mail: reid.joel@mayo.edu

Stephan D. Voss, M.D.
Diagnostic Imaging
Dana-Farber/Harvard Cancer Center
300 Longwood Avenue
Boston, MA 2115
Phone: (617) 355-8377
Fax: (617) 730-0573
Email: stephan.voss@childrens.harvard.edu

STUDY PHARMACIST
Olga Militano, PharmD
Children's Oncology Group
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1517
Fax: (626) 445-4334
E-mail: omilitano@childrensoncologygroup.org

ALLIANCE NCTN STUDY CHAMPION
Gary K. Schwartz, MD
Columbia University/Herbert Irving Cancer Center
Division of Medical Oncology
177 Fort Washington Ave, 6GN-435 Milstein Hospital
New York, NY 10032 US
Phone: (212) 305-8615
Email: gks2123@columbia.edu

COG OPERATIONS STAFF
PROTOCOL COORDINATOR
Alina Stout, BS
Children's Oncology Group – Operations Center
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1566
Fax: (626) 445-4334
E-mail: astout@childrensoncologygroup.org

RESEARCH COORDINATOR
Lorraine Sarmiento, MHA
Children's Oncology Group – Operations Center
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1755
Fax: (626) 445-4334
E-mail: lsarmiento@childrensoncologygroup.org

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

AGENT
XL184 (cabozantinib, NSC# 761968)

IND Sponsor: NCI

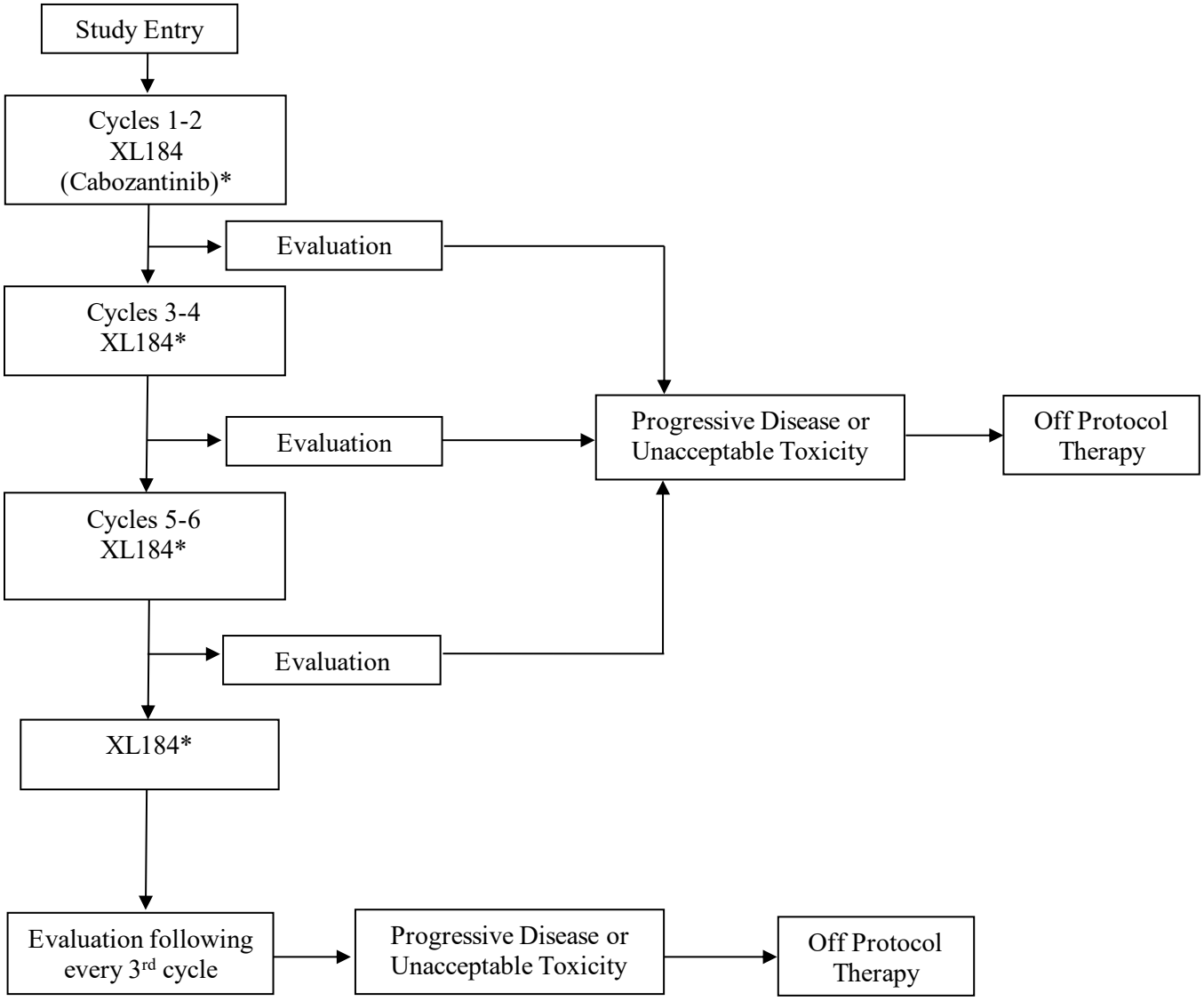
SEE SECTION 7.2 FOR SPECIMEN SHIPPING ADDRESSES

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about your 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 is an oral small molecule inhibitor of multiple tyrosine kinases including MET, VEGFR2 and RET, which are potential therapeutic targets in many pediatric and adult solid tumors. Preclinical *in vivo* studies have shown that XL184 inhibits these kinases resulting in decreased tumor and endothelial cell proliferation, increased apoptosis, tumor growth inhibition, and tumor regression. XL184 is approved for adults with progressive, metastatic medullary thyroid carcinoma (MTC) and advanced renal cell carcinoma (RCC), and has shown preliminary clinical activity in glioblastoma, differentiated thyroid carcinoma, hepatocellular carcinoma (HCC), urothelial, endometrial, breast, and non-small cell lung cancer (NSCLC). In the ongoing COG/pilot consortium pediatric phase 1 trial of XL184, ADVL1211, partial responses and prolonged disease stabilization have been observed in several solid tumors at doses that were tolerable. This open label two-stage phase 2 trial includes the following solid tumor strata: Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), osteosarcoma, Wilms tumor (non-statistical cohort) and other rare solid tumors (non-statistical cohort). XL184 will be administered orally once daily on a continuous dosing schedule of 28 day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram). The primary endpoint for the selected disease strata except osteosarcoma will be the objective response rate. We will also evaluate progression free survival (PFS), time to progression, overall survival, and if feasible, compare PFS to historical controls. For the osteosarcoma stratum, a two-stage design that incorporates dual end points of objective response based on RECIST criteria and treatment success as defined by stable disease for $\geq$ 4 months will be utilized. Pharmacokinetics and pharmacodynamics of XL184 in pediatric and adolescent patients will also be further studied.

EXPERIMENTAL DESIGN SCHEMA



*XL184 (Cabozantinib) will be given on a continuous dosing schedule. A cycle is 28 days.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aim

1.1.1 To determine the objective response rate (complete response + partial response) of XL184 in children and young adults in the following disease strata:

- Ewing sarcoma
- Rhabdomyosarcoma (RMS)
- Non rhabdomyosarcoma soft tissue sarcomas (STS) including microphthalmia transcription factor associated STS (alveolar soft part sarcoma (ASPS) and clear cell sarcoma (CCS))
- Wilms tumor (non-statistical cohort)
- Rare tumors (non-statistical cohort)
    - Medullary thyroid carcinoma (MTC)
    - Renal cell carcinoma (RCC)
    - Hepatocellular carcinoma (HCC)
    - Hepatoblastoma
    - Adrenocortical carcinoma
    - Pediatric solid tumors (including CNS tumors) with known molecular alterations in the targets of XL184 (i.e., MET amplification, overexpression, activating mutation, MET translocation, MET exon skipping mutations, activating RET mutations, RET rearrangement, overexpression or activation of AXL)

1.1.2 To estimate whether XL184 therapy either improves the disease control rate at 4 months in patients with recurrent measurable osteosarcoma as compared to a historical COG experience or produces an objective response rate.

1.2 Secondary Aims

1.2.1 To further define XL184 related toxicities in pediatric, adolescent and young adult patients.

1.2.2 To further define XL184 pharmacokinetics in the pediatric and adolescent patients.

1.2.3 To estimate 1-year time to progression, progression free survival (PFS) and overall survival for each stratum, and if feasible to compare to historical controls.

1.3 Exploratory Aims

1.3.1 To assess the effect of XL184 on patients' immune cell subsets.

1.3.2 To obtain tumor tissue (snap frozen, FFPE blocks, or unstained slides) from diagnosis, recurrence, or both, for possible future studies.

2.0 BACKGROUND

2.1 Rationale for Development

There is a great need for the development of novel and effective therapies for pediatric patients with refractory solid tumors and for tumors for which no standard therapy exists. XL184 is a small molecule inhibitor of multiple tyrosine kinases including MET (IC_{50} 8nm), VEGFR2 (IC_{50} 2nm), RET (IC_{50} 85nm), KIT (IC_{50} 5nm), FLT3 (IC_{50}11 nm) and TIE-2. Other recognized targets of XL184 include AXL, FMS, ROS1, TRKA, TRKB, TYRO3, MER, VEGFR1, and VEGFR3. XL184 has a broad spectrum of activity *in vitro* and *in vivo* in xenograft models that include medullary thyroid cancer, lung cancer, breast cancer, and glioblastoma.[1,2] XL184 is approved for adults with progressive, metastatic MTC and advanced RCC who have received prior anti-angiogenic therapy. It has also shown preliminary clinical activity in glioblastoma, differentiated thyroid carcinoma, HCC, urothelial, endometrial, breast, and non-small cell lung cancer (NSCLC).[1,3-7] There is a strong scientific rationale for the evaluation of XL184 in pediatric solid tumors: MET and its ligand HGF have been shown to be deregulated in many human cancers and correlate with poor prognosis.[8] MET and VEGFR2 are important mediators of tumor growth and angiogenesis, and aberrant MET/HGF signaling pathway is particularly associated with tumor invasiveness and metastasis.[1,9] In the ongoing COG/pilot consortium pediatric phase 1 trial of XL184, ADVL1211, partial responses and prolonged disease stabilization were observed in several solid tumor types at doses that were tolerable. This trial will assess the activity of XL184 in select pediatric solid tumors.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

XL184 has shown to inhibit several kinases in biochemical assays with potent inhibition of VEGFR2, MET (including MET with activating kinase domain mutations Y1248H, D1246N, or K1262R), KIT, RET, AXL, TIE2, and FLT3 (IC50 ranging from 0.035 – 14.6 nmol/L). In cellular assays, inhibition of phosphorylation of MET, VEGFR2, KIT, FLT3, and AXl was noted at IC50s ranging from 1.9-77 nmol/L. XL184 has shown dose-dependent inhibition of tumor growth in a variety of xenograft models including human breast, lung, MTC, transgenic RIP-Tag2 model of pancreatic cancer and rat glioma.[1,2]

MET, VEGFR, and RET are potential therapeutic targets in pediatric sarcomas, Wilms tumor, and other rare solid tumors. In soft tissue and bony sarcomas, tumor VEGF expression has been shown to positively correlate with increased tumor stage, tumor grade, increased risk of local and distant tumor metastasis, and lower overall survival.[10] Over-expression of MET has been described in osteosarcoma and Ewing sarcoma, and MET expression has been shown to correlate with aggressive phenotype and poor prognosis.[11-13] MET is a transcriptional target of PAX3 and PAX7 and MET is highly expressed in alveolar RMS cell lines.[14] In alveolar RMS and embryonal RMS cell lines, HGF induces locomotion, chemotaxis, adhesion to umbilical vein and endothelial cells, trans-matrigel migration, matrix metalloproteinase secretion, and increased survival upon exposure to chemo- or radiation therapy.[15] MET and HGF are highly expressed in malignant peripheral nerve sheath tumors (MPNST) and phosphorylated MET levels were shown to be of prognostic significance.[16] Co-expression of HGF and

MET correlated with higher grade and poorer prognosis in synovial sarcoma tumor samples.[17] Inhibition of MET has been shown to inhibit proliferation, survival, invasion, migration, anchorage independent growth, and increase apoptosis in osteosarcoma, RMS, and MPNST cell lines and inhibit tumor growth in xenograft models.[11-17] Microphthalmia transcription factor associated sarcomas such as alveolar soft part sarcomas (ASPS) and clear cell sarcomas (CCS) are characterized by specific translocations leading to deregulation of microphthalmia transcription factor (MITF) family of proteins, which up-regulates MET expression.[18] MET is a direct transcriptional target of TFE3-ASPL fusion protein that arises from the t(X;17)(p11;q25) translocation observed in all cases of ASPS and is highly expressed and activated in ASPS. Inhibition of MET has been shown to decrease cell growth in cell lines containing endogenous TFE3 fusion proteins.[19] The majority of cases of CCS have a t(12:22)(q13:q12) translocation resulting in the production of a chimeric transcription factor, EWS-ATF1, which activates MITF and leads to MET expression. MET expression was shown to be critical for invasion and survival in CCS cell lines and inhibition of HGF/MET pathway inhibited cell proliferation and viability in vitro, and suppressed tumor growth in xenograft models. Case reports of responses to the anti-angiogenic agents sunitinib and sorafenib have been described in patients with CCS, suggesting that MET and VEGFR are potential therapeutic targets in these tumors. [18,20]

Over-expression of MET has been documented in primary liver cancers such as hepatoblastoma and HCC.[21] The β catenin pathway has been implicated in the development of hepatoblastoma, and MET has been shown to contribute to aberrant β catenin expression by wnt-independent activation in a majority of cases of hepatoblastoma.[22] In HCC, high MET expression correlates with increased incidence of intra-hepatic metastasis and poor survival.[23] MET inhibition has been shown to inhibit proliferation and induce apoptosis in MET-positive HCC cell lines and inhibit tumor growth in xenograft models.[24] The VEGF pathway is a known target in RCC, and MET is a potential target particularly for pediatric RCC, as TFE+ RCC is now thought to account for close to 70% of pediatric RCC cases. TFE+ RCC is characterized by translocations involving the TFE3 gene (member of the microphthalmia transcription factor family) commonly found with fusion partners ASPL (at 17q25) or the PRCC gene (at 1q21), which leads to up-regulation of MET as MET is a direct transcriptional target of TFE3 fusion proteins.[19,25,26] In the Pediatric Pre-clinical Testing Program (PPTP), XL184 demonstrated activity in Wilms tumor *in-vivo* xenograft models, with 2/3 cell lines (KT-11 and KT 13) showing complete tumor growth control at Day 21. [Personal communication Dr. Malcolm Smith]

Expression levels of cabozantinib targets were evaluated in several indications using the R2 database, a genomics analysis and visualization platform (http://hgserver1.amc.nl/cgi-bin/r2/main.cgi, accessed September 2016 (personal communication Malcolm Smith)). A portion of the Ewing's sarcoma tumor samples show elevated AXL, MER, MET and KIT expression and a portion of rhabdomyosarcoma (RMS) samples show elevated AXL, MER and KIT, compared to normal tissue. For renal cell carcinoma (RCC) elevated expression of AXL, MET and RET was observed in a subset of samples. Moreover, cabozantinib has been approved for adults with RCC. A large portion of the hepatoblastoma samples had elevated MER expression compared to normal tissue. A subset of

glioblastoma (GBM) samples, a pediatric solid tumor with CNS involvement, had elevated expression of AXL and MER. While two datasets for thyroid cancer were available, one set had a single medullary thyroid carcinoma (MTC) sample and the other had no MTC samples. But cabozantinib has been approved for MTC in adults. No normal tissue was available for hepatocellular carcinoma (HCC) or clear cell sarcoma (melanoma) but elevated MET levels in these indications have been reported previously.[21,27,28] The adrenocortical carcinoma (ACC) data did not include normal tissue, but the MET pathway has been shown to be important in this malignancy and cabozantinib has shown activity in a preclinical models of ACC.[29] In Wilms tumors, MER had higher expression in a small number of samples, but the Wilms tumor dataset is small (39 samples; 5 controls), so may not adequately represent cabozantinib-relevant targets. Cabozantinib has activity in Wilms tumor xenograft models (personal communication, Malcolm Smith).

Based on the above extensive literature review as well as review of available on line databases of know potential targets of XL184, the following disease strata are proposed for evaluation in the phase 2 study: Ewing sarcoma, rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcomas (STS) including microphthalmia transcription factor associated STS (alveolar soft part sarcoma (ASPS) and clear cell sarcoma (CCS), osteosarcoma, Wilms tumor and rare tumors (medullary thyroid carcinoma (MTC), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), hepatoblastoma , adrenocortical carcinoma). In addition, to ensure that any pediatric solid tumor (including CNS tumors) with known molecular alterations in the targets of XL184 (i.e., MET amplification, overexpression, activating mutation, MET translocation, MET exon skipping mutations, activating RET mutations, RET rearrangement, overexpression or activation of AXL), a separate strata is included to allow enrollment of any tumor not in one of the outline strata that has documentation of the alteration from a CLIA certified laboratory.

2.2.2 Animal Toxicology

The toxicity profile of XL184 was studied in mice, rats, beagle dogs, and cynomolgus monkeys and included single dose and repeat dose studies, reproductive, developmental toxicity, and genotoxicity studies. These studies identified GI tract, bone marrow, lymphoid tissues, reproductive tract tissues, endocrine tissues, kidney and skin as target tissues for XL184-related toxicity. Additionally, histopathologic changes were also noted in bone, central nervous system (CNS) tissues and liver/gall bladder. No significant adverse effects on neurobehavioral or respiratory function were observed in rats, or in cardiovascular or electrocardiographic parameters (including QTc) in dogs at plasma exposures (AUC values) ≥ 10-fold higher than clinically relevant plasma exposures. XL184 associated adverse effects were generally dose-related, reversible upon discontinuation of the drug, and correlated with clinical findings. XL184 was shown to reduce fertility in both male and female rats. It was also embryotoxic in rats and caused fetal malformations in rats and rabbits.[1]

2.2.3 Preclinical Pharmacology

In vitro metabolism and drug-drug interaction studies showed that XL184 highly protein bound (99.9% at 0.2 and 1 µM, and 99.7% at 10 µM). It is metabolized primarily by amide cleavage and demethylation or oxidation, and subsequent

sulfation. XL184 is a substrate of CYP3A4 but not an inducer of CYP1A2, CYP2B6, or CYP3A4.[1]

Preclinical pharmacokinetics of a liquid aqueous formulation of XL184 studied in mice, rats, dogs, and monkeys showed moderate to high oral bioavailability with 80-86% in rats, 87% in dogs, 73% in monkeys and 42-51% in mice. Oral bioavailability was lower with capsule formulation in dogs (18%) and monkeys (13%). In rats and dogs, the peak concentration (Cmax) and drug exposure (AUC) of XL184 increased less than dose-proportionally with increasing single oral doses, and generally dose-proportionally with repeat daily oral dosing. Moderate accumulation was noted with repeat daily dosing in rats (≤ 4-fold), however this was not observed in dogs (≤ 2-fold increase).[1]

2.3 Adult Studies

2.3.1 Adult Phase 1 Studies

In the initial phase 1 trial of XL184 in adults with advanced solid tumors, two different schedules of administration and formulations of XL184 were evaluated in 85 patients. Dose levels studied included escalating doses of 0.08 to 11.52 mg/kg given on an intermittent schedule once daily for 5 days followed by 9 days rest with a suspension formulation, continuous fixed daily dosing of 175 or 265 mg with a suspension formulation, or continuous fixed daily dosing of 175 or 250 mg with capsule formulation (doses in salt weights). This study concluded 175 mg dose given continuously in capsule formulation as the maximum tolerated dose (MTD). Dose limiting toxicities (DLTs) included Grade 3 palmar-plantar erythrodysesthesia (PPE), Grade 3 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, Grade 3 lipase elevation, and Grade 2-3 mucositis. Most frequent treatment-related adverse effects observed (>20% of patients) were diarrhea, fatigue, decreased appetite, nausea, PPE, rash, increased AST, vomiting, and mucosal inflammation. 10/35 MTC patients had a confirmed objective response.[4] Although the MTD in the initial phase 1 trial was 175 mg daily, a significant percentage of patients receiving this dose required dose-reductions for toxicity, and lower doses were found to be better tolerated in subsequent trials. Doses as low as 40 mg PO daily were determined to be active and tolerable based on Week 6 bone scan response rate in men with castration resistant prostate cancer (CRPC) and bone metastasis and a dose of 60 mg PO daily was used in many recent single agent trials.[30]

2.3.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

XL184 pharmacokinetics were evaluated in the phase 1 trial described above. The study showed dose proportional increase in Cmax and AUC. After repeat daily dosing, terminal half-life values was 91.3 ± 33.3 hours, and apparent steady-state plasma levels were reached by Day 15. Steady-state exposure (AUC) was 4-5 fold higher compared with day 1 exposure, suggesting accumulation with repeat daily dosing.[4]

From a population pharmacokinetics (PopPK) analysis in patients with MTC who received repeated oral daily dosing of XL184 (cabozantinib) capsules at 140 mg, the predicted effective half-life of XL184 is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the estimated clearance

(CL/F) at steady-state is 4.4 L/h. The terminal half-life was approximately 120 hours, median time to maximum plasma concentrations (T_{max}) for XL184 was noted to range from 2 to 5 hours post-dose after oral administration of XL184 (cabozantinib) capsule. Accumulation was noted with repeat dosing, with mean exposure 4- to 5-fold higher with daily dosing compared with a single dose administration and steady state was achieved by Day 15. In another PopPK analysis that was conducted in subjects with RCC who received repeated oral daily XL184 (cabozantinib) tablet dosing at 60 mg (with dose reductions to 40 mg and 20 mg permitted per protocol) and healthy subjects who received a single oral XL184 tablet dose of 20, 40, or 60 mg, the predicted terminal plasma half-life of XL184 was approximately 99 h; the terminal phase volume of distribution (Vz) was approximately 319 L; and the CL/F at steady-state was estimated to be approximately 2.2 L/h for a white male subject. Food may interfere with XL184 absorption and a high-fat meal was shown to increase Cmax and AUC values by 41% and 57% respectively. XL184 is highly protein bound in human plasma (≥ 99.7%), is a substrate of CYP3A4 in vitro, and elimination in feces and urine has been noted.[1,31]

In a phase 2 trial of XL184 in urothelial carcinoma (NCT01688999), an association of clinical outcome with systemic immunity was demonstrated. Patients with low regulatory T-cells (Treg) at baseline had an improved partial response rate and improved PFS, and changes in Treg PD-1 and myeloid-derived suppressor cells (MDSC) CD40 expression were also associated with response suggesting that they may serve as prognostic markers in patients with advanced urothelial carcinoma.[32] Significant associations were seen with overall survival and PFS in analysis of monocyte subsets, MDSC subsets, Treg subsets, effector T-cells, and Th1 and Th2 cell populations, all analyzed by multiparameter flow cytometry, and in gene expression in peripheral blood, analyzed by RT-qPCR or NanoString technology [Personal communication with Jane Trepel].

2.3.3 Efficacy (Phase 2 and 3 studies)

XL184 capsules 140 mg orally once daily was approved for adults with progressive, metastatic MTC based on a phase 3 2:1 randomized, placebo-controlled trial of 330 patients with metastatic medullary thyroid cancer in which patients in the XL184 arm had an improved median PFS of 11.2 months compared to 4 months for those in the placebo arm (HR 0.28, 95% CI 0.19, 0.40, p<0.001).[36] XL184 tablets 60 mg PO daily (free base equivalent) has also been approved for patients with advanced RCC who have received prior anti-angiogenic therapy, based on improvement in PFS in patients receiving XL184 (60 mg PO daily) compared to everolimus (10 mg PO daily) in a phase 3 randomized study. The median PFS was 7.4 months in the XL184 arm compared to 3.8 months in everolimus arm (HR 0.58 (95% CI: 0.45, 0.74); p<0.0001), and the median overall survival in the intent-to-treat population was 21.4 and 16.5 months in the XL184 and everolimus arms respectively [HR 0.66 (95% CI: 0.53, 0.83); p=0.0003]. Confirmed response rate was 17% (95% CI: 13, 22) in the XL184 arm and 3% (95% CI: 2, 6) in the everolimus arm.[7,33] XL184 has also shown preliminary clinical activity in early phase trials in glioblastoma, differentiated thyroid carcinoma, HCC, breast, and NSCLC.[1,5,34,35] Ongoing adult trials include a randomized phase 3 trial for HCC and phase 2 trials in many cancer types including endometrial carcinoma, urothelial cancers, soft tissue sarcomas, bone sarcomas,

and advanced solid tumors with bone metastasis. Other ongoing trials include combination of XL184 with panitumumab (colorectal cancer), nivolumab +/- ipilimumab (urothelial cancer), and traztumumab (breast cancer with brain metastasis).

2.4 Pediatric Studies

2.4.1 Pediatric Phase 1 Studies

An ongoing COG/Pilot Consortium phase 1 trial (ADVL1211) of XL184 in pediatric patients with solid tumors is nearing completion. This trial enrolled patients at 3 dose levels: 30 mg/m^2, 40 mg/m^2, and 55 mg/m^2 once daily on a continuous dosing schedule. In this trial, 41 patients were enrolled of whom 36 patients were fully evaluable. Patients with a variety of solid tumors enrolled: MTC (n=5), osteosarcoma (n=2), Ewing sarcoma (n=4), rhabdomyosarcoma (n=2), other soft tissue sarcoma (n=4), Wilms tumor (n=2), hepatoblastoma (n=2), HCC (n=2), RCC (n=3), CNS tumors (n=9), and other (n=6). Cycle 1 DLTs were fatigue, headache, proteinuria, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), palmar-plantar erythrodysesthesia, oral mucositis, ALT increase, lipase increase, and bilirubin increase. The most frequent adverse events were increased ALT, hypertension, proteinuria, diarrhea, thrombocytopenia, fatigue, hypothyroidism, nausea, anorexia, palmar-plantar erythrodysesthesia, neutropenia, and vomiting. Based on DLTs in cycle 1 and in later cycles requiring dose reductions, the 40 mg/m^2/day on a continuous schedule (1 cycle = 28 days) was determined to be the recommended phase 2 dose. This dose corresponds to an adult fixed dose of 72 mg/day, which is similar to the current adult recommended dose of 60 mg/dose/day. Based on central review, partial responses were seen in 2/5 patients with MTC, one patient with Wilms tumor, and one patient with clear cell sarcoma. In addition, 7 patients experienced stable disease and received ≥ 8 treatment cycles (1 patient each with paraganglioma, Ewing sarcoma, synovial sarcoma, ependymoma, and alveolar soft part sarcoma, and 2 patients with MTC). A CTEP sponsored phase 2 study conducted by INCA investigators in patients greater than 12 years of age with recurrent/relapsed osteosarcoma and Ewing sarcoma is also currently ongoing.

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Pharmacokinetics of XL184 were evaluated in the COG/Pilot Consortium phase 1 trial (ADVL1211). A preliminary (October 2014) pharmacokinetic analysis was performed using available plasma concentration data from 37 subjects enrolled in ongoing study XL184-011 (ADVL1211). Steady state pharmacokinetics were analyzed in 32 patients where full set of samples were available on Cycle 1 day 22. Drug exposure (AUC) was similar for the 3 dose levels (30 mg/m^2, 40 mg/m^2, and 55 mg/m^2) evaluated with no dose proportional increase in exposure. The peak concentration (C_{max}) was also similar across the 3 doses levels. The BSA-normalized oral clearance appeared to be similar across the dose levels with a mean ± SD value of 1649 ± 754 L/h/m^2 for all patients. BSA-normalized Cl/F values were similar in females and males (1539 ± 547 L/h/m^2 versus 1835 ± 940 L/h/m^2), and were higher in children ages 12 or younger compared to older children (1889 ± 828 L/h/m^2 versus 1533 ± 694 L/h/m^2); however, this did not reach statistical significance (p value 0.31, Wilcoxon rank sum test). Since the elimination half-life could not be calculated for most patients, an accumulation

ratio was calculated from the plasma concentrations measured 4 hours after drug administration on day 1 and day 21. The half-life was then calculated from this value. The accumulation ratio was 4.3 ± 3.9 and the half-life was 66.2 ± 64.7 hours. Estimates of the cabozantinib pharmacokinetic parameters are summarized below:

Dose Level	30 mg/m^2/d	40 mg/m^2/d	55 mg/m^2/d
N	6	16	10
C_{max}, ng/ml	2025 ± 658 (32%)	1693 ± 692 (41%)	2389 ± 802 (34%)
T_{max}, h	5.24 ± 8.93 (170%)	7.38 ± 8.46 (115%)	4.7 ± 6.57 (140%)
AUC_{0-24h}, h*ng/ml	32216 ± 8022 (25%)	30010 ±10985 (37%)	38101 ± 12785 (34%)
Cl/f, ml/h	1621 ± 430 (26%)	2210 ± 857 (39%)	2307 ± 1045 (45%)
Cl/f/m^2, ml/h	1140 ± 357 (31%)	1809 ± 872 (48%)	1790 ± 638 (36%)
Accumulation Ratio $C_{4hr,day21}$/ $C_{4hr,day1}$	5.25 ± 2.17 (41%)	4.72 ± 5.06 (107%)	2.82 ± 1.23 (44%)
Accumulation Adjusted $t_{1/2}$, h	78.7 ± 36.3 (46%)	79.1 ± 86.3 (109%)	37.8 ± 20.8 (55%)

In light of this PK variability observed in study ADVL1211, additional PK sampling is proposed for the planned Ph2 study in order to determine more reliable and precise PK data for cabozantinib in the pediatric population.

Assays of circulating plasma markers prior to (baseline) and after administration of XL184 (cycle 1 day 21 and day 28) including AXL, interleukin 6, osteopontin, tissue inhibitor of metalloproteinase 1, carbonic anhydrase 9, HGF, sMET, PlGF, sVEGFR2, and erythropoietin have been completed, and the data is currently being analyzed.

2.5 Pneumothorax

As of 7 November 2016, the following observations have been made with regards to pneumothorax cases in subjects exposed to cabozantinib:

- Ten of the 60 patients accrued in the NCI-CTEP sarcoma trial 9620 have experienced Grade 1 – Grade 3 pneumothorax (16.7%). Four of the 10 patients experienced Grade 1 or Grade 2 pneumothorax events and the remaining 6 experienced Grade 3 events. Overall, the median age of the 10 patients experiencing pneumothorax was 19.5 years (range 13-45 years), with 8 males and 2 females. Five of the 10 patients received cabozantinib for Ewing sarcoma and 5 for osteosarcoma.

  Upon review, all 10 patients had metastatic pulmonary lesions at study entry: 7 bilateral and 3 unilateral. Other confounding risk-factors for pneumothorax were identified in 4 of the 10 patients: Marfanoid morphotype; post-surgical pleuro-pulmonary fistula following a thoracic surgery at approximately 2 months after cabozantinib discontinuation; prior Staph aureus pneumopathy and preexisting pleural metastases. All 10 patients had resolution of pneumothorax: resolution occurred in 8 patients with treatment that involved O_2 therapy or procedures such as drain placement, silver nitrate/talc pleurodesis, subtotal pleurectomy and spontaneously without treatment in 2 patients. Cabozantinib therapy was continued or restarted in 5 of the 10 patients after pneumothorax was resolved.

- In the cabozantinib development program, 21/2584 (0.8%) patients exposed to cabozantinib in unblinded, controlled and open-label, Exelixis-sponsored trials, irrespective of causality association, grade or seriousness, have been documented to have sustained one or more pneumothoraces. Seven of the 21 patients apparently experienced their events in association with either traumatic rib fractures or invasive medical procedures. In the remaining 14 patients, potential confounders were identified in the majority of cases and included: lung and/or mediastinal metastases (n=13), probable pneumonia (n=5), pleural metastases (n=4), prior history of pneumothorax (n=3), chronic obstructive lung disease/bullous lung disease (n=3), probable bronchial obstruction (n=2); and baseline cavitary lesions (n=1).

- In the postmarketing setting, 4 cases of pneumothorax were reported with Cometriq™ and 0 cases with Cabometyx™. None of the cases were medically confirmed and information regarding diagnosis and clinical course was limited. Possible confounders included pneumonia in two and lung metastases in one case.

2.5.1 Published Pneumothorax Rates in Sarcoma Patients

Information about the prevalence and the risk factors of pneumothorax in sarcoma patients has been limited. In the published literature, spontaneous pneumothorax has been described at an approximately 5% rate in untreated osteosarcoma and Ewing sarcoma patients with pulmonary metastases, with a high frequency of recurring episodes up to 30% in some series.[36] Multiple reports suggest that therapy with anti-angiogenic agents may increase the frequency of this event, especially in young patients. A frequency as high as 25% has been observed in patients treated with a combination of sorafenib, bevacizumab and cyclophosphamide.[37,38] Nakano and colleagues reported a pneumothorax incidence of 10.3% in 58 children with soft tissue sarcomas treated with pazopanib. Further, the maximum diameter of lung metastases ≥ 30 mm and a history of pneumothorax before pazopanib treatment were significantly predictive of pneumothorax in their study.[39] Histologies associated with pneumothorax included rhabdoid tumor, synovial sarcoma, osteosarcoma, Ewing sarcoma, Wilms' tumor, and renal cell carcinoma. Cavitation of pulmonary nodules in response to antiangiogenic therapy has been observed to be associated with pneumothorax.[37]

2.6 Overview of Proposed Pediatric Phase 2 Trial

This will be an open label two-stage phase 2 trial in the following solid tumor strata: Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), osteosarcoma, Wilms tumor (non-statistical cohort) and other rare solid tumors (non-statistical cohort). The XL184 dose for this trial will be 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram), the recommended phase 2 dose determined from ADVL1211. XL184 will be administered orally once daily (20 and 60 mg tablets) on a continuous dosing schedule for cycles of 28 days with no rest period between cycles. Dosing will be performed based on body surface area (BSA), and rounded to the nearest 20 mg using a dosing nomogram as used in ADVL1211. Treatment will continue until tumor progression or unacceptable toxicity.

The primary endpoint for all non-osteosarcoma disease strata will be the objective response rate. In each of the statistical cohorts, 13 patients will be enrolled on the first stage. If at least 1 response is noted, the study will proceed to the second stage where up to an

additional 7 patients may be enrolled. If 3 or more responses are noted, the drug will be considered to have sufficient activity to suggest further evaluation in that strata. We will also evaluate PFS, time to progression, and overall survival, and if feasible, compare PFS to historical controls to assess if XL184 may demonstrate activity via tumor stabilization rather than tumor shrinkage. For the osteosarcoma stratum, a two-stage design that incorporates dual end points of objective response based on RECIST criteria (CR+PR) and treatment success as defined by stable disease for ≥ 4 months will be utilized (see section 9.4 for details). This end point has been used in recent COG phase 2 trials for osteosarcoma as it is felt that tumor shrinkage may not be always be observed in bone-based lesions and some agents may demonstrate activity by prolonged disease stabilization. Toxicity will be graded using version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0). Pharmacokinetics of XL184 will be further studied in pediatric and adolescent patients, as pharmacokinetic studies on the pediatric phase 1 trial ADVL1211 were performed on a small sample size, and showed significant variability. To gain additional information on pharmacokinetics of XL184 in the pediatric population especially in a subpopulation of different age groups, additional pharmacokinetic studies will be performed on this study. The effect of XL184 on patients' immune cells will be evaluated by collecting blood samples prior to and after treatment with XL184, as an association of clinical outcome with systemic immunity has been demonstrated in a phase 2 trial of XL184 in urothelial carcinoma (NCT01688999). Tumor tissue (snap frozen, FFPE blocks, or unstained slides), if available, from diagnosis, relapse, or both, will also be collected for potential future studies.

2.7 Rationale for Inclusion of Osteosarcoma Cohort (Amendment #1)

There is a strong biologic rationale for targeting VEGF and MET in osteosarcoma. Elevated tumor and circulating levels of VEGF have been shown to positively correlate with increased pulmonary metastasis in osteosarcoma and may be associated with worse prognosis[10]. MET overexpression has been observed in >80% of osteosarcoma tissue samples, and MET expression was shown to correlate with aggressive phenotype and poor prognosis. Overexpression of MET by lentiviral genetransfer converted human osteoblast cells into osteosarcomas, and tumorigenesis and transformation were abolished when MET expression and signaling was impaired by shRNA or dominant negative MET receptor. PF-2341066, an orally available MET inhibitor inhibited proliferation, survival, invasion and clonogenecity in osteosarcoma cell lines and tumor growth and associated osteolysis and extracortical bone matrix formation in nude mice osteosarcoma xenograft models.[12,13]

3.0 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number.

COG sites: This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Non-COG sites: Fax the patient registration information (demography) to the Cancer Trials Support Unit (CTSU) registrar at 1-888-691-8039. Sites may notify the registration office of an incoming fax by calling 1888-462-3009; the office hours are 9:00 – 5:30 pm Eastern Time, Monday – Friday. The CTSU registrar will then register the patient within the COG system on behalf of the institution and obtain a COG patient ID number. The CTSU registrar will provide the COG patient ID number to the site, which can then enroll the patient in the OPEN system.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

NOTE: In order for a COG institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

3.1.2 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.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

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. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. However, these sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study so that the study approval can be applied to those institutions. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available for the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions: https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.5 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 5 calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible and will not be able to receive further protocol therapy.**

See Section 3.2 for timing requirements for eligibility studies. **Note: Repeat laboratory and imaging studies may be required if enrollment and start of therapy do not occur on the same day.**

3.1.6 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.

3.1.7 Participation in Biology Studies (COG sites)
In order to minimize the potential for non-compliance once enrolled, patients/guardians must be made aware that some of the biology research studies are mandatory and understand that a number of non-standard blood samples will be required.

3.2 Eligibility: Inclusion Criteria

Important note: The inclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.

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 > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow biopsy and/or aspirate, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

3.2.1 Age: Patients must be ≥ 2 and ≤ 30 years of age at the time of study entry for all strata except upper age limit of ≤ 18 years of age for MTC, RCC and HCC.

3.2.2 Body Surface Area (BSA): Patients must have a body surface area ≥ 0.35 m^2.

3.2.3 Diagnosis: Patients must have recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. Patients must have had histologic verification of one of the malignancies listed below at original diagnosis or at relapse.

- Ewing sarcoma
- Rhabdomyosarcoma (RMS)
- Non-rhabdomyosarcoma soft tissue sarcomas (STS) including microphthalmia transcription factor associated STS (alveolar soft part sarcoma (ASPS) and clear cell sarcoma (CCS))
- Osteosarcoma
- Wilms tumor
- Rare tumors
    - Medullary thyroid carcinoma (MTC)

- Renal cell carcinoma (RCC)
- Hepatocellular carcinoma (HCC)
- Hepatoblastoma
- Adrenocortical carcinoma
- Pediatric solid tumors (including CNS tumors) with known molecular alterations in the targets of XL184 (i.e., MET amplification, overexpression, activating mutation, MET translocation, MET exon skipping mutations, activating RET mutations, RET rearrangement, overexpression or activation of AXL). Documentation of the alteration from a CLIA certified laboratory will be required.

Note: Documentation of any known tumor molecular alterations and RET mutation status for patients with MTC (germline) must be uploaded via the RAVE system.

3.2.4 Disease Status

3.2.4.1 Patients must have radiographically measurable disease.

Measurable disease is defined as the presence of at least one lesion on MRI or CT scan that can be accurately measured with the longest diameter a minimum of 10 mm in at least one dimension (CT scan slice thickness no greater than 5 mm).

Note: The following do NOT qualify as measurable disease:

- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans)
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurement parameters noted above.

3.2.5 Performance Level

Patients must have a Lansky or Karnofsky performance status score of ≥ 50, corresponding to ECOG categories 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. 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.
(See https://members.childrensoncologygroup.org/prot/reference_materials.asp)

3.2.6 Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

3.2.6.1 Myelosuppressive chemotherapy:

3.2.6.1.1 Solid Tumors:
Patients with solid tumors must not have received myelosuppressive chemotherapy within 3 weeks of enrollment onto this study (6 weeks if prior nitrosourea).

3.2.6.2 Hematopoietic growth factors: At least 7 days must have elapsed since the completion of therapy with a growth factor. At least 14 days must have elapsed after receiving pegfilgrastim.

3.2.6.3 Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for commercial and investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

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

3.2.6.5 Radiotherapy: ≥ 2 weeks must have elapsed since local palliative XRT (small port); ≥ 6 weeks must have elapsed since treatment with therapeutic doses of MIBG; ≥ 3 months must have elapsed if prior craniospinal XRT was received, if ≥ 50% of the pelvis was irradiated, or if TBI was received; ≥ 6 weeks must have elapsed if other substantial bone marrow irradiation was given.

Subjects should not have any clinically relevant ongoing complications from prior radiation therapy (i.e., radiation esophagitis or other inflammation of the viscera).

3.2.6.6 Stem Cell Transplant or Rescue without TBI: No evidence of active graft vs. host disease and ≥ 2 months must have elapsed since transplant.

3.2.6.7 Study specific limitations on prior therapy: Not previously received XL184 or another MET/HGF inhibitor (tivantinib or crizotinib). There are no limits on number of prior therapeutic regimens. Patients who have been treated with prior VEGF pathway, or RET inhibitors (except XL184) may be eligible.

3.2.7 Organ Function Requirements

3.2.7.1 Adequate Bone Marrow Function Defined As:

3.2.7.1.1 For patients with solid tumors without bone marrow involvement:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 100,000/μL (transfusion independent, defined as not receiving platelet transfusions within a

7 day period prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions).

3.2.7.1.2 For patients with solid tumors and known bone marrow metastatic disease:
- Peripheral absolute neutrophil count (ANC) ≥ 750/μL
- Platelet count ≥ 50,000/μL
- Hemoglobin ≥ 8.0 g/dL

Transfusions are permitted to meet both the platelet and hemoglobin criteria. Patients must not be known to be refractory to red blood cell or platelet transfusions.

3.2.7.2 Adequate Renal Function Defined As:
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 **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

3.2.7.3 Adequate Liver Function Defined As:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L (3x ULN) (for the purpose of this study, the ULN for SGPT is 45 U/L)
- Serum albumin ≥ 2.8 g/dL.

3.2.7.4 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).

3.2.7.5 Central Nervous System Function Defined As:

- Patients with a known seizure disorder who are receiving non-enzyme inducing anticonvulsants and have well-controlled seizures may be enrolled. See Appendix VII for a list of recommended non-enzyme inducing anticonvulsants.
- CNS toxicity ≤ Grade 2 with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

3.2.7.6 Adequate Blood Pressure Control defined as:
A blood pressure (BP) ≤ the 95th percentile for age, height, and gender for pediatric patients < 18 years old (Appendix V) and ≤ 140/90 mmHg for patients ≥ 18 years old. BP should be measured as described in Section 5.5, and patients should not be receiving medication for treatment of hypertension (except patients with Wilms tumor and RCC who may be eligible if on stable doses of no more than one anti-hypertensive medication with a baseline BP ≤ ULN for pediatric patients and ≤ 140/90 for adult patients). Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP.

3.2.7.7 Adequate Coagulation Defined as:

- INR ≤ 1.5

3.2.7.8 Adequate Pancreatic Function Defined as:

- Serum amylase ≤ 1.5 x ULN
- Serum lipase ≤ 1.5 x ULN

3.3 Eligibility: Exclusion Criteria

Important note: The exclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.

3.3.1 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.

3.3.2 Concomitant Medications

3.3.2.1 Growth factor(s): Growth factors that support platelet or white cell number or function must not have been administered within the 7 days prior to enrollment (14 days if pegfilgrastim).

3.3.2.2 Corticosteroids: Patients requiring corticosteroids who have not been on a stable or decreasing dose of corticosteroid for the 7 days prior to

enrollment are not eligible. If used to modify immune adverse events related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

3.3.2.3 Previous treatment with XL184 (cabozantinib) or another MET/HGF inhibitor (tivantinib, crizotinib).

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

3.3.2.5 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

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

3.3.2.7 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 II.

3.3.2.8 Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin, and Factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel) are prohibited.

Note: Low-dose aspirin for cardioprotection (per local applicable guidelines) and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 6 weeks before first dose of study treatment, and who have had no complications from a thromboembolic event or the anticoagulation regimen.

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

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

3.3.3 Patients who are unable to swallow intact tablets are not eligible.

3.3.4 Patients who have an uncontrolled infection are not eligible.

3.3.5 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.

3.3.6 Patients with active bleeding are not eligible. Specifically, no clinically significant GI bleeding, GI perforation, intra-abdominal abscess or fistula for 6 months prior to enrollment, no hemoptysis or other signs of pulmonary hemorrhage for 3 months prior to enrollment. 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). In patients with CNS tumors, an MRI with ECHO gradient sequences would be required to exclude presence of petechial hemorrhages.

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

- Major surgical procedure, laparoscopic procedure, or open biopsy 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 catheter, peripherally inserted central catheter (PICC)) and at least 7 days prior to enrollment for a 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

NOTE: For purposes of this study, bone marrow aspirate and biopsy are not considered surgical procedures and therefore are permitted within 14 days prior to start of protocol therapy.

3.3.8 Patients who have had significant traumatic injury within 28 days prior to enrollment are not eligible.

3.3.9 Patients with any medical or surgical conditions that would interfere with gastrointestinal absorption of the study drug are not eligible.

3.4 Regulatory

3.4.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.4.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Open label two-stage single arm study, with XL184 administered at 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2) on a continuous dosing schedule (one cycle = 28 days). Based on patients' BSA, there may be days that the dose will not be administered. The weekly dosing schedule can be found in Appendix IV. Dosing will be performed based on body surface area (BSA), and rounded to the nearest 20 mg using a dosing nomogram (see Appendix IV). Treatment will continue until tumor progression or unacceptable toxicity.

4.1.1 Dose Reduction

Dose reductions will be allowed for toxicities as outlined in Section 5.0 for patients who recover to eligibility criteria as outlined in Section 3.2 within 21 days of drug interruption.

4.1.2 Dose Escalation

There will be no drug dose escalation.

4.1.3 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 3.2.7 and has not experienced study-drug related adverse events warranting permanent discontinuation.

4.1.4 Concomitant Therapy

4.1.4.1 No other cancer chemotherapy, radiotherapy, or immunomodulating agents will be used.

4.1.4.2 Medications that are strong inhibitors or inducers of CYP3A4 should be avoided (see Appendix II). 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.

4.1.4.3 In vitro data indicate that XL184 is an inhibitor of P-glycoprotein (P-gp) transport activity. Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use

caution when administering XL-184 with drugs known to be P-gp substrates (e.g., fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.). XL184 is also a substrate of drug transporter MRP2, which may result in an increased plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirdine, efavirenz, and emtricitabine

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

4.1.4.5 XL184 has been associated with prolonged QTc, so medications that prolong or may prolong QTc should be avoided when possible (see Appendix VIII). If other medications that prolong QTc or may prolong QTc have to be used concomitantly, then QTc should be carefully monitored.

4.1.4.6 XL184 is highly protein bound (99.9%). Use caution when coadministering XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol).

4.1.4.7 Patient drug information handout and wallet card should be provided to patients on study, see Appendix X.

4.1.5 Study Specific Supportive Care:

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See Section 4.1.4 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 VI).

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.

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.

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]).

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.2 Cycle 1

4.2.1 Therapy Delivery Map – Cycle 1 This Therapy Delivery Map (TDM) relates to Cycle 1. Each cycle lasts 28 days.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 3.2.7. Extensive treatment details are in Section 4.2.3.
This TDM is on 1 page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
XL184 (cabozantinib)	PO	40 mg/m^2/day	1-28	See Appendix IV for dosing nomogram. The cumulative weekly dose is 280 mg/m^2. XL184 should be taken at approximately the same time each day on an empty stomach; patients should fast 2 hours before and 1 hour after taking the drug.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**XL184** ____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg	a-n
		2	_____mg	
		3	_____mg	
		4	_____mg	
		5	_____mg	
		6	_____mg	
		7	_____mg	
		8	_____mg	a
		9	_____mg	
		10	_____mg	
		11	_____mg	
		12	_____mg	
		13	_____mg	
		14	_____mg	
		15	_____mg	a, c, d, k
		16	_____mg	
		17	_____mg	
		18	_____mg	
		19	_____mg	
		20	_____mg	
		21	_____mg	
		22	_____mg	a, m
		23	_____mg	
		24	_____mg	
		25	_____mg	
		26	_____mg	
		27	_____mg	
		28	_____mg	g, i, k

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Cycle 1

4.2.2 Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Hx/PE with VS including BP. Prior to Cycle 1 and weekly during Cycle 1. Please see Section 5.5 for additional guidance regarding BP.
b. Wt/Ht/Performance status.
c. CBC/diff/platelets. Prior to Cycle 1 and every 2 weeks during Cycle 1.
d. Electrolytes, BUN, creatinine, Ca^{++}, PO_4, Mg^{++}, AST, ALT, bilirubin, albumin, urinalysis, amylase, lipase. Prior to Cycle 1 and every 2 weeks during Cycle 1. See Section 5.4 for dose modifications due to proteinuria.
e. TSH. Patients found to have an abnormal TSH level should have a free T4 level measured. Patients who enter the study on thyroid replacement should have their medication adjusted to maintain TSH in the normal range.
f. PT/INR/APTT.
g. ECG including QTc interval. Prior to Cycle 1 and at the end of Cycle 1.
h. Tumor disease evaluation. Prior to Cycle 1.
i. CEA, calcitonin (for patients with MTC only). Prior to Cycle 1 and at the end of Cycle 1. Calcitonin measurements should be obtained in the fasting state.
j. X-ray tibial growth plate. Prior to start of therapy in all patients ≤ 18 years of age at enrollment. See Section 5.10.1 for details.
k. Patient diary. Every other week during Cycle 1. For patient diary see Appendix III.
l. Pharmacodynamics. See Section 7.2.2 for details.
m. Pharmacokinetics. Cycle 1. See Section 7.2.1 for details.
n. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to the start of each cycle; sexually active patients must use an acceptable method of birth control.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Cycle 1

4.2.3 Treatment Details: Cycle 1

One cycle of XL184 treatment is described below. A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility Section 3.2.7.

XL184: PO
Days: 1-28
Dose: 40 mg/m^2/day

Dosing will be performed based on body surface area (BSA), and rounded to the nearest 20 mg using the dosing nomogram (see Appendix IV). The cumulative weekly dose is 280 mg/m^2. Treatment will continue until tumor progression or unacceptable toxicity.

XL184 will be administered orally at approximately the same time each day.

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 IV). 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 every 2 weeks during Cycle 1.

If a patient vomits after the dose of XL184 is administered, the dose should not be repeated. The tablet should be taken with a large glass of water on an empty stomach, and patient should not eat 2 hours before or 1 hour after each dose of XL184. The tablet should not be crushed or broken. Furthermore, a missed dose should not be taken within 12 hours of the next dose.

Patients should not eat grapefruit or drink grapefruit juice while being treated with XL184.

A note should be made in the patient diary if any of the above events take place.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of cycle, the next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.7), whichever occurs later.

Cycle 1

4.3 Cycles 2 & 3

4.3.1 Therapy Delivery Map – Cycles 2 & 3

This Therapy Delivery Map (TDM) relates to Cycles 2 and 3. Each cycle lasts 28 days. Treatment may continue in the absence of disease progression or unacceptable toxicity. Use a copy of this page once for Cycle 2 and once for Cycle 3 (please note cycle number below).

_____
Patient COG ID number

_____
DOB

Criteria to start each cycle are listed in Section 3.2.7. Extensive treatment details are in Section 4.3.3. This TDM is on 1 page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
XL184 (cabozantinib)	PO	40 mg/m^2/day	1-28	See Appendix IV for dosing nomogram. The cumulative weekly dose is 280 mg/m^2. XL184 should be taken at approximately the same time each day on an empty stomach; patients should fast 2 hours before and 1 hour after taking the drug.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	XL184 ____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg	a-e, g, i, j
		2		
		3		
		4		
		5		
		6		
		7		
		8		
		9		
		10		
		11		
		12		
		13		
		14		
		15		a, c, d
		16		
		17		
		18		
		19		
		20		
		21		
		22		
		23		
		24		
		25		
		26		
		27		
		28	_____mg	f#, h, k#, l#

#Cycle 2 only. See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Cycles 2 & 3

4.3.2 Required Observations in Cycles 2 &3

a. Hx/PE with VS including BP. Every 2 weeks. Please see Section 5.5 for additional guidance regarding BP.
b. Wt /Ht/Performance status. Day 1 of each Cycle.
c. CBC/diff/platelets. Every 2 weeks.
d. Electrolytes, BUN, creatinine, Ca^{++}, PO_4, Mg^{++}, AST, ALT, albumin, bilirubin, urinalysis, amylase, lipase. Every 2 weeks. See Section 5.4 for dose modifications due to proteinuria.
e. TSH. Day 1 of each cycle. Patients found to have an abnormal TSH level should have a free T4 level measured. See Section 5.10.2 for details and management of thyroid toxicity.
f. ECG including QTc interval. End of Cycle 2.
g. X-ray tibial growth plate. Prior to Cycle 2 in patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained. See Section 5.10.1 for details and management of growth plate toxicity.
h. Patient diary. End of each cycle. For patient diary see Appendix III.
i. Pharmacodynamics. Prior to Cycles 2 and 3. See Section 7.2.2 for details.
j. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to the start of each cycle; sexually active patients must use an acceptable method of birth control.
k. Tumor disease evaluation. End of Cycle 2. 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.
l. CEA, calcitonin (for patients with MTC only). End of Cycle 2. Calcitonin measurements should be obtained in the fasting state.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Cycles 2 & 3

4.3.3 Treatment Details: Cycles 2 & 3

One cycle of XL184 treatment is described below. A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility Section 3.2.7.

XL184: PO
Days: 1-28
Dose: 40 mg/m^2/day

Dosing will be performed based on body surface area (BSA), and rounded to the nearest 20 mg using the dosing nomogram (see Appendix IV). The cumulative weekly dose is 280 mg/m^2. Treatment will continue until tumor progression or unacceptable toxicity.

XL184 will be administered orally at approximately the same time each day as prescribed.

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 IV). 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. The tablet should be taken with a large glass of water on an empty stomach, and patient should not eat 2 hours before or 1 hour after each dose of XL184. The tablet should not be crushed or broken but be swallowed whole. Furthermore, a missed dose should not be taken within 12 hours of the next dose.

Patients should not eat grapefruit or drink grapefruit juice while being treated with XL184.

A note should be made in the patient diary if any of the above events take place.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of cycle, the next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.7), whichever occurs later.

Cycles 2 & 3

4.4 All Subsequent Cycles

4.4.1 Therapy Delivery Map – All Subsequent Cycles	
This Therapy Delivery Map (TDM) relates to all subsequent cycles. Each cycle lasts 28 days. Treatment may continue in the absence of disease progression or unacceptable toxicity. Use a copy of this page once for each cycle (please note cycle number below).	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 3.2.7. Extensive treatment details are in Section 4.4.3.
This TDM is on 1 page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
XL184 (cabozantinib)	PO	40 mg/m^2/day	1-28	See Appendix IV for dosing nomogram. The cumulative weekly dose is 280 mg/m^2. XL184 should be taken at approximately the same time each day on an empty stomach; patients should fast 2 hours before and 1 hour after taking the drug.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	XL184 ____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____ mg	a-e, (f-h)*, i#, k
		2		
		3		
		4		
		5		
		6		
		7		
		8		
		9		
		10		
		11		
		12		
		13		
		14		
		15		
		16		
		17		
		18		
		19		
		20		
		21		
		22		
		23		
		24		
		25		
		26		
		27	↓	
		28	_____ mg	j

*Prior to Cycle 5 and 7, and every 3rd cycle thereafter. #Prior to Cycle 5 and every 6 cycles thereafter.
See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

All Subsequent Cycles

4.4.2 Required Observations in All Subsequent Cycles

a. Hx/PE with VS including BP. Day 1 of each cycle. Please see Section 5.5 for additional guidance regarding BP.
b. Wt/Ht/Performance status. Day 1 of each cycle.
c. CBC/diff/platelets. Day 1 of each cycle.
d. Electrolytes, BUN, creatinine, Ca^{++}, PO_4, Mg^{++}, bilirubin, AST, ALT, albumin, urinalysis, amylase, lipase. Day 1 of each cycle. See Section 5.4 for dose modifications due to proteinuria.
e. TSH. Day 1 of each cycle. Patients found to have an abnormal TSH level should have a free T4 level measured. See Section 5.10.2 for details and management of thyroid toxicity.
f. ECG including QTc interval. Prior to Cycle 5 and 7 and then every 3rd cycle.
g. Tumor disease evaluation. Prior to Cycle 5 and 7 and then every 3rd cycle. 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.
h. CEA, calcitonin (for patients with MTC only). Prior to Cycle 5 and 7 and then every 3rd cycle. Calcitonin measurements should be obtained in the fasting state.
i. X-ray tibial growth plate. Prior to Cycle 5 and every 6 cycles thereafter in patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained. See Section 5.10.1 for details and management of growth plate toxicity.
j. Patient diary. End of each cycle. For patient diary see Appendix III.
k. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to the start of each cycle; sexually active patients must use an acceptable method of birth control.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.4.3 Treatment Details: All Subsequent Cycles

One cycle of XL184 treatment is described below. A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility Section 3.2.7.

XL184: PO
Days: 1-28
Dose: 40 mg/m^2/day

Dosing will be performed based on body surface area (BSA), and rounded to the nearest 20 mg using the dosing nomogram (see Appendix IV). The cumulative weekly dose is 280 mg/m^2. Treatment will continue until tumor progression or unacceptable toxicity.

XL184 will be administered orally at approximately the same time each day as prescribed.

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 IV). 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. The tablet should be taken with a large glass of water on an empty stomach, and patient should not eat 2 hours before or 1 hour after each dose of XL184. The tablet should not be crushed or broken. Furthermore, a missed dose should not be taken within 12 hours of the next dose.

Patients should not eat grapefruit or drink grapefruit juice while being treated with XL184.

A note should be made in the patient diary if any of the above events take place.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of cycle, the next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.7), whichever occurs later.

5.0 DEFINITIONS AND DOSE MODIFICATION FOR TOXICITY

All dose modifications should be based on the worst preceding toxicity. The severity of adverse events will be graded utilizing the NCI CTCAE, Version 5.0.

5.1 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are at least (possibly, probably or definitely) attributable to XL184.

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

5.1.1 Non-Hematological Dose-Limiting Toxicity

- Any Grade 4 non-hematological toxicity

- Any Grade 3 non-hematological toxicity with the specific exception of:
  - Grade 3 nausea and vomiting of less < 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 within 7 days of study drug interruption and that do not recur upon re-challenge with study drug. Note: For the purposes of this trial the ULN for ALT is defined as 45 U/L and the ULN for AST is defined as 50 U/L. See Section 5.7 for dose modifications for liver toxicity. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See appendix XI for toxicity-specific grading table.
  - Grade 3 fever or infection < 5 days duration.
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia and/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 5.8 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

- 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

- Dose-limiting hypertension
  - Any Grade 4 hypertension
  - A blood pressure > 25 mmHg above the ULN confirmed by repeated measurement on the same day is dose limiting. For pediatric patients ULN is the 95th percentile for age, height, and gender (Appendix V) and for patients ≥ 18 years of age ULN is 140/90 mmHg.
  - In patients who begin antihypertensive therapy a blood pressure > 10 mmHg but ≤ 25 mmHg above the ULN (Appendix V) for > 14 days is dose limiting..

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

- Grade 2 or higher allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.1.2 Hematological dose limiting toxicity

- In patients evaluable for hematological toxicity (see Section 3.2.7.1),
  - Grade 4 thrombocytopenia (platelet count < 25,000/μL) or Grade 4 neutropenia, not due to malignant infiltration.

- Myelosuppression that causes a delay of > 21 days between treatment cycles.

- In patients with CNS tumors, requirement of platelet transfusion(s) for platelets ≤ 50,000/mm3 on more than one occasion during a cycle will be considered a DLT. 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.

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

5.2 Dose Modifications for Hematological Toxicity

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 dose that was previously not tolerated.

5.2.1 If a patient experiences Grade 4 neutropenia or Grade 4 thrombocytopenia, the treatment will be held. Counts should be checked twice weekly during this time. If the toxicity resolves to meet eligibility parameters within 21 days of drug discontinuation, the patient may resume treatment at the next lower dose level (see Section 5.11). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

5.2.2 If toxicity does not resolve to meet eligibility parameters within 21 days of drug discontinuation, the patient must be removed from protocol therapy.

5.2.3 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. For patients with BSA 0.35-0.39, only 1 dose reduction will be allowed as the lowest weekly administered dose is 60 mg/week.

5.3 Dose Modifications for Non-Hematological Toxicity

5.3.1 XL184 will be discontinued in cases of serious toxicities such as GI perforation, fistula formation, significant bleeding, significant thrombotic events (such as myocardial infarction, cerebral infarction, other serious arterial thromboembolic events), Grade 4 hypertension, reversible posterior leukoencephalopathy syndrome, or osteonecrosis of the jaw. For other toxicities, if a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.1.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 21 days of drug discontinuation, the patient may resume treatment at the next lower dose level (see Section 5.11). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

5.3.2 If toxicity does not resolve to meet eligibility or baseline parameters within 21 days of drug discontinuation, the patient must be removed from protocol therapy. The exception to this is Grade 3 weight loss as it is unlikely that the patient would return to baseline within 21 days. Patients who experience Grade 3 weight loss may resume study medication after 21 days with a dose-reduction (see Section 5.11) 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.

5.3.3 Two dose reductions will be allowed for toxicity. If a patient experiences a dose limiting toxicity after two dose reductions, the patient must be removed from protocol therapy. For patients with BSA 0.35-0.39, only 1 dose reduction will be allowed as the lowest weekly administered dose is 60 mg/week.

5.4 Dose Modifications for Proteinuria

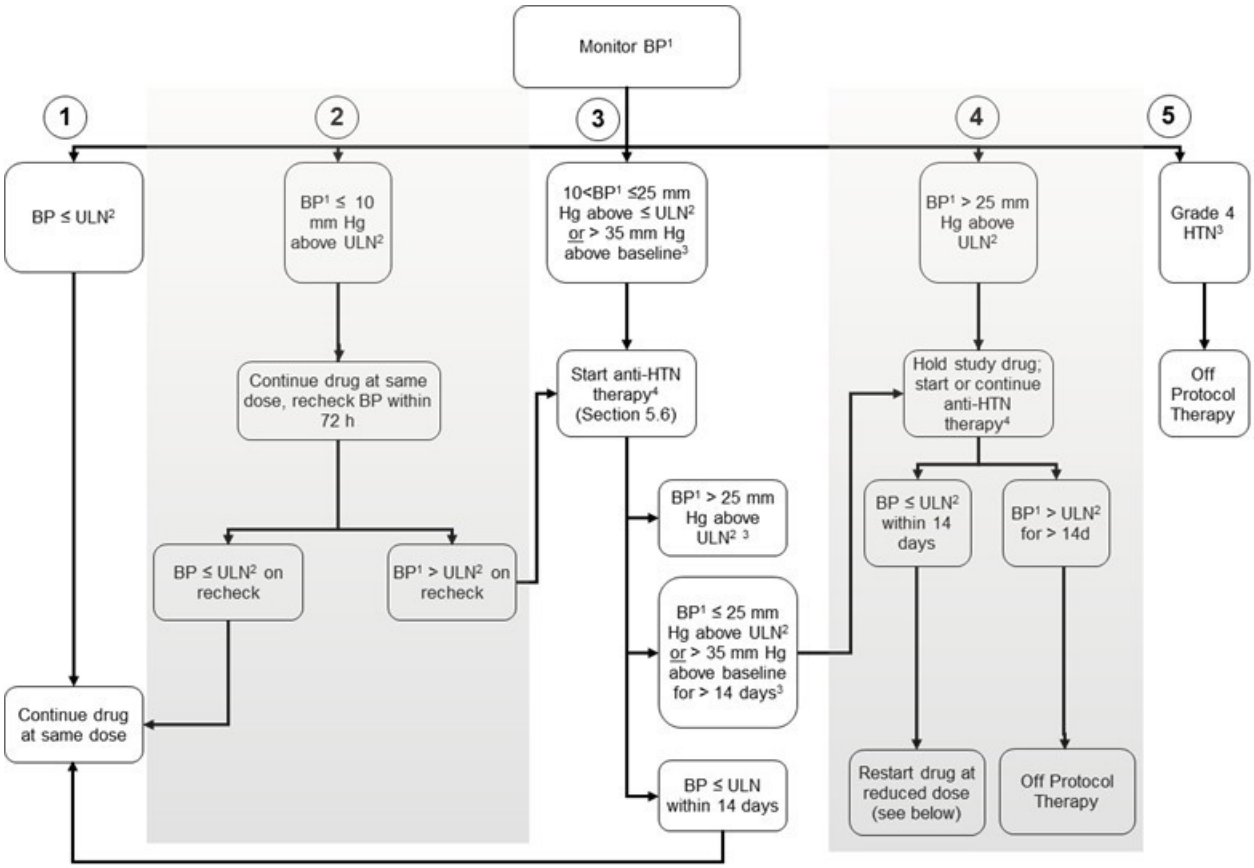
Proteinuria has been reported with XL184 in adult studies and pediatric trial ADVL1211.

- 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 ≥ 21 days then remove from protocol therapy. If the urine protein/creatinine (P/C) ratio decreases to ≤ 1.9 in < 21 days then resume XL184 at a lower dose as outlined in Section 5.11.
- Monitor the UPC weekly for 2 consecutive weeks once protocol therapy resumes.

5.5 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 (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender for pediatric patients (See Appendix V) For adult patients (ages ≥ 18 years), the ULN is 140/90 mmHg.
- 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.

[1] 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 within the ULN (Upper Limit of Normal).
[2] ULN for pediatric patients is a BP equal to the 95th percentile for age, height, and gender-appropriate normal values (see Appendix V). For adult patients (ages ≥ 18 years) the ULN is 140/90 mmHg.
[3] 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 mm Hg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.
[4] Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ ULN, continue XL184 at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN, 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 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 ULN on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy, 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 ULN 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 (see Section 5.11).
        - 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 (see Section 5.11).
        - If the BP is > ULN for > 14 days, the patient is Off Protocol Therapy.

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the ULN **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 (see Section 5.11).
    - If the BP is > ULN for >14 days, the patient is Off Protocol Therapy.

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.

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 < ULN.

5.6 Dose Modifications for Thromboembolic Events

Subjects who develop a pulmonary embolism (PE) or deep venous thrombosis (DVT) should have XL184 treatment held until therapeutic anticoagulation with heparins (eg, LMWH) is established. (Note: therapeutic anticoagulation with oral anticoagulants or oral platelet inhibitors such as clopidogrel is not allowed in this study). XL184 treatment may be resumed in subjects who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from XL184 treatment (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.) During anticoagulation treatment, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests according to institutional guidelines. If there are any signs of clinically relevant bleedings, XL184 treatment should be interrupted immediately and the investigator/ sponsor contacted to discuss further study participation. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the investigator/ sponsor.

Arterial thrombotic events (e.g., transient ischemic attack, myocardial infarction) have been observed in studies with XL184. Subjects should be evaluated for preexisting risk factors for arterial thrombotic events and cardiac or thromboembolic events that occurred before initiation of study treatment. XL184 treatment should be discontinued in subjects who develop an acute myocardial infarction, cerebral infarction or any other clinically relevant arterial thromboembolic complication.

5.7 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 regardless of the patient's baseline, and the ULN for AST is defined as 50 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 are 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 5.1.1. The XL184 will be reduced according to Section 5.11 when eligibility criteria are met.

5.8 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 5.1.1. XL184 will then be dose-reduced according to Section 5.11 when eligibility criteria are met.

5.9 Dose Modifications for Diarrhea

See Appendix VI 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 Section 5.11.

5.10 Monitoring for Specific Toxicities

5.10.1 Growth Plate Toxicity

Patients ≤ 18 years of age at enrollment 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 every 6 cycles thereafter 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, 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.

5.10.2 Thyroid Toxicity

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 below.

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 5.3 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.

5.10.3 QT Prolongation

If the average QTcF from the three ECGs is > 500 ms or increased by > 60 ms above baseline.

The following actions must be taken:

- Withhold study treatment
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management.
- Consider cardiology consultation for asymptomatic subjects for evaluation and management.
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated.
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (See Appendix VIII for a list of drugs that prolong QTc).

- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Study treatment may be restarted at a reduced dose level if **all** of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms or increase of > 60 ms above baseline is not confirmed according to protocol procedures
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 msec or return to ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than XL184 administration and is treatable/has been resolved
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment.

Following re-initiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

All study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after re-initiation of study treatment at a reduced dose

5.11 XL184 Dose Reduction Table

XL184 (Cabozantinib) **40 mg/m²/day**		
BSA (m²)	**Weekly Dose/Schedule for 1st Dose Reduction due to Toxicity**	**Weekly Dose/Schedule for 2nd Dose Reduction due to Toxicity**
0.35 – 0.39	60 mg = 20 mg M, W, F (or Day 1, 3, 5 of each week)	Off therapy
0.40 – 0.45	80 mg = 20 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)	60 mg = 20 mg M, W, F (or Day 1, 3, 5 of each week)
0.46 – 0.55	100 mg = 20 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	60 mg = 20 mg M, W, F (or Day 1, 3, 5 of each week)
0.56 – 0.64	120 mg = 20 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)	80 mg = 20 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)
0.65 – 0.78	140 mg = 20 mg Daily	100 mg = 20 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
0.79 – 0.90	160 mg = 40 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)	120 mg = 20 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)
0.91 – 1.09	200 mg = 40 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	140 mg = 20 mg Daily
1.10 – 1.17	200 mg = 40 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	140 mg = 20 mg Daily
1.18 – 1.36	240 mg = 40 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)	160 mg = 40 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)
1.37 – 1.65	300 mg = 60 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	200 mg = 40 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
1.66 – 1.85	360 mg = 60 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)	240 mg = 40 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)
1.86 – 2.07	420 mg = 60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
≥ 2.08	420 mg = 60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)

6.0 DRUG INFORMATION

6.1 XL184

(Cabometyx®, cabozantinib s-malate) NSC# 761968 **(04/04/19)**

Source and Pharmacology:
XL184 (cabozantinib) is an oral small molecule potent inhibitor of proinvasive receptor tyrosine kinases (RTKs), including AXL, FLT-3, KIT, MER, MET, RET, ROS1, TIE-2, TRKB, and VEGFR-1, -2, and -3. Most notably, it strongly inhibits VEGFR-2, MET, and RET. Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and *in vivo* pharmacodynamic activity of XL184 against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies. Treatment with XL184 results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration, and is associated with pro-apoptotic effects. These effects translate into significant tumor growth inhibition or tumor regression after XL184 treatment in multiple tumor models including metastatic medullary thyroid cancer (MTC), breast cancer, lung carcinoma, and glioblastoma. XL184 is currently approved for the treatment of patients with progressive MTC and advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

XL184 has shown clinical activity in adults with castration resistant prostate cancer, ovarian cancer, glioblastoma, differentiated thyroid carcinoma, renal cell carcinoma, hepatocellular carcinoma, breast, and non-small cell lung cancer. There is a strong scientific rationale for the evaluation of XL184 in pediatric solid tumors: over-expression of MET has been described in osteosarcoma and Ewing sarcoma and has been shown to correlate with aggressive phenotype and poor prognosis. MET is a transcriptional target of PAX3 and PAX7 and is highly expressed in alveolar rhabdomyosarcoma cell lines. Co-expression of HGF and MET correlated with higher grade and poorer prognosis in synovial sarcoma tumor samples. High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC).

Following oral administration of XL184 capsules, median time to peak plasma concentrations (Tmax) ranged from 2-5 hours post-dose. XL184 Cmax and AUC increased 41% and 57%, respectively, following a high fat meal relative to fasted condition in healthy volunteers; therefore, XL184 should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each XL184 dose). The oral volume of distribution (V/F) of XL184 is approximately 349 L. XL184 is highly protein bound (≥ 99.9%). Terminal-phase half-life ($t_{1/2,z}$) values are 59.1 to 136 hours and the clearance (CL/F) at steady- state is estimated to be 4.2 L/hr. Apparent steady-state plasma levels are reached by Day 15. This agent is primary excreted in feces (54%) and urine (27%). Pharmacokinetics of XL184 have not been studied in pediatric patients and patients with severe hepatic or renal impairment.

Potential drug interactions:
In vitro, XL184 is a substrate of CYP3A4 and a weak substrate of CYP2C9. Chronic use of strong CYP3A4 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, phenobarbital, and St. John's wort) or inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) should be avoided while taking XL184. Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

In vitro data indicate that XL184 is an inhibitor of P-glycoprotein transport activity. Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 with drugs known to be P-gp

substrates (e.g., fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.).

XL184 is also a substrate of drug transporter MRP2, which may result in an increase plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirdine, efavirenz, emtricitabine.

QTc prolongation:
Use caution when administering XL184 in patients with QT prolongation risk, a history of QT interval prolongation, or who are receiving antiarrhythmic drugs. Concomitant use of strong CYP3A4 inhibitors should be avoided as it may increase XL184 plasma concentrations. Refer to the protocol for QTcF criteria.

Patient Care Implications
Women of childbearing potential must use highly effective contraception while receiving XL184 (cabozantinib) and for 4 months after the last dose. Breastfeeding is not allowed while on study. Sexually active males must use highly effective contraception while on study and for 4 months after the last dose.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
XL184 (Cabozantinib, NSC 761968)

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 3219 patients*. Below is the CAEPR for XL184 (Cabozantinib).

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 2.4, December 17, 2018[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			**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)***

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dry mouth		***Dry mouth (Gr 2)***
	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		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	
		Transient ischemic attacks	

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RENAL AND URINARY DISORDERS			
	Hematuria		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	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)***
	Hair color changes		***Hair color changes (Gr 1)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
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, Hemoptysis, 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) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism; Hypopituitarism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); 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; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis
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); Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; 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 (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail changes; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; 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.

Formulation and Stability:
XL184 is available in 20 mg and 60 mg tablet. The tablets are yellow film coated containing XL184 equivalent to 20 mg and 60 mg of XL184. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per HDPE bottle.

XL184 should be dispensed in its original container; however, the tablets can be dispensed in a pill cup with an expiration date not to exceed 24 hours. It can also be repackaged in a pharmacy dispensing bottle with expiration date not to exceed 7 days.

XL184 (Cabozantinib) Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910 / Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

Store intact bottles at controlled room temperature, 20^0 to 25^0C (68^0 to 77^0F); temperature excursions are permitted between 15° C and 30° C (59° F to 86° F) [see USP Controlled Room Temperature].

If a storage temperature excursion is identified, promptly return XL184 (Cabozantinib) to 20° to 25°C (68° to 77° F) and quarantine the supplies. Provide a detailed report of the excursion (including

documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability testing of the intact bottles is ongoing. XL184 (cabozantinib) must be dispensed in original bottles. However, repackaging XL184 (cabozantinib) for a short period of time is acceptable and limited to:

- Up to 24 hours when dispensed in an open container such as a pill cup.
- Up to 7 days when dispensed in a closed container (e.g., a pharmacy dispensing bottle).

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.
XL184 is administered orally on an empty stomach (do not eat 2 hours before or 1 hour after each dose of cabozantinib). Do not crush or chew. Take the dose with a full glass of water approximately at the same time each day. Do not take missed dose within 12 hours of the next dose.
Hazardous agent: use appropriate precautions for handling and disposal.

Supplier:
XL184 is supplied by Exelixis and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.
Do not use commercial supply.

Obtaining the Agent
Agent Ordering
NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. 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), NIH Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

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, a "current" password, and active person registration status. 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.

Agent Accountability
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.

Agent Returns:
Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at:

http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs. The appropriate forms may be obtained at: http://ctep.cancer.gov/forms/docs/return_form.pdf.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

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

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 End of Therapy& Follow-up

STUDIES TO BE OBTAINED	End of Therapy
History	X
Physical Exam with VS	X
Ht, Wt, BSA	X
Performance Status	X
Pregnancy test*	X
CBC, differential, platelets	X
Urinalysis	X
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X
Creatinine, SGPT, bilirubin	X
Total protein/albumin	X
Tumor Disease Evaluation	X

CEA and calcitonin (for patients with MTC only)	X

*For female patients of childbearing potential.

Follow-up on this study is required at 30 days from the last date of protocol therapy, 6 months for the first year from the last date of protocol therapy and annually thereafter for up to five years from the date of study entry.

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs).

7.2 Correlative Biology Studies

7.2.1 Pharmacokinetics

Pharmacokinetic (PK) studies will be **required** for the first 18 patients ≥ 2 to < 9 years of age at enrollment and **optional** for all patients ≥ 9 to < 19 years of age at enrollment at COG member sites.

Patients enrolled in mandatory PK studies must consent to PK collection and agree to provide all required PK samples.

7.2.1.1 Sample Collection and Handling Instructions

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

Sampling Schedule and Collection

- Blood samples will be obtained at the following time points:
  - Cycle 1, Day 1: prior to dose; 2, 4, 8, and 20-28 hours after dose.
  - Cycle 1, Day 22 (± 2 days): trough level prior to dose and 2-4 hours post dose. As patients may not be receiving the drug on all days of the week, care should be taken to draw PK on a day when drug is actually administered.
  - Cycle 2, Day 1: prior to dose
  - Cycle 3, Day 1: prior to dose

- For each time point, 3 mL of blood must be collected in a chilled K_2-EDTA Vacutainer tubes (lavender top)

- For Cycle 1 Day 1 samples:
  - Record the exact time and date each sample is drawn and the time the drug is given.

- For Cycle 1 Day 22 samples:
  - Record the exact time and date each sample is drawn and the actual date and time the last dose of drug was administered prior to the collection of the trough sample.

Sample Processing and Labeling

- 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.

- Each tube must be labeled with the patient's COG I.D. and study number. (ADVL1622), and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

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.

7.2.2 Pharmacodynamics

For patients who provide consent, the effect of XL184 on immune cell subsets and immune gene signature will be analyzed by collecting blood samples at baseline (Cycle 1 Day 1, prior to 1st dose), Cycles 2 and 3 Day 1 pre-treatment.

7.2.2.1 Sample Collection and Handling Instructions

Sampling Schedule and Collection

- Blood samples will be obtained at the following time points:
  - Cycle 1, Day 1: prior to first dose
  - Cycle 2, Day 1: prior to dose
  - Cycle 3, Day 1: prior to dose

- For each time point, the following samples will be required:
  - 8 mL CPT citrate tube
  - 2.5 mL PAXgene blood RNA tube

Sample Processing and Labeling

- Please notify the lab by email (Jane Trepel- trepel@helix.nih.gov; Min-Jung Lee- leemin@mail.nih.gov; Sunmin Lee-lees@pop.nci.nih.gov) that the blood draw has been **scheduled**.

- Immediately after blood collection, blood tubes should be carefully inverted several times.

- Samples should be collected Monday through Thursday only, to arrive Tuesday through Friday. Do not ship to arrive on a government holiday. Samples may be shipped at room temp. A refrigerant gel pack such as the ThermoSafe Polar Pack PP24 Refrigerant Gel Pack should be included.

- Each tube must be labeled with the patient's COG I.D. and study number (ADVL1622), and the date and time the sample was drawn. Data should be recorded on the Pharmacodynamic Study Form, which must accompany the sample(s).

Sample Shipping Instructions

Notify the lab when the sample is being shipped, including in the email the FedEx tracking number. Send samples by **FedEx Priority Overnight** Shipping. The NIH is not open on weekends or government holidays. Be careful not to ship any samples to arrive on a Saturday, Sunday or government holiday. If you are not certain whether the government will be open please send an email to the addresses below at any time and we will respond as quickly as possible.

Ship Monday-Thursday only by FedEx Priority Overnight to:

Trepel Lab, Developmental Therapeutics Branch, NCI, NIH
Bldg 10, Rm 12C208
10 Center Drive
Bethesda, MD 20892
Phone: 301-496-1547

Please notify the lab by email (Jane Trepel trepel@helix.nih.gov; Min-Jung Lee leemin@mail.nih.gov; Sunmin Lee lees@pop.nci.nih.gov) when the sample is **being shipped** and include the tracking number.

Refer to the Trepel Lab Manual for additional details related to this correlative study.

7.2.3 Tissue Banking Study

Submission of tumor tissue to be banked for future research studies is strongly encouraged. Tumor tissue obtained as a result of biopsy or resection at initial diagnosis, and/or of a suspected disease recurrence site prior to therapy, and/or of a suspected disease recurrence during the first 12 months from the time of enrollment is requested for banking. Snap frozen, formalin-fixed and paraffin-embedded (FFPE) blocks or unstained slides (at least 10 cut sequentially from the same block) will be accepted.

COG sites: if a block or unstained slides have been submitted already on APEC14B1 (Project:EveryChild), additional tissue is not required.

Sample Labeling and Shipping
Label biology specimens with:

- the patient's COG ID number
- specimen type (primary or metastatic)
- collection date

Include the surgical pathology ID (SPID) number and block number in the labeling when submitting a block or slides.

Include a transmittal form, pathology report and operative report with each shipment.

The Biopathology Center (BPC) will provide a specimen procurement kit for shipping frozen tumor tissue to the BPC. Kits are provided to sites in the US and Canada only.

COG sites: Kits are ordered via the BPC Kit Management application. To access the application click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application.

Non-COG Sites: Sites can order kits online via the Kit Management link http://ricapps.nationwidechildrens.org/BPCKitManagement/.

- Snap frozen tissue must be sent on dry ice. Using at least 4 lbs. total, layer dry ice in the bottom of the kit until it is approximately one third full. Place the frozen specimens on top of the dry ice. Cover the specimens with dry ice until the compartment is almost completely full. Secure the foam lid. Remember to include the COG Specimen Transmittal Form, pathology report and operative report with each shipment. Close the outer lid of the kit and tape with filament or other durable packing tape.

- Attach a label to the top of the kit. COG sites will access the Kit Management application to print a FedEx shipping label. Non-COG sites should contact the BPC by phone (800-347- 2486) or email (BPCBank@nationwidechildrens.org) to request a shipping label. A blank label is provided in the kit to use when printing the shipping label. **A shipping label will only be provided when frozen tissue is submitted.** Blocks and slides must be shipped using the institution's courier account or regular mail. Complete the dry ice label (UN 1845) and secure both this label and the Exempt Human Specimen label to the side of the box.

Send samples to:
Biopathology Center Nationwide Children's Hospital
Protocol ADVL1622
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

**Be sure to include the room number. Packages received without the room number may be returned to the sender.*

Specimens should be shipped Monday through Thursday by Priority Overnight for delivery Tuesday through Friday. Do not ship **any** of the specimens for this protocol to the BPC for Saturday delivery.

7.3 Central Review

The pertinent imaging studies (CT, MR, etc.) of those patients who respond to therapy or have long term stable disease on protocol therapy will be centrally reviewed. COG Operations Center will notify the Imaging Research Center of any patient requiring central review. The Imaging Research Center will then request that the treating institution forward the pertinent images for central review. The central image evaluation results will be entered into Rave for review and for data analysis.

Long term stable disease for central review is defined as having at least 6 consecutive cycles of stable disease for the non-osteosarcoma strata and at least 4 consecutive cycles for the osteosarcoma stratum.

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

Institutions that are not connected via the ImageInBox can send the images on hard copy film, CD ROM, DVD, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1622) and date, and shipped to Syed Aamer at the address below:

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

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal From Protocol Therapy

a) Progressive disease.
b) Adverse Events requiring removal from protocol therapy, as stated in Section 5.0.
c) Patients who receive concurrent anticancer or investigational therapy, as stated in Section 4.1.4.
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Physician determines it is in patient's best interest.
f) Repeat eligibility studies (if required) are outside the parameters required for eligibility.
g) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
h) Patients who develop a second malignant neoplasm.

i) Pregnancy.
j) Study is terminated by sponsor.

Patients who are removed from protocol therapy (except for 8.1.f) are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Entry into another COG study with tumor therapeutic intent (e.g., at recurrence).
d) Patient does not receive protocol treatment after study enrollment.
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

9.1.1 Non-osteosarcoma strata

Three disease strata have been identified for reporting upon completion of evaluation of each particular disease stratum ("primary disease groups"). These strata are: (1) Ewing sarcoma; (2) rhabdomyosarcoma; and (3) non-rhabdomyosarcoma soft tissue sarcoma. The evaluation rule is described in Section 9.2 below.

In addition to the three main strata, enrollment into each of the following tumor groups ("secondary strata"): (4) Wilms tumor, and (5) rare tumors (medullary thyroid carcinoma, renal cell carcinoma, hepatocellular carcinoma, hepatoblastoma, adrenocortical carcinoma, and pediatric solid tumors with known molecular alterations in the targets of XL184); will be open to accrual. If thirteen response-evaluable patients of a particular histology are enrolled in any of the secondary strata, the two-stage design described in Section 9.2 below will be applied to that particular histology. (That is, up to seven additional response-evaluable patients with that tumor type may be studied.)

If two of the three primary disease strata (Ewing sarcoma, rhabdomyosarcoma, and non-rhabdomyosarcoma STS) have met their accrual and one remains open, the Cancer Therapy Evaluation Program (CTEP) and the ADVL1622 Investigators will discuss the study timeline.

Review of patient accrual onto recent phase 2 solid tumor studies indicates the following entry rates for the various tumors under study can be expected:

Disease Group/Strata	Patients/Year
Ewing sarcoma	18
Rhabdomyosarcoma	18
Non-rhabdomyosarcoma STS	10

With these entry rates, the probability of accruing 13 patients to complete the initial stage of evaluation in the three primary disease groups within 19 months is 80% and within 24 months is 90%. The corresponding probability for enrolling 20 patients in the three named disease categories within 28 months is 80% and within 37.5 months is 90%. The study will likely require 2 to 3 years for sufficient patient enrollments to evaluate response in the primary disease groups. If activity is detected in any category, further trials in subcategories of category may be conducted at the discretion of the Developmental Therapeutics Steering and study committees. If all three statistical cohorts are finished accruing (either all 20 patients or 13 patients with the early stopping criterion met), the Study Committee will evaluate the non-statistical strata and make a decision whether to continue accrual to those strata. A minimum of 39 patients and a maximum of 110 patients are anticipated to get either 13 or 20 patients evaluable for response in each statistical stratum.

9.1.2 Osteosarcoma Cohort

Review of patient accrual onto recent phase 2 solid tumor studies indicates the following entry rates for the osteosarcoma stratum can be expected:

Disease Group/Strata	Patients/Year
Osteosarcoma	22

With this entry rate, the probability of accruing 19 patients to complete the initial stage of evaluation in the osteosarcoma stratum within 12.3 months is 80% and within 18.2 months is 90%. The corresponding probability for enrolling 29 patients in the osteosarcoma stratum within 20 months is 80% and within 26 months is 90%. The osteosarcoma will likely require 1.5 to 2.5 years for sufficient patient enrollments to evaluate response in osteosarcoma. A minimum of 19 patients and a maximum of 36 patients are anticipated to get either 19 or 29 patients evaluable for response in the osteosarcoma stratum.

When the evaluation of the statistical strata (Ewing's sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma STS, and osteosarcoma) is complete, enrollment to the study will be terminated. The non-statistical cohorts will remain open to enrollment until the statistical strata are closed to accrual unless the DVL committee leadership indicates further enrollment on the secondary strata is warranted.

9.2 Study Design

9.2.1 Non-osteosarcoma Strata

The primary endpoint for the non-osteosarcoma strata will be objective response by RECIST criteria v 1.1. The best response of disease to XL184 (defined in Section 10.4) will be examined separately in each of the 3 primary disease groups. If 13 patients of the same histology enroll on either of the secondary strata (i.e., 13 Wilms tumor patients or 13 of the same type of eligible rare tumor patients), then the rule below will be applied to that group of patients. The following Simon's minimax two-stage design will be used in all the non-osteosarcoma strata.

	Cumulative Number of Responses	Decision
Stage 1: Enter 13 patients	0	Terminate the trial early: agent ineffective
	1 or more	Inconclusive result, continue trial (proceed to Stage 2)
Stage 2: Enter 7 additional patients	2 or fewer	Terminate the trial: agent ineffective
	3 or more	Terminate the trial: agent effective

We will consider the agent not of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If the agent has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.074 (type I error),

and the trial will have an expected sample size of 16.4 with 51.3% probability of early termination. If the agent has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.903 (power against the alternative hypothesis $p = 0.25$). An expanded table of possibilities is below:

True response rate	Probability of stopping early for lack of activity	Probability of identifying agent as effective	Expected number of patients accrued
5%	0.513	0.074	16.41
10%	0.254	0.317	18.22
15%	0.121	0.586	19.15
20%	0.055	0.786	19.62
25%	0.024	0.903	19.83
30%	0.010	0.961	19.93
35%	0.004	0.986	19.97

9.2.2 Osteosarcoma stratum-specific Design

For the osteosarcoma stratum, patients will be enrolled in two stages. In the first stage, 19 disease control and RECIST response evaluable patients will be enrolled. Each patient will be evaluated for both outcome measures: (1) disease control success; and (2) RECIST response (CR or PR *v.* not CR or PR). The decision rule for the two stage study design is summarized as:

	Cumulative response results	Decision
Stage 1: Enter 19 patients	≤4 disease control successes AND ≤1 RECIST responders	Terminate the trial early: agent ineffective
	≥5 disease control successes OR ≥2 RECIST responders	Inconclusive result, continue trial (proceed to Stage 2)
Stage 2: Enter 10 additional patients	≤8 disease control successes AND ≤4 RECIST responders	Terminate the trial: agent ineffective
	≥9 disease control successes OR ≥5 RECIST responders	Terminate the trial: agent effective

Design Characteristics: Each patient enrolled will be evaluated for: (1) complete or partial response as defined by the RECIST criteria where the first evaluation of CR or PR is made at or before the end of the sixth cycle of study therapy (denoted as R below); or (2) stable disease after four months of therapy or at the end of the sixth cycle, whichever occurs first (denoted as S below). We will not be interested in promoting the agent for further investigation if the probability of response in any particular individual is less than or equal to 0.05 ($P(R) \leq 0.05$) and the probability of remaining analytic event free in any particular individual is less than or equal to 0.20 ($P(S) \leq 0.20$). We will be interested in promoting the agent for further investigation if the probability of response in any particular individual is

at least 0.22 (P(R)≥0.22) **or** the probability of remaining analytic event free in any particular individual is at least 0.42 (P(S)≥0.42).

For the calculations below, it is assumed $Pr(S \mid R) = 0.90$.

The statistical characteristics of this design are:

Probability of four month disease control	Probability of RECIST response	Probability of Stopping After Stage 1 (and concluding the drug is ineffective)	Probability of Concluding the Drug is Ineffective at the Conclusion of the Trial	Probability of Concluding the Drug is Effective at the Conclusion of the Trial
0.20	0.05	0.56	0.89	0.11
0.42	0.22	0.014	0.05	0.95
0.42	0.05	0.044	0.096	0.904
0.20	0.22	0.056	0.21	0.79

9.3 Methods of Analysis

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. A patient will be counted only once for a given toxicity for the worst grade of that toxicity reported for that patient. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen.

Time-to-event analyses (time to progression, progression-free survival, and overall survival) will be computed when all patients in a stratum have at least one year of follow-up.

9.3.1 RECIST Response Criteria for all strata

Response criteria are described in Section 10. A RECIST responder is defined as a patient who achieves a best response (as defined in Section 10.6) of PR or CR on the study. Response rates will be calculated as the percent of RECIST response-evaluable patients who are responders, and confidence intervals will be constructed accounting for the two-stage design.

9.3.2 Disease control for osteosarcoma stratum

Any patient who is evaluated free of all detectable disease (complete response) or is considered as having a partial response or is considered as having stable disease ('at least stable disease') after four months of therapy or at the end of the sixth cycle, whichever occurs first, will be considered a disease control success.

Any evaluable patient who does not meet the criteria for disease control success (complete response, partial response or stable disease) will be considered to not have experienced disease control success.

In particular, any patient who dies because of treatment-related toxicity during the first six cycles of therapy and/or within the first four months since starting treatment will be considered not to have experienced disease control success. Also, any patient who is eligible, receives one dose of XL184 and is lost to follow-up at (for example) the end of cycle 2 will not be considered a disease control success (complete response, partial response or stable disease)

Patients who are not evaluable for both disease control and response evaluation may be replaced for the purposes of the statistical rule.

9.3.3 Osteosarcoma Estimation of Disease Control and RECIST Response Rates

P(R) and P(S) for the osteosarcoma cohort will be estimated using the maximum likelihood estimates, viz.

$$\mathrm{P(R)} \hat{=} \hat{p}_{\mathrm{R}} = \frac{\text{Number of Patients Considered as PR or CR}}{\text{Number of Response-Evaluable Patients in Cohort}}$$

$$\mathrm{P(S)} \hat{=} \hat{p}_{\mathrm{S}} = \frac{\text{Number of Patients with Disease Control at 4 Months}}{\text{Number of Response-Evaluable Patients in Cohort}}$$

Confidence intervals will be constructed using the approximate normal distribution of each of the estimates and their asymptotic variances:

$$\mathrm{V}(\hat{p}_{\mathrm{R}}) \hat{=} \frac{\hat{p}_{\mathrm{R}}(1-\hat{p}_{\mathrm{R}})}{\text{Number of Response-Evaluable Patients in Cohort}}$$

$$\mathrm{V}(\hat{p}_{\mathrm{S}}) \hat{=} \frac{\hat{p}_{\mathrm{S}}(1-\hat{p}_{\mathrm{S}})}{\text{Number of Response-Evaluable Patients in Cohort}}$$

9.3.4 Adverse Event Monitoring Rule

We will use a Bayesian rule to monitor for protocol-specific toxicities. We will assume a beta prior distribution with $\alpha = 0.52$ and $\beta = 2.08$. At least once per month, we will calculate the posterior probability (given the data) that the probability of protocol-specific toxicity exceeds the 20% threshold:

$$P(p_{\text{protocol-specific toxicities}} > 20\% \mid \text{Data}) = \int_{0.2}^{1} \frac{\binom{n}{x} p^{x}(1-p)^{n-x} \frac{\Gamma(2.6)}{\Gamma(0.52)\Gamma(2.08)} p^{-0.48}(1-p)^{1.08}}{\int_{0}^{1} \binom{n}{x} q^{x}(1-q)^{n-x} \frac{\Gamma(2.6)}{\Gamma(0.52)\Gamma(2.08)} q^{-0.48}(1-q)^{1.08} dq} dp$$

Here n is the number of protocol-specific toxicity-evaluable cycles and x is the number of such cycles on which a protocol-specific toxicity event is observed. Examples of situations in which this rule will indicate protocol-specific toxicities have been noted and are presented below:

Number of failures	Number of patient-cycles
2	6
3	10
4	14
5	19
6	23
7	28
8	32
9	37
10	41
11	46
12	51

13	55
14	60

Protocol-specific toxicities of interest include fatigue, headache, proteinuria, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), palmar-plantar erythrodysesthesia, oral mucositis, ALT increase, lipase increase, bilirubin increase, diarrhea, thrombocytopenia, hypothyroidism, nausea, anorexia, neutropenia, weight loss and vomiting.

If there is strong evidence (posterior probability of at least 70% with at least 2 observed toxicities) that there is a per course protocol-specific toxicity probability of more than 20%, such information will be presented to the DSMC.

9.4 Evaluability for Response

Any patient who is enrolled and receives at least one dose of XL184 will be considered evaluable for response and disease control provided: (1) the patient demonstrates progressive disease or death while on protocol therapy; or (2) the patient is observed on protocol therapy for at least one cycle and the tumor is not removed surgically prior to the time complete response or partial response is confirmed, or (3) the patient demonstrates a complete or partial response as confirmed according to protocol criteria. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in Section 10.2. The evaluation period for determination of the best response will be 6 treatment cycles. All other patients will be considered non-responders. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. See Section 7.3 regarding shipping instructions. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

9.5 Evaluability for Toxicity

All patients who receive at least one dose of XL184 according to protocol guidelines will be considered in the evaluation of toxicity.

9.6 Evaluability for Pharmacokinetic Analysis

Any patient who is enrolled, participates in the PK study, and receives the full dose of XL184 on Cycle 1 Day 1 will be considered evaluable for PK analysis provided that the patient completes Cycle 1 Day 1 sample collection.

Because PK can be evaluated in many different ways depending on how PK parameters are presented, the statistical analysis of the PK studies will proceed as follows:

1) A descriptive analysis of the pharmacokinetic parameters of cabozantinib will be performed to define Day 1 systemic exposure. Parameters to be collected are: AUC (0-24h), C_{max}, T_{max}, and accumulation (the concentration before the dose on Day 22 divided by the concentration 24 hours after the Day 1 dose). The PK parameters will be summarized with the following summary statistics: mean, median, range, and standard deviations (numbers and distribution permitting).

2) The PK data in this study will be combined with the PK data from ADVL1211 for a population PK analysis to evaluate the effect of age on the clearance of XL184. The effect of age will be analyzed using the likelihood ratio test as implemented in the program NONMEM.

9.7 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native		1			**1**
Asian	2	4			**6**
Native Hawaiian or Other Pacific Islander					
Black or African American	4	17			**21**
White	47	44	8	19	**118**
More Than One Race					
Total	**53**	**66**	**8**	**19**	**146**

This distribution was derived from the patients on ADVL0821, ADVL0921, and AOST1521 with diagnoses among the primary disease groups.

9.8 Analysis of the Pharmacokinetic Parameters

PK will be required in the first 18 patients less than 9 years of age, then not done on the remaining patients in this age group. PK will be optional for all patients 9–18 years old. PK will not be done in patients older than 18.

The clearance will be measured in the 2–8-year-olds (<9 year olds) and compared to historical data from ADVL1211. The test will be a one-sample equivalence test (using the two one-sided test (TOST) methodology of Schuirmann)[40] of log(Clearance) compared to the historical data with mean 7.584 and standard deviation 0.383 on the log scale. The lower and upper equivalence boundaries will be 60% and 140%, respectively (–0.512 and 0.336 on the log scale). Equivalence will be declared if the two-sided 95% confidence interval on the log scale is entirely contained within the interval (–0.512, 0.336). The power of the test for various combinations of the true population mean and standard deviation in the 2–8-year-old population are displayed below.

Power for sample size $n = 18$				
Ratio of means on raw scale	Difference of means on log scale	Actual variability on log scale ($\sigma_0 = 0.383$)		
		σ_0	$1.25\sigma_0$	$1.5\sigma_0$
0.90	–0.105	98.5%	88.2%	67.3%
0.95	–0.051	97.8%	86.7%	66.0%
1.00	0.000	93.9%	79.1%	59.2%
1.05	0.049	84.8%	66.3%	48.7%

1.10	0.095	69.4%	50.5%	36.6%

If the true population mean and standard deviation are identical to the historical data (i.e., ratio of means on raw scale = 1 and actual variability on log scale = $\sigma_0 = 0.383$), the test will have 93.9% power to declare equivalence. If the true population mean is equal to the historical data, the test will still have 79.1% power to declare equivalence if the variability on the log scale is 25% higher than expected and 59.2% power if the variability on the log scale is 50% higher than expected.

If the trial is closed prior to enrolling 18 patients less than 9 years of age, the PK analysis will be done on just the enrolled patients.

9.9 Analysis of Biological and Correlative Endpoints

The association between the host immune system and response to XL184 will be assessed in an exploratory manner. Immune biomarkers will be divided at their observed median at baseline, Cycle 2 Day 1 (pre dose), and Cycle 3 Day 1 (pre dose), as well as with respect to change from baseline. Then, each biomarker will be correlated with the clinical outcomes of objective response and progression free survival.

Objective response will be assessed using the exact conditional test of proportions and progression-free survival will be assessed using the Log-rank test with hazard ratios estimated from a Cox proportional hazards regression model.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. The descriptions and grading scales found in the revised CTCAE version 5.0 will be utilized for reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0, which can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.). Additionally, toxicities are to be reported on the appropriate case report forms.

10.2 Response Criteria

As outlined, patients will be assigned to one of the following categories for assessment of response: solid tumor and measurable disease (Section 10.3 below). Note: Neuroblastoma patients who do not have MIBG positive lesions or bone marrow involvement should be assessed for response as solid tumor patients with measurable disease.

10.3 Response Criteria for Patients with Solid Tumors (non-CNS)

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[41] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v 1.1 criteria.

10.3.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm (CT scan slice thickness no greater than 5 mm). The investigator will identify up to 5 measurable lesions to be followed

for response. Previously irradiated lesions must demonstrate clear evidence of progression to be considered measurable.

Serial measurements of lesions are to be done with appropriate imaging modalities, e.g., CT or MRI. Bone scans cannot be used to measure lesions. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

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

10.3.3 End-of-Cycle Response
Note: Please also see Table 1 in Section 10.6.

a) Complete Response (CR)
Disappearance of all target and non-target lesions. Normalization of urinary catecholamines (for patients with neuroblastoma), or other tumor markers if abnormal or elevated at study enrollment.

b) Partial Response (PR)
At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment. No new lesions or progression of any non-target measurable lesion.

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

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

10.3.4 Overall Best Response Assessment
Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described in Section 10.6.

10.4 Response Criteria for Neuroblastoma Patients with ^{123}I-MIBG Positive Lesions

10.4.1 MIBG Positive Lesions
Patients with measurable disease who have a positive MIBG scan at the start of therapy should also be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans.

10.4.2 The following criteria will be used to report MIBG response by the treating institution:
- **Complete Response:** Complete resolution of all MIBG positive lesions
- **Partial Response:** Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions.

- **Stable Disease:** No change in MIBG scan in number of positive lesions (includes patients who have same number of positive lesions but decreased density).
- **Progressive Disease:** Development of new MIBG positive lesions.

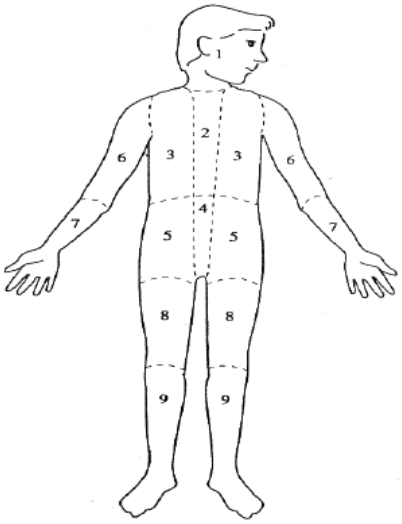
10.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 7.3 for details on transferring images to the Imaging Research Center.

NOTE: This scoring is NOT required to be done by the treating institution for end of course response assessments.

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

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

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



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

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 3 weeks apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan

10.4.4 Overall Best Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described in Table 2 in Section 10.6.

10.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

10.5.1 Bone Marrow Involvement

Bone Marrow response is 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 3 weeks apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.
- Progressive Disease:
  - 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%).
  - 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 3 weeks apart.
- Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

10.5.2 Overall Best Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described in Section 10.6.

10.6 Best Response (Solid Tumors)

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

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

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

Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

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

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

10.7 Response Criteria for Patients with CNS Tumors

10.7.1 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.

10.7.2 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 and non-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 product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

10.7.3 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.

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

10.7.5 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 10.6 from a sequence of overall response assessments.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting table assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
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 a serious adverse drug experience 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.

11.3 Specific Examples for Expedited Reporting

11.3.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting table in this protocol.

11.3.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered serious AEs.

11.3.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: ***"Newborn deaths occurring during the first 28 days after birth"***
- Sudden Death NOS: A sudden (defined as instant or within one hour of the

onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 "Disease progression)"*** under the system organ class (SOC) of "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.3.4 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 metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI 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:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

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

11.3.5 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.

11.3.6 Pregnancy, Fetal Death, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.3.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to

be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.3.6.2 **Pregnancy Loss (Fetal Death)**
Pregnancy loss is defined in CTCAE as "Death in utero."

Any pregnancy loss should be reported expeditiously, as **Grade 4 *"Pregnancy loss"*** under the ***"Pregnancy, puerperium and perinatal conditions"* SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death

11.3.6.3 **Death Neonatal**
Neonatal death, defined in CTCAE as ***Newborn deaths occurring during the first 28 days after birth"*** needs to be reported expeditiously, as **Grade 4 "Death neonatal" under the "General disorders and administration" SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4 Reporting Requirements for Specialized AEs

11.4.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.4.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.
ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.4.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.5 Exceptions to Expedited Reporting

11.5.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.5.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting table for this protocol.

11.6 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.7 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting and are located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTCAE.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897-7497. In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in

must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- 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 event, 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 the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (e.g., H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **(301) 230-0159** (back-up: (301) 897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**

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

11.8 Reporting Table for Late Phase 2 and Phase 3 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]

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) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

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. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

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 notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1] SAEs 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 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.9 Protocol Specific Additional Instructions and Reporting Exceptions

- **Grades 1- 4 myelosuppression (anemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia) do not require expedited reporting unless it is associated with hospitalization.**

11.10 Routine Reporting of Adverse Events

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and Grade 3 and higher Adverse Events.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG website with each protocol under "Data Collection/Specimens". A submission schedule is included.

12.1 CDUS

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

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

12.3 CRADA/CTA

NCI/ DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA), a Cooperative Research and Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative 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 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 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 NCI, 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 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 Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available 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.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the ADVL1622 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Click on the By Lead Organization folder to expand
- Click on the COG link to expand, then select trial protocol ADVL1622
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for ADVL1622 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

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

Online: www.ctsu.org (members' section) → Regulatory Submission Portal
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
Fax: 215-569-0206
Phone: 1-866-651-2878
Mail: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Weak Inhibitors	Inducers
alfentanil[4,5]	atazanavir	aprepitant	alprazolam	armodafinil
amiodarone[4]	boceprevir	cimetidine	amiodarone	barbiturates
aprepitant/fosaprepitant[5]	clarithromycin	conivaptan	amlodipine	bosentan
atorvastatin[5]	cobicistat	crizotinib	atorvastatin	carbamazepine
benzodiazepines	darunavir	cyclosporine	bicalutamide	deferasirox
bortezomib	delavirdine	diltiazem	cilostazol	echinacea
brentuximab	grapefruit[3]	dronedarone	cimetidine	efavirenz
budesonide[5]	grapefruit juice[3]	erythromycin	ciprofloxacin	etravirine
buspirone[5]	indinavir	fluconazole	cyclosporine	fosphenytoin
calcium channel blockers	itraconazole	fosamprenavir	fosaprepitant	glucocorticoids[2]
cisapride	ketoconazole	grapefruit[3]	fluvoxamine	modafinil
citalopram/escitalopram	lopinavir/ritonavir	grapefruit juice[3]	isoniazid	nafcillin
conivaptan[5]	nefazodone	imatinib	nicardipine	nevirapine
glucocorticoids[2]	nelfinavir	mifepristone	propofol	oxcarbazepine
crizotinib	posaconazole	nilotinib	quinidine	phenobarbital
cyclosporine[4]	ritonavir	verapamil	ranolazine	phenytoin
cyclophosphamide	saquinavir			pioglitazone
dapsone	telaprevir			primidone
darifenacin[5]	telithromycin			rifabutin
darunavir[5]	voriconazole			rifampin
dasatinib[5]				rifapentin
dihydroergotamine				ritonavir
docetaxel				St. John's wort
doxorubicin				topiramate
dronedarone[5]				
eletriptan[5]				
ergotamine[4]				
eplerenone[5]				
erlotinib				
esomeprazole				
estrogens				
etoposide				
everolimus[5]				
felodipine[5]				
fentanyl[4]				
fosaprepitant				
gefitinib				
haloperidol				
HIV antiretrovirals				
HMG Co-A inhibitors[5]				
ifosfamide				
imatinib				
indinavir[5]				
irinotecan				
itraconazole				

ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] modafinil montelukast nefazodone nilotinib nisoldipine[5] omeprazole ondansetron paclitaxel pazopanib quetiapine[5] quinidine[4] saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sunitinib tacrolimus[4,5] telaprevir tamoxifen temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP3A4 isozyme, however, the degree of that inhibition is unknown.
[2] Refer to Section 4.1.4.3 regarding use of corticosteroids. Dexamethasone is considered a weak CYP3A4 inducer.
[3] The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4] Narrow therapeutic range substrates
[5] Sensitive substrates

APPENDIX III: XL184 PATIENT DIARY

COG Patient ID_____ Patient Initials_____ 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. You will take the tablet with a large glass of water on an empty stomach. Do not eat 2 hours before or 1 hour after each dose of XL184. Do not crush or break the tablet. Furthermore, do not take a missed dose within 12 hours of the next dose. Do not eat grapefruit or drink grapefruit juice while being treated with XL184. 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 after each treatment cycle. Your institution will upload this document into RAVE 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 IV.

EXAMPLE						
WEEK 1	***Date***	***Time***		***20 mg***	***60 mg***	***Comments***
Day 1: Friday	*5/27/16*	*8:30*	*(AM) / PM*	*# prescribed: 3* *# taken: 3*	*# prescribed: 0* *# taken: 0*	*He felt nauseated an hour after taking the drug but did not vomit.*

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: XL184 DOSING NOMOGRAM

If a patient's dose is reduced due to toxicity, any future XL184 total weekly dose should not exceed a previously un-tolerated dose.

See Section 5.11 for the XL184 dose reduction table.

XL184 (Cabozantinib) 40 mg/m²/day	
BSA (m²)	**Weekly Dose/ Schedule for Initial Dosing**
0.35 – 0.39	100 mg = 20 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
0.40 – 0.45	120 mg =20 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)
0.46 – 0.55	140 mg =20 mg Daily
0.56 – 0.64	160 mg = 40 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)
0.65 – 0.78	200 mg = 40 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
0.79 – 0.90	240 mg = 40 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)
0.91 – 1.09	280 mg = 40 mg Daily
1.10 – 1.17	300 mg = 60 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
1.18 – 1.36	360 mg = 60 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)
1.37 – 1.65	420 mg = 60 mg Daily
1.66 – 1.85	480 mg = 80 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)
1.86 – 2.07	560 mg = 80 mg Daily
≥ 2.08	600 mg = 100 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)

APPENDIX V: 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 5.1.1 for definition of dose limiting hypertension, Section 5.5 for management and grading of 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 5.1.1 for definition of dose limiting hypertension, Section 5.5 for management and grading of 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 VI: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

You should purchase or will be given a prescription for loperamide to have available to 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.

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__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 (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (5 mL [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 (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 6 mg (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (10 mL [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 (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 4 hours. Do not exceed 8 mg (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (10 mL [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 (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 2 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 4 hours. Do not exceed 12 mg (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (20 mL [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 (10 mL [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 (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg (80 mL or 16 teaspoonfuls) per day.

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

Recommended Non-enzyme inducing anticonvulsants
Clonazepam
Diazepam
Ethosuximide
Ezogabine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Lorazepam
Perampanel
Tiagabine
Topiramate
Valproic Acid
Zonisamide
Unacceptable Enzyme inducing anticonvulsants
Carbamazepine
Felbamate
Phenobarbital
Fosphenytoin
Phenytoin
Primidone
Oxcarbazepine

APPENDIX VIII: MEDICATIONS ASSOCIATED WITH PROLONGED QTC

The use of the following medications should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references. For the most current list of medications, please refer to the following reference:
Woosley, RL and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date December 2nd, 2016, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

Medications that prolong QTc	
Amiodarone	Flecainide
Anagrelide	Fluconazole
Arsenic trioxide	Haloperidol
Azithromycin	Ibutilide
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Ciprofloxacin	Ondansetron
Citalopram	Pentamidine
Clarithromycin	Pimozide
Disopyramide	Procainamide
Dofetilide	Propofol
Domperidone	Quinidine
Droperidol	Sevoflurane
Dronedarone	Sotalol
Erythromycin	Thioridazine
Escitalopram	Vandetanib

Medications that MAY prolong QTc	
Aripiprazole	Lapatinib
Bortezomib	Lenvatinib
Bosutinib	Leuprolide
Ceritinib	Mirtazapine
Clomipramine	Nicardipine
Crizotinib	Nilotinib
Dabrafenib	Olanzapine
Dasatinib	Osimertinib
Degarelix	Pazopanib
Desipramine	Promethazine
Dolasetron	Risperidone
Eribulin mesylate	Sorafenib
Famotidine	Sunitinib
Foscarnet	Tacrolimus
Gemifloxacin	Vemurafenib
Granisetron	Venlafaxine
Isradipine	Vorinostat

APPENDIX IX: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1622
(for children from 7 through 12 years of age)

A study of the drug XL184 (cabozantinib) in children with a cancer that has come back after treatment or is difficult to treat

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment or you have a cancer that is difficult to treat.

2. We are asking you to take part in a research study because your cancer has come back or is hard to treat. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have. We will do this by trying a new medicine to treat your cancer.

3. Children who are part of this study will be treated with a cancer-fighting medicine called XL184. You will also have regular tests and exams done more often while you are in this study. The doctors want to see if XL184 will make children with your type of cancer get better. We don't know if XL184 will work well to get rid of your cancer. That is why we are doing this study.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that XL184 may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from XL184 than other treatments. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood. We want to see how your body handles XL184. Some of these samples are collected when you may not need to have a blood sample taken and may require extra needle sticks. You can still take part in this study even if you don't allow us to collect some of the extra blood samples for research. We are also asking your permission to keep some of the tumor tissue that may have been removed during your diagnosis and/or earlier treatment and any that is removed with procedures that happen while you are on this study. We would like to save the tumor tissue for tests in the future.

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1622
(for teens from 13 through 17 years of age)

A study of the drug XL184 (cabozantinib) in children with a cancer that has come back after treatment or is difficult to treat

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment or you have a cancer that is difficult to treat.

2. We are asking you to take part in a research study because your cancer has come back or is hard to treat. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.

3. Children and teens who are part of this study will be given a cancer-fighting medicine called XL184. XL184 blocks pathways that are involved in the growth of tumors and blood vessels that supply tumors. XL184 has been approved by the Food and Drug Administration (FDA) for another illness, but not for your cancer. The dose of XL184 used in this study was found to be well tolerated in children and teens.

4. You will take XL184 every day. You may continue to receive XL184 for as long as you do not have bad effects from it and your cancer does not get any worse. You will also have exams and tests done that are part of normal cancer care. But, the exams and tests will be done more often while you are being treated with XL184. The doctors want to see if XL184 will make children and teens with your type of cancer get better. We don't know if XL184 is better than other medicines. That is why we are doing this study.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that XL184 may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from XL184 than other treatments. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

8. We are asking your permission to collect additional blood. We want to see how your body handles XL184. Some of these samples are collected when you may not need to have a blood sample taken and may require extra needle sticks. You can still take part in this study even if you don't allow us to collect the extra blood samples for research. We are also asking your permission to keep some of the tumor tissue that may have been removed during your diagnosis and/or earlier treatment and any that is removed with procedures that happen while you are on this study. We would like to save the tumor tissue for tests in the future.

APPENDIX X: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **XL184 (cabozantinib).** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:
XL184 (cabozantinib) interacts with a certain specific enzyme in your liver, a certain transport protein that helps move drugs in and out of cells, and the heart's electrical activity (QTc prolongation) .

- The enzyme in question is **CYP 3A4**. XL184 (cabozantinib) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.
- The protein in question are **P-glycoprotein (P-gp) and MRP2.** XL184 (cabozantinib) is an inhibitor of P-gp and may be affected by other drugs that are "substrates." XL184 is also a substrate of MRP2 and may be affected by other drugs that are "inhibitor" or "inducers" of MRP2.
- XL184 (cabozantinib) may affect the heart's electrical activity causing QTc prolongation. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.
XL184 (cabozantinib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.
Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:
XL184 (cabozantinib) must be used very carefully with other medicines that use certain **liver enzyme, transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP3A4, substrate of P-gp, or any medicine associated with greater risk for having QTc prolongation."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Do not drink or eat grapefruit/juice or Seville oranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug XL184 (cabozantinib). This clinical trial is sponsored by the NCI. XL184 (cabozantinib) may interact with drugs that are **processed by your liver, or use certain transport proteins in your body or affect the electrical activity of your heart**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

XL184 (cabozantinib) must be used very carefully with other medicines that interact with **CYP3A4 enzyme, transporter proteins (P-gp) and MRP2, or drugs that may trigger your heart's electrical activity (QTc prolongation)**.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors CYP3A4; P-gp substrates; or drugs that cause risks for QTc prolongation."**
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

APPENDIX XI: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for SGPT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L - ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for SGOT is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L - ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

REFERENCES

1. Exelixis: Investigator's Brochure for Cabozantinib (XL184), (ed 11.0), 2015
2. 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 10:2298-308, 2011
3. Elisei R, Schlumberger MJ, Muller SP, et al: Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 31:3639-46, 2013
4. 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
5. Smith DC, Smith MR, Sweeney C, et al: Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. J Clin Oncol 31:412-9, 2013
6. FDA: Cometriq Prescribing Information. 2012
7. FDA: Cabometyx Prescribing Information. 2016
8. Christensen JG, Burrows J, Salgia R: c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. Cancer Lett 225:1-26, 2005
9. Birchmeier C, Birchmeier W, Gherardi E, et al: Met, metastasis, motility and more. Nat Rev Mol Cell Biol 4:915-25, 2003
10. DuBois S, Demetri G: Markers of angiogenesis and clinical features in patients with sarcoma. Cancer 109:813-9, 2007
11. Fleuren ED, Roeffen MH, Leenders WP, et al: Expression and clinical relevance of MET and ALK in Ewing sarcomas. Int J Cancer 133:427-36, 2013
12. Patane S, Avnet S, Coltella N, et al: MET overexpression turns human primary osteoblasts into osteosarcomas. Cancer Res 66:4750-7, 2006
13. Sampson ER, Martin BA, Morris AE, et al: The orally bioavailable met inhibitor PF-2341066 inhibits osteosarcoma growth and osteolysis/matrix production in a xenograft model. J Bone Miner Res 26:1283-94, 2011
14. Taulli R, Scuoppo C, Bersani F, et al: Validation of met as a therapeutic target in alveolar and embryonal rhabdomyosarcoma. Cancer Res 66:4742-9, 2006
15. Jankowski K, Kucia M, Wysoczynski M, et al: Both hepatocyte growth factor (HGF) and stromal-derived factor-1 regulate the metastatic behavior of human rhabdomyosarcoma cells, but only HGF enhances their resistance to radiochemotherapy. Cancer Res 63:7926-35, 2003
16. Torres KE, Zhu QS, Bill K, et al: Activated MET is a molecular prognosticator and potential therapeutic target for malignant peripheral nerve sheath tumors. Clin Cancer Res 17:3943-55, 2011
17. Oda Y, Sakamoto A, Saito T, et al: Expression of hepatocyte growth factor (HGF)/scatter factor and its receptor c-MET correlates with poor prognosis in synovial sarcoma. Hum Pathol 31:185-92, 2000
18. Stacchiotti S, Marrari A, Dei Tos AP, et al: Targeted therapies in rare sarcomas: IMT, ASPS, SFT, PEComa, and CCS. Hematol Oncol Clin North Am 27:1049-61, 2013
19. Tsuda M, Davis IJ, Argani P, et al: TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res 67:919-29, 2007
20. Davis IJ, McFadden AW, Zhang Y, et al: Identification of the receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor, as therapeutic targets in clear cell sarcoma. Cancer Res 70:639-45, 2010
21. Park WS, Dong SM, Kim SY, et al: Somatic mutations in the kinase domain of the Met/hepatocyte growth factor receptor gene in childhood hepatocellular carcinomas. Cancer Res 59:307-10, 1999
22. Purcell R, Childs M, Maibach R, et al: HGF/c-Met related activation of beta-catenin in hepatoblastoma. J Exp Clin Cancer Res 30:96, 2011
23. Ueki T, Fujimoto J, Suzuki T, et al: Expression of hepatocyte growth factor and its receptor c-met proto-oncogene in hepatocellular carcinoma. Hepatology 25:862-6, 1997

24. You H, Ding W, Dang H, et al: c-Met represents a potential therapeutic target for personalized treatment in hepatocellular carcinoma. Hepatology 54:879-89, 2011
25. Geller JI, Argani P, Adeniran A, et al: Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer 112:1607-16, 2008
26. Philips GK, Atkins MB: New agents and new targets for renal cell carcinoma. Am Soc Clin Oncol Educ Book:e222-7, 2014
27. Wallenius V, Hisaoka M, Helou K, et al: Overexpression of the hepatocyte growth factor (HGF) receptor (Met) and presence of a truncated and activated intracellular HGF receptor fragment in locally aggressive/malignant human musculoskeletal tumors. Am J Pathol 156:821-9, 2000
28. Hisaoka M, Ishida T, Kuo TT, et al: Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis of 33 cases. Am J Surg Pathol 32:452-60, 2008
29. Phan LM, Fuentes-Mattei E, Wu W, et al: Hepatocyte Growth Factor/cMET Pathway Activation Enhances Cancer Hallmarks in Adrenocortical Carcinoma. Cancer Res 75:4131-42, 2015
30. Lee RJ, Saylor PJ, Michaelson MD, et al: A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. Clin Cancer Res 19:3088-94, 2013
31. Nguyen L, Holland J, Miles D, et al: Pharmacokinetic (PK) drug interaction studies of cabozantinib: Effect of CYP3A inducer rifampin and inhibitor ketoconazole on cabozantinib plasma PK and effect of cabozantinib on CYP2C8 probe substrate rosiglitazone plasma PK. J Clin Pharmacol 55:1012-23, 2015
32. Andrea Borghese Apolo YT M-JL, Sunmin Lee, Ari Frosch, Seth M. Steinberg, James L. Gulley, Jeffrey Schlom, Donald P Bottaro, Jane B.Trepel: Effect of cabozantinib on immunosuppressive subsets in metastatic urothelial carcinoma. J Clin Oncol 32, 2014
33. Choueiri TK, Escudier B, Powles T, et al: Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 373:1814-23, 2015
34. Cabanillas ME, Brose MS, Holland J, et al: A phase I study of cabozantinib (XL184) in patients with differentiated thyroid cancer. Thyroid 24:1508-14, 2014
35. Drilon A, Wang L, Hasanovic A, et al: Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 3:630-5, 2013
36. Hoag JB, Sherman M, Fasihuddin Q, et al: A comprehensive review of spontaneous pneumothorax complicating sarcoma. Chest 138:510-8, 2010
37. Interiano RB, McCarville MB, Wu J, et al: Pneumothorax as a complication of combination antiangiogenic therapy in children and young adults with refractory/recurrent solid tumors. J Pediatr Surg 50:1484-9, 2015
38. van der Graaf WT, Blay JY, Chawla SP, et al: Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379:1879-86, 2012
39. Nakano K, Motoi N, Tomomatsu J, et al: Risk factors for pneumothorax in advanced and/or metastatic soft tissue sarcoma patients during pazopanib treatment: a single-institute analysis. BMC Cancer 16:750, 2016
40. Schuirmann DJ: A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 15:657-80, 1987
41. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009