SUMMARY OF CHANGES – Protocol

For Protocol Amendment # to:

NCI Protocol #: 9620
Local Protocol #: CABONE

NCI Version Date: 04/04/2019
Protocol Date: 04/04/2019

Please provide a list of changes from the previous CTEP approved version of the protocol. The list shall identify by page and section each change made to a protocol document with hyperlinks to the section in the protocol document. All changes shall be described in a point-by-point format (i.e., Page 3, section 1.2, replace 'xyz' and insert 'abc'). When appropriate, a brief justification for the change should be included.

As requested by your request for Amendment, protocol has been updated.

#	Section	Comments
1.	Protocol	1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy: Protocol Cover Page: Page Number(s): 5 Version Date: 04/04/2019
2.	Section 7.1	2) Revision of the Protocol CAEPR: Protocol Section(s) for Insertion of Revised CAEPR (Version 2.4, December 17, 2018): 7.1 Page Number(s): 54 • The SPEER grades have been updated. • The section below utilizes CTCAE 5.0 language unless otherwise noted. • Added New Risk: • Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Anal mucositis; Atrioventricular block complete; Budd-Chiari syndrome; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest wall pain; Death NOS; Dysphasia; Ejection fraction decreased; Gastroesophageal reflux disease; Gastrointestinal pain; General disorders and administration site conditions - Other (general physical health deterioration); Gingival pain; Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatorenal syndrome); Hoarseness; Hypothermia; Pain of skin; Pelvic pain; Periodontal disease; Scrotal pain; Sinus bradycardia; Sinus tachycardia; Skin hypopigmentation; Sudden death NOS; Thyroid stimulating hormone increased; Toothache; Vaginal inflammation; Vaginal perforation

#	Section	Comments

		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Generalized muscle weakness; Hematuria; Hypophosphatemia
		  • Changed to Rare but Serious from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Intracranial hemorrhage; Ischemia cerebrovascular; Stroke; Transient ischemic attacks
		
		• Decrease in Risk Attribution:
		  • Changed to Less Likely from Likely: Voice alteration
		  • Changed to Also Reported on XL184 Trials But With Insufficient Evidence for Attribution from Less Likely: Acute kidney injury
		
		• Provided Further Clarification:
		  • Footnote #8 has been updated to "Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Hemoptysis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC" from "Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC."
		  • Musculoskeletal and connective tissue disorder - Other (muscle spasm) (*CTCAE 4.0 language*) is now reported as Muscle cramp.
		  • Skin and subcutaneous tissue disorders - Other (hair color changes) (*CTCAE 4.0 language*) is now reported as Hair color changes.
		  • Acute coronary syndrome is now reported as part of Chest pain - cardiac.
		  • Endocrine disorders - Other (hypopituitarism) (*CTCAE 4.0 language*) is now reported as Hypopituitarism.
		  • Gastrointestinal disorders - Other (gastroenteritis) is now reported as part of Infection.
		  • Gastrointestinal disorders - Other (anal fissure) (*CTCAE 4.0 language*) is now reported as Anal fissure.
		  • Investigations - Other (blood lactate dehydrogenase increased) (*CTCAE 4.0 language*) is now reported as Blood lactate dehydrogenase increased.
		  • Investigations - Other (eosinophil count increased) *(CTCAE 4.0 language)* is now reported as Eosinophilia under the BLOOD AND LYMPHATIC SYSTEM DISORDERS SOC.
		  • Investigations - Other (glucose urine present) *(CTCAE 4.0 language)* is now reported as Glucosuria under the RENAL AND URINARY DISORDERS SOC.
		  • Musculoskeletal and connective tissue disorder - Other (osteonecrosis) (*CTCAE 4.0 language*) is now reported as Osteonecrosis.
		  • Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis) (*CTCAE 4.0 language*) is now reported as Rhabdomyolysis.
		  • Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage) (*CTCAE 4.0 language*) is now reported as Tumor hemorrhage.

#	Section	Comments
		• Nervous system disorders - Other (cerebral hematoma) is now reported as part of Hematoma under the VASCULAR DISORDERS SOC. • Nervous system disorders - Other (spinal cord compression) (*CTCAE 4.0 language*) is now reported as Spinal cord compression. • Renal and urinary disorders - Other (azotemia) is now part of Acute kidney injury. • Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain) (*CTCAE 4.0 language*) is now reported as Oropharyngeal pain. • Skin and subcutaneous tissue disorders - Other (splinter hemorrhage) is now reported as Nail changes. PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.4, and associated risk information for the ICD, to the most recent CAEPR Version 2.3. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.3), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

NCI Protocol #: *9620*

Local Protocol #: CABONE.

TITLE: A Phase 2 Study of XL184 (Cabozantinib) in treating patients with relapsed Osteosarcomas and Ewing Sarcomas

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Exelixis Supplied Agent: XL184 (cabozantinib) (NSC 761968)

Below, please describe the IND Status of this study by choosing IND #/Sponsor OR Exemption from IND requirements, making sure to delete the inapplicable field(s).

IND #: 116059
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original, Version 9.0, 04/04/2019

SCHEMA

SYNOPSIS

A Phase II study of XL 184 (Cabozantinib) in treating patients with relapsed Osteosarcomas and Ewing Sarcomas	
PROTOCOL CODE	**NCI Protocol 9620**
PRINCIPAL INVESTIGATOR	Italiano Antoine, MD, PhD Institut Bergonie Department of Medical Oncology 229 cours de l'Argonne 33000 Bordeaux, France Tel : + 33 5 56 33 33 33 Fax : + 33 5 56 33 04 85 a.italiano@bordeaux.unicancer.fr
STUDY OBJECTIVES **Primary**	To evaluate the antitumor activity of cabozantinib in terms of : • Osteosarcoma: 6-month non-progression (Complete response, partial response and stable disease) and 6-month objective response (Complete response, partial response) rates (composite endpoint) as per the Response Evaluation Criteria in Solid Tumors, Revised RECIST v1.1. • Ewing sarcoma: 6-month objective response as per the revised RECIST v1.1.
Secondary	• Ewing sarcoma only: 6-month objective response rate Both strata: • Best overall response (as per the revised RECIST v1.1); • 1- and 2-year progression-free survival; • 1- and 2-year overall survival; • Cabozantinib safety; • To assess the ability of metabolic tumor response as measured by FDG-PET at the end of one cycle of treatment to predict PFS. • Translational research: to determine and compare tumor expression of MET, phospho-MET and circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) prior to and following administration of cabozantinib.
STUDY DESIGN	Single-arm phase 2 clinical trials with two strata: - Osteosarcoma: dual-endpoint design. - Ewing sarcoma: optimal 2-stage Simon's design.
STUDY POPULATION	Patients aged 12 years or older with unresectable locally advanced or metastatic osteosarcoma or Ewing sarcoma
INCLUSION CRITERIA	1. Patients must have histologically confirmed diagnosis of osteosarcoma or Ewing sarcoma by central review, except if the diagnosis was already confirmed by the RRePS (Réseau de Référence en Pathologie des Sarcomes et des Tissus Mous et des Viscères) network. 2. Relapsed disease after standard chemotherapy. 3. Patients must have measurable disease (lesion in previously irradiated field could be considered as measurable if progressive at inclusion) defined as per RECIST v1.1 with at least one lesion that can be measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan. 4. Age ≥12 years. 5. ECOG performance status ≤1 (see Appendix A). 6. Life expectancy of greater than 3 months. 7. Patients must have normal organ and marrow function as defined below:

	- leukocytes ≥3,000/mcL - absolute neutrophil count ≥1,500/mcL - lymphocyte count ≥1,000/mcL - platelets ≥100,000/mcL - total bilirubin ≤1.5 × ULN - AST(SGOT)/ALT(SGPT) ≤3.0 × institutional upper limit of normal - creatinin ≤1.5 × ULN OR creatinine clearance ≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal (Cockcroft formula, see Appendix I). - hemoglobin ≥9 g/dL - serum albumin ≥2.8g/dL - lipase <2.0 × ULN and no radiologic or clinical evidence of pancreatitis - urine protein/creatinine, ratio (UPCR) ≤1 - serum phosphorus, calcium, magnesium, and potassium ≥ LLN 8. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons. 9. The effects of Cabozantinib on the developing human fetus are unknown. For this reason and because tyrosine kinase inhibitors agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (see below) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of Cabozantinib administration. Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (*e.g.*, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s). 10. Metastatic or unresectable locally advanced. 11. Documented disease progression (as per RECIST v1.1) before study entry. For patients with osteosarcoma, this progression will be confirmed by central review on the basis of two CT scan or MRI obtained at less than 6 months in the period of 12 months prior to inclusion. 12. Ability to understand and the willingness to sign a written informed consent document. 13. In accordance with French Regulatory Authorities: Patients with French Social Security in compliance with the French law relating to biomedical research (Article L.1121-11 of French Public Health Code).
EXCLUSION CRITERIA	1. The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (*e.g.*, cytokines or antibodies) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment. 2. Prior treatment with Cabozantinib. 3. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before the first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not

	eligible. 4. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment. Note: Subjects with prostate cancer currently receiving LHRH or GnRH agonists may be maintained on these agents. 5. The subject has received any other type of investigational agent within 28 days before the first dose of study treatment. 6. The subject has not recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs. 7. The subject has a primary brain tumor. 8. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 2 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment. 9. The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 7 days before the first dose of study treatment. 10. The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (*e.g.*, clopidogrel). Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted. 11. The subject requires chronic concomitant treatment of strong CYP3A4 inducers (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort). Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. 12. The subject has experienced any of the following: • clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment • hemoptysis of ≥0.5 teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment • any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment 13. The subject has radiographic evidence of cavitating pulmonary lesion(s). 14. The subject has tumor in contact with, invading or encasing any major blood vessels. 15. The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib. 16. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions: 1. Cardiovascular disorders including: a) Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening b) Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment

	c) Any history of congenital long QT syndrome d) Any of the following within 6 months before the first dose of study treatment: • unstable angina pectoris • clinically-significant cardiac arrhythmias • stroke (including TIA, or other ischemic event) • myocardial infarction • thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study) 2. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including: a) Any of the following within 28 days before the first dose of study treatment • intra-abdominal tumor/metastases invading GI mucosa • any evidence of active peptic ulcer disease, patients must be completely recovered • any evidence of inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, patients must be completely recovered from these conditions • malabsorption syndrome b) Any of the following within 6 months before the first dose of study treatment: • abdominal fistula • gastrointestinal perforation • bowel obstruction or gastric outlet obstruction • intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before the first dose of study treatment. 3. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy 4. Other clinically significant disorders such as: a) active infection requiring systemic treatment within 28 days before the first dose of study treatment b) serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment c) history of organ transplant d) concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment e) history of major surgery as follows: i. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment. ii. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not

	eligible 17. The subject is unable to swallow tablets. 18. The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before treatment. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard. 19. The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee. 20. The subject has had evidence within 2 years of the start of study treatment of another malignancy which required systemic treatment 21. History of allergic reactions attributed to compounds of similar chemical or biologic composition to Cabozantinib. 22. Pregnant women are excluded from this study because Cabozantinib is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Cabozantinib, breastfeeding should be discontinued if the mother is treated with Cabozantinib. These potential risks may also apply to other agents used in this study. 23. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Cabozantinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated. 24. Participation to a study involving a medical or therapeutic intervention in the last 30 days. 25. Prior participation in this study.
STUDY POPULATION **Translational research study**	All patients included in the trial are eligible for the translational research study. Only those patients that voluntarily sign the Informed Consent Form for translational study will participate. The refusal for participation in the translational study will not affect the patients' participation in this clinical trial. Available paraffin-embedded tumor tissue.
NUMBER OF PATIENTS	Osteosarcoma: - single-arm phase 2 trial based on a dual-endpoint design - 41 eligible and evaluable patients. 45 to be recruited. Ewing sarcoma: - single-arm phase 2 trial based on an optimal two-stage Simon's design - 41 eligible and evaluable patients. 45 to be recruited
NUMBER OF SITES	This is a multicenter study with 11 centres. Young patient age between 12 – 15 could be included in only 6 centers (Bordeaux, Lyon, Villejuif, Lille, Marseille and Paris). A complete list of investigators will be provided as a separate document.
STUDY DRUG	**Formulation**: XL 184 (Cabozantinib) – Available in 20 mg and 60 mg tablet. Tablets are yellow film coated. 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 bottle. **Route of administration**: Oral **Administered dose:** to take without food , and not eat for at least 2 hours before and 1 hour after taking it: - for patients ≥16 years: 60 mg - For patients ≥12 years < 16 years: 40 mg/m² (Chuck *et al*., 2014) **Treatment schedule**: Daily, day 1-28 during 4 weeks (ie. 1 cycle)

EFFICACY EVALUATIONS	Patients will be evaluated for efficacy if they receive at least one complete or two incomplete cycles of Cabozantinib, and if they have at least one disease measurement recorded not less than eight weeks after treatment onset (except for in case of early disease progression). Antitumor activity will be assessed using RECIST v1.1 on a set of measurable lesions identified at baseline as target lesions and followed until disease progression by the appropriate method (computed tomography [CT] scan or magnetic resonance imaging [MRI]). Radiological and clinical (whenever appropriate) tumor assessment will be performed at baseline and every eight weeks until evidence of disease progression (PD). Whenever the criteria of response are met, the appropriate imaging tests will be repeated at least four weeks later in order to confirm the response. Efficacy will be evaluated based on 6-month non-progression and 6-month objective response (composite primary endpoint) for osteosarcoma and 6-month objective response rate (ORR - primary endpoint) for Ewing sarcoma. Secondary endpoints include 6-month ORR for Ewing sarcoma, as well as for both strata: best overall response, 1- and 2-year PFS, and 1- and 2-year OS. Primary endpoint efficacy analyses will be based on radiological data reviewed by an independent expert radiologist.
SAFETY EVALUATIONS	Patients will be evaluable for safety if they have received at least one dose of Cabozantinib. All AEs will be graded according to the CTEP CTCAE Version 4.0. Safety profile will be continuously followed during treatment and up to 30 days after the last Cabozantinib dose or until the start of a new antitumor therapy, whichever occurs first.

STUDY ASSESSMENTS

	SCREENING	CYCLE 1				CYCLES 2 à 4				CYCLE N	End of treatment (30-37 days)
		D1	D8	D15	D22	D1	D8	D15	D22		
XL184		X ……..continuous ……X									
Informed consent	X										
Demographics	X										
Medical History	X										
Concomitant treatments	X	X ……X									X
Physical exam	X	X	X	X	X	X		X		X	X
Vital signs[a]	X	X	X	X	X	X		X		X	X
Height	X										
Weight	X	X	X	X	X	X		X		X	X
Performance status	X	X	X	X	X	X		X		X	X
Clinical laboratory test[b]	X	X	X	X	X	X		X		X	X
Urinalysis and UPCR	X	X	X	X	X	X		X		X	X
PT/INR, PTT	X	X				X				X	
TFTs (TSH, free T3, free T4)	X	X				X				X	
ECG[f]	X	X				X				X	X
Toxicity		X ……X									X
Tumor measurement	X	Repeated every 2 cycles (ie. 8 weeks). Documentation (radiologic) must be provided for patients removed from study for progressive disease									
Chest X-ray						X[h]				X[h]	
B-HCG [c] (if indicated)	X	X				X				X	X
Blood samples		X[d]		X[d]	X[d]						
PET-FDG	X[g]				**D28**						
Biopsy for translational research	X				X[e]						

a: Heart rate, blood pressure, temperature
b: CBC, differential, platelets, albumin, alkaline phosphatase, SGOT [AST], SGPT [ALT], amylase, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyltransferase (GGT), glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein
c: Serum test 10-14 days and within 24 hours prior to the first dose of XL 184. Pregnancy test must be repeated at least once every month thereafter (serum or urine).
d: on Day 1, Day 15 and Day 28 of cycle 1
e: to be performed on Day 1 of cycle 1 predose and on Day 28 of Cycle 1 postdose on the same scanner for the two evaluation
f: Required in triplicate at baseline. Three ECG should be obtained within 30 minutes but at least 3 minutes apart.
g: to be done within 1 week prior do Day 1 of Cycle 1
h: to be performed at the end of cycle 1, 3, 5, etc… every 8 weeks between each tumor evaluation

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the antitumor activity of cabozantinib:

- for Ewing sarcomas, in terms of 6-month objective response as per the Response Evaluation Criteria in Solid Tumors, Revised (RECIST v1.1)
- for osteosarcoma, in terms of 6-month objective response (Complete response, partial response) and 6-month non-progression (Complete response, partial response and stable disease), as per RECIST v1.1.

1.2 Secondary Objectives

Ewing sarcoma only:

- 6-month objective response

For each stratum (Ewing sarcoma and osteosarcoma):

- Best overall response (as per the revised RECIST v1.1);
- 1- and 2-year progression-free survival;
- 1- and 2-year overall survival;
- Cabozantinib safety;
- To assess the ability of metabolic tumor response as measured by FDG-PET at the end of one cycle of treatment to predict PFS;
- Translational research: to determine and compare tumor expression of MET, phosphor-MET and circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) prior to and following administration of Cabozantinib.

2. BACKGROUND

The incidence of osteosarcoma and Ewing sarcoma are of 150 and 80 new cases/year respectively. The 5-overall survival rate is 60-70%.

2.1 Osteosarcoma

Bone tumors make up about 3–5% of childhood cancers and less than 1% of cancers in adults. Of these, osteosarcoma (OSS) is the most commonly diagnosed primary malignant bone tumor. OSS is a primary mesenchymal malignant tumor of bone characterized by the production of osteoid or immature bone by the malignant cells.

Despite its rarity, OSS is the most common primary malignancy of bone in children and adolescents, and the fifth most common malignancy among adolescents and young adults aged 15 to 19 (Stiller et al. 2006). Indeed, OSS incidence rate has two peaks of about 4 per million per year, one in children and young adults ≤ 24 years, and the second after 60 (Mirabello *et al.*, 2009).

Use of chemotherapy in the neoadjuvant/adjuvant setting has dramatically improved overall survival (OS) in OSS. Most active agents in OSS are anthracyclines, platinum salts, ifosfamide

and methotrexate given in combination in different protocols (Bramwell *et al*., 1997). At relapse, combination protocols with the same drugs are favoured when complete surgery of the metastases is considered achievable. However, patients (pts) not amenable to this strategy have a very poor prognosis and there is no standard therapy in this setting (Ferrari *et al*., 2003; Chou *et al*., 2005; Gelderblom *et al*., 2011).

2.2 Ewing sarcoma

Ewing sarcoma (ES) is the second most frequent bone tumors in children and may arise also in soft tissues. This disease encompasses tumors formerly known as Askin's tumor, Peripheral Neuroectodermal Tumor (PNET) and the Ewing Sarcoma Family of Tumors (ESFT) (Hawkins *et al*., 2011). ES is most common in the second decade of life with an annual incidence of about 225 cases in North America in children between 1 and 20 years of age (Esiashvili *et al*., 2008). Patients with Ewing sarcoma who present with localized disease have a favorable 5-year event free survival of around 70% due to the advent of multimodal therapy that includes chemotherapy, surgery and/or radiation (Grier *et al*., 2003 and Paulussen *et al*., 2008).

In 25% of ES cases, there is evidence of metastatic disease at presentation (Bernstein *et al*., 2006; Subbiah *et al*., 2009). The prognosis of patients with metastatic tumors at drops significantly compared to localized tumor cases (Paulussen *et al*. 1998). Patients with combined bone, bone marrow, and lung metastases have been shown to have a 4-year event free survival (EFS) rate of as low as 14% (Paulussen *et al*. 1998). Treatment regimens include chemotherapy in combination with radiation therapy. Intense therapies that include higher doses of chemotherapy, sometimes along with total body radiation and stem cell support, have not shown increased EFS rates (Meyers *et al*., 2001; Miser *et al*. 2007). Improving cure rates and increasing EFS rates have proved to be a challenge in patients presenting with metastatic disease, and potential molecular therapies are likely the means through which the prognosis may be improved.

30% of patients with initial localized disease will suffer from recurrent tumors either locally, distally, or some combination of the two, and their prognosis remains poor (Jurgens *et al*., 1988). Upon recurrence, chances of survival have been estimated at less that 20–25% (Ahrens *et al*., 1999). There is no specific treatment regimen established for recurrent cases. Therefore, there is a great need to develop new approaches or therapies for the treatment of this tumor that target the biology of the disease.

2.3 Cabozantinib – XL 184

XL184 (cabozantinib) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, 2015). The primary targets of Cabozantinib are MET (c-MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2. Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in *vivo* pharmacodynamic activity of Cabozantinib against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

RTKs regulate many processes including cell growth and survival, organ morphogenesis,

neovascularization, and tissue repair (Christensen *et al.*, 2005). Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand have been implicated as causative factors in the development and progression of numerous human cancers.

The RTK c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF) (Christensen *et al.*, 2005). c-Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (*e.g.*, renal tubular cells, gland formation, *etc.*), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo* (Investigator's Brochure, 2015). C-Met-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

Evidence linking c-Met and HGF as causative or progression factors in human cancers include: (1) the overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; (2) the correlation of receptor and ligand overexpression with disease severity and outcome; (3) genetic alteration of c-Met by mutation of gene amplification in multiple cancer types; (4) introduction of c-Met and HGF (or mutant c-Met) into cell lines, conferred the properties of tumorgenicity and metastatic propensity on engineered cells; (5) introduction of c-Met or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) the inhibition of c-Met or HGF function with dominant-negative receptors, antibody antagonists (both Met and HGF), and biologic antagonists (*e.g.*, NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination *in vivo* (Christensen *et al.*, 2005).

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity (Liu *et al.*, 2010), either by means of c-Met kinase overexpression (Comoglio *et al.*, 2008), activating c-Met gene mutations and/or amplification (Comoglio *et al.*, 2008; Jeffers et al., 1997; Schmidt et al., 1997), or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF (Birchmeier *et al.*, 2003; Boccaccio and Comoglio, 2006). These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of c-Met has been correlated with poor clinical prognosis (Birchmeier *et al.*, 2003).

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability (Roskoski, 2008). Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer (Tugues *et al.*, 2011). High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (*i.e.*, therapy-resistant) breast cancer and poor survival.

In Vivo Activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors (Paez-Ribes *et al*., 2009). In RIP-Tag2 transgenic mice, tumors treated with Cabozantinib were smaller (P <0.05) than in mice treated with vehicle or an anti-VEGF antibody, but were also less invasive (P <0.05) and had no liver metastases (Sennino *et al*., 2009). All mice treated with Cabozantinib (n = 6) survived until 20 weeks, but none treated with vehicle (n = 14) or anti-VEGF antibody (n = 8) reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days (You *et al*., 2011). Tumors were 35% smaller after Cabozantinib treatment than corresponding values for vehicle control mice. c-Met protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg (Yakes *et al*., 2011). Cabozantinib increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, Cabozantinib disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. Cabozantinib treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors (P <0.001) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses (P <0.01), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after which tumors began growing at a rate similar to vehicle-treated control tumors. In addition, Cabozantinib inhibited tumor growth (P <0.001) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, P <0.0001) when compared with predose tumor weights. Subchronic administration of Cabozantinib was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both c-Met and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone (Zhang *et al*., 2010). ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive Cabozantinib or vehicle daily (qd) for 7 weeks of treatment (Investigator's brochure, 2015). Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from Cabozantinib treated animals appeared mostly normal. Thus, Cabozantinib treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

Nonclinical Pharmacodynamics

In mice, the effective dose resulting in 50% inhibition (ED_{50}) of targets was achieved at well tolerated doses of Cabozantinib and at plasma exposures comparable to exposure observed in clinical trials (Investigator's Brochure, 2015). Cabozantinib produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after

administration of a single dose of Cabozantinib. This extended inhibition occurred in a manner that was generally predicted by plasma exposure, *i.e.*, inhibition was diminished when plasma levels fell below approximately 20 µM for c-Met, 5 µM for VEGFR2, and 23 µM for TIE-2.

Once daily administration of Cabozantinib resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg (Investigator's Brochure, 2015). Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of Cabozantinib, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met (Yakes *et al*., 2011). This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

Nonclinical Pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27 µM were associated with efficacy (Investigator's Brochure, 2015). In rats, plasma concentrations in the range of 5 to 15 µM were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations as low as 0.1 µM were observed at highly efficacious doses in mice. These results were consistent with *in vivo* target modulation studies in mice which demonstrated long (4- to 10-hour) durations of action, and indicated that continuous high exposure was not required to maintain efficacy.

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats (Investigator's Brochure, 2015). In rats, the oral bioavailability of Cabozantinib dosed as a solid was approximately 100% of XL184 dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [C_{max}] and area under the time-concentration curve from 0 to t hours post-dose [AUC_{0-t}] values) associated with single Cabozantinib oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg) (Investigator's Brochure, 2015). With repeat daily oral dosing in rats, systemic exposure (AUC_{0-t} values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The C_{max} and AUC_{0-t} values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to Cabozantinib in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters (C_{max} and AUC_{0-t} values) associated with single Cabozantinib oral doses in dogs increased less than dose-proportionally with increasing XL184 dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption (Investigator's Brochure, 2015). With repeat daily dosing, exposure (C_{max} and AUC_{0-24} values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

Toxicology

In rodents and non-rodents, histopathological changes associated with Cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues (Investigator's Brochure, 2015). Histopathological changes present in the bone and pancreas were considered secondary to Cabozantinib administration. Adverse effects following oral exposure to Cabozantinib were generally dose-related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, Cabozantinib administration resulted in decreased fertility in male and female rats, in embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen) when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg Cabozantinib capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, Cabozantinib was negative in an *S. typhimurium/E.coli* bacterial mutagenicity study, an *in vitro* chromosome aberration study using human peripheral blood lymphocytes, and an *in vivo* mouse bone marrow micronucleus study (Investigator's Brochure, 2015). In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in Cabozantinib -treated rats or on cardiovascular function in Cabozantinib -treated dogs.

Clinical Experience

As of May 4, 2011, 1003 patients have been studied in 12 ongoing Exelixis-sponsored clinical trials with Cabozantinib treatment 1) as a single agent at does ranging from 0.08 to 11.52 mg/kg on an intermittent dosing schedule, 2) from 25 to 265 mg (19.7-209 mg freebase equivalent weight) on a fixed daily dosing schedule and 3) in combination with temozolomide (TMZ) and radiation therapy (RT), or with erlotinib (Exelixis Communication, 2011). The maximum tolerated dose (MTD) on once daily (qd) by mouth (PO) dosing schedule was determined to be 175 mg L-malate salt (or approximately 138 mg freebase equivalent weight).

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2013). Safety and efficacy information, from the 2011 Investigator's Brochure, is summarized below.

Phase I Studies

Study **XL184-001** was a phase 1 dose-escalation study in subjects with solid tumors. Eighty-five subjects, across 13 dosing levels (DL) ranging from 0.08 mg/kg qd (using powder-in-bottle [PIB] suspension on a 5 days on, 9 days off schedule) to 265 qd (using capsules [25 and/or 100mg] for two, 14-day cycles) were enrolled. The capsule MTD was determined to be 175 mg qd (Kurzrock *et al*., 2011). Of the 35 subjects with medullary thyroid cancer (MTC) and measureable disease enrolled in the dose expansion phase, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%) had tumor shrinkage of ≥30%, and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects.

In Study **XL184-002**, treatment of subjects with newly diagnosed glioblastoma (GB) consisted of cabozantinib in combination with TMZ with or without radiation therapy. Enrollment has been terminated and no clinical efficacy data is presented in the 2011 Investigator's Brochure. All adverse events (AEs) were assessed with respect to combination treatment and not the individual components. Nineteen patients were evaluated for AEs, the most common grade 3 or higher included neutropenia (21%), thrombocytopenia (16%), leucopenia (16%), and hypertension (11%). Myelosuppression, including prolonged pancytopenia, is a dose-limiting toxicity (DLTs) associated with TMZ use. The frequency at which bone marrow toxicity was observed in this study is consistent with the TMZ prescribing information.

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

Study **XL184-005** is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg cabozantinib, dosed as one 100-mg tablet) or Reference (100 mg cabozantinib, dosed as two 50-mg capsules), according to a randomization scheme. Each dosing was administered under fasting conditions, and blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib PK. See "Pharmacokinetics" section for results.

In Study **XL184-008**, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are evaluated for any potential clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8. The effect of qd dosing of 175 mg cabozantinib and a single dose of rosiglitazone will be evaluated. In 11 patients evaluated for AEs, the most common grade 3 or higher AEs were fatigue (9%), hypophosphatemia (27%), blood amylase increase (9%), and hyponatremia (9%).

In a phase 1 study, **CA205-001**, Japanese subjects with advanced or metastatic solid tumors for whom the standard of care is ineffective or inappropriate, received cabozantinib at a starting dose of 75 mg PO qd. Two of the three subjects in the first cohort experienced DLTs of proteinuria and thrombocytopenia. Because of a change in study sponsor, this study was reinitiated as **XL184-014.** One additional subject was enrolled as of May 2011 at 50 mg PO qd.

Study **XL184-202** was a phase 1b/2 trial that evaluated the safety and tolerability of cabozantinib and erlotinib administered in combination in non-small-cell lung cancer (NSCLC) subjects. Of the 64 subjects enrolled in the phase 1 dose-escalation portion of the study, all but two had been previously treated with and progressed on erlotinib therapy. A cPR was observed in 5 subjects (8%) and 24 subjects (37%) had SD/PR ≥4 months. The most common grade 3 or higher AEs in

the phase 1 portion included diarrhea (44%), fatigue (22%), hypokalemia (11%), decreased appetite (6%), dyspnea (14%), lipase increase (6%), hypomagnesemia (6%), and dehydration (5%). Twenty-eight subjects were enrolled in the phase 2 portion of the study, in which subjects who had received clinical benefit from erlotinib and subsequently experienced progressive disease (PD), received single-agent cabozantinib or cabozantinib with erlotinib. AEs ≥grade 3 included dehydration (8%) and hypertension (8%). One patient, who was treated with single-agent cabozantinib, had a cPR.

Phase 2 Studies

In a phase 2 study, **XL184-201**, subjects with progressive or recurrent GB in first or second relapse were enrolled to receive cabozantinib qd as a single agent. Group A received an initial dose of 175 mg (Group A), subsequent cohorts (Groups B and C) received an initial dose of 125 mg. Forty-six subjects were enrolled in Group A, and a total of 176 subjects were enrolled in Groups B/C. Fifty-seven subjects experienced one or more serious adverse events (SAEs) that were assessed to be related to treatment, including five fatal related.

Study **XL184-203** is a phase 2 randomized discontinuation trial. Subjects are enrolled into one of nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg qd for 12 weeks. Of the 531 subjects enrolled in this study as of May 2011, 92 experienced one or more SAEs that were assessed to be related to treatment with cabozantinib, including seven fatal related SAEs.

Study **XL184-205** is a randomized phase 2 trial for subjects with grade IV astrocytic tumors in first or second relapse. Subjects received one of four regimens: 25 mg qd (Arm 1) continuously, 75 mg qd (Arm 2) continuously, 125 mg qd for 2 weeks followed by 50 mg qd continuously (Arm 3) and 125 mg qd on an intermittent 3 week on/1 week off schedule (Arm 4). A total of 19 subjects were accrued before the study was terminated. Three subjects were rolled over to maintenance Study XL184-900. One subject experienced an SAE assessed to be related to treatment with cabozantinib.

Study **XL184-301** is a blind trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo. SAEs reported in Study XL184-301 are: one grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5).

Adverse Events

The clinical studies with Cabozantinib are ongoing and thus the AE data from the clinical database as of March 1, 2011 and May 4, 2011 do not yet include all SAEs (Exelixis Communication, 2011). As of March 2011, AE data are available for 913 subjects who have been dosed with XL184 (806 in single-agent studies and 107 in combination studies of XL184 with erlotinib, rosiglitazone, or TMZ ± radiation) (Investigator's Brochure, 2015). Data from the 806 subjects who received single-agent Cabozantinib show that the most frequently (>20%) observed AEs regardless of causality were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia, and

hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, and proteinuria, have been observed in the single-agent and combination Cabozantinib studies. The most commonly reported SAEs that were assessed as related to study treatment with Cabozantinib (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

There have been 15 grade 5 AEs related to study treatment: GI hemorrhage (two subjects), PE (two subjects), respiratory failure (two subjects), respiratory disorder (one subject), hemoptysis (one subject), death due to unknown cause (two subjects), intracranial hemorrhage (one subject), intestinal perforation (one subject), enterocutaneous fistula (one subject), hemorrhage (presumed to be hemoptysis; one subject), and diverticular perforation, peritonitis (one subject) (Investigator's Brochure, 2015).

Pharmacokinetics

Pharmacokinetic analysis of 74 patients in trial **XL184-001** showed dose proportional increases in maximum plasma concentration (C_{max}) and AUC both for PIB (dose range 0.08-11.52 mg/kg) and the capsule formulation (dose range: 125 to 175 mg) (Kurzrock, 2011). Terminal-phase half-life ($t_{1/2,z}$) values were 59.1 to 136 hours (Investigator's Brochure, 2015). After repeat dosing, $t_{1/2,z}$ values (mean ± standard deviation) for XL184 were 91.3 ± 33.3 hours (n = 23), and apparent steady-state plasma levels were reached by Day 15 (Kurzrock, 2011). Steady-state clearance for the 175 mg capsule dose derived from repeat dose data was 4.2 ± 1.5 L/h. Patients who received 175 mg capsules had four- to five-fold higher steady-state exposure (AUC) compared with Day 1 (7.68 ± 2.85 mcg·h/mL; n = 23 vs. 41.6 ± 15.3 mcg·h/mL; n = 23), indicating that Cabozantinib accumulated with repeat daily dosing. There was no significant difference in exposure between patients with MTC and those without MTC.

Based on the preliminary PK data from 23 subjects in **XL184-005** who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal $t_{1/2,\,z}$ of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours (Exelixis Communication, 2012). The median time to the maximum plasma concentration (t_{max}) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for C_{max} and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% C_{max}: 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable timepoint or to infinity [$AUC_{0\text{-last}}$ or $AUC_{0\text{-inf}}$]: 40-43% for the tablet formulation, 43% for the capsule formulation). The geometric mean C_{max} of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

Based on the preliminary PK data from 46 subjects who completed both treatments on trial **XL184-004**, a high-fat meal did not appear to alter the terminal $t_{1/2,\,z}$ of cabozantinib [mean $t_{1/2,\,z}$: 131 hours (fed) vs 128 hours (fasted)]. The high-fat meal significantly increased the median t_{max}

to 6 hours from 4 hours (fasted). The high-fat meal also significantly increased both the cabozantinib C_{max} and AUC values by 39% and 56%, respectively. The geometric mean ratio of C_{max} fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of $AUC_{0\text{-last}}$ fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib must be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

2.4 Rationale

MET was originally identified as the protein product of the translocated promoter region (TPR)-MET transforming oncogene, which was derived from an osteosarcoma cell line (Cooper *et al.*, 1984). MET play a crucial role in tumorigenesis in several cancer types. Its activation in tumors most frequently occurs via increased transcription and expression. MET overexpression results in constitutive MET enzymatic activity that stimulates additional MET transcription, resulting in a paracrine positive-feedback loop supporting proliferation and dissemination of cancer cells. Aberrant MET activation through an autocrine feedback loop has been detected in several tumors models (Ferracini *et al.*, 1996; Koochekpour *et al.*, 1997; Tuck *et al.*, 1996) and is a common feature of OS (Ferracini *et al.*, 1995; Rong *et al.*, 1993). Several studies have demonstrated how the HGF/SF and MET receptors might function together in activating biological properties that may contribute to osteosarcoma progression (Rong *et al.*, 1993; Coltella *et al.*, 2003; Patane *et al.*, 2006; De Maria *et al.*, 2009; Dani *et al.*, 2012). Indeed, wild-type or constitutively activated Met has been shown to drive osteoblast transformation (Patane *et al.*, 2006). Moreover, introduction of dominant-negative Met inhibits the in vivo tumorigenicity of osteosarcoma cells (Patane *et al.*, 2006). A role for MET in Ewing sarcoma tumorigenesis has also been identified recently (Fleuren *et al.*, 2013).

Interestingly, pharmacologic inhibition of Met signaling as a therapeutic strategy has been validated in several preclinical models of osteosarcoma and Ewing sarcomas. For instance, the Met inhibitors K252a (Coltella *et al.*, 2003), PF-2341066 (Sampson *et al.*, 2011) and cabozantinib (Fleuren *et al.*, 2013) selectively inhibited the proliferation of human OS and Ewing sarcoma cells and xenografts.

Aberrant angiogenesis is also crucial for sustained OS and ES growth and metastasis. VEGFA is abundantly expressed in 74.1% of osteosarcoma cases, and patients with VEGFA-positive osteosarcomas had significantly worse tumor-free survival rates than patients with VEGFA-negative osteosarcomas (Yang *et al.*, 2011). A similar prognostic impact has been observed in ES patients (DuBois *et al.*, 2010). Agents targeting angiogenesis have shown promising results in in vitro and in vivo preclinical models of OS and ES (DuBois *et al.*, 2010; Brave *et al.*, 2011; Scharf *et al.*, 2013; Cassinelli *et al.*, 2013). Preliminary clinical data suggest also that targeting angiogenesis could represent an efficient approach in the field of advanced OS and ES. For instance, treatment with cediranib (Recentin, AZD2171, AstraZeneca Pharmaceuticals, Wilmington, Delaware, USA), an orally available small molecule which inhibits VEGFR-1, VEGFR-2 and VEGFR-3, has been associated with objective responses in patients with metastatic OS and ES enrolled in a phase I trial (Fox *et al.*, 2008).

As indicated above (section 2.3) cabozantinib is a small molecule which target both the c-Met and VEGFR2 signalling pathways. This drug has shown promising pre-clinical activity in in vitro and in vivo OS and ES models consistent with its known anti-MET and anti-angiogenic

activity (Smith *et al.*, 2013). Altogether, these data support a phase 2 study of cabozantinib in the field of advanced OS and ES.

2.5 Correlative Studies Background

See section 9.1.

3. PATIENT SELECTION

Young patient age between 12 – 15 could be included in only 6 centers (Bordeaux, Lyon, Villejuif, Lille, Marseille and Paris)

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed diagnosis of osteosarcoma or Ewing sarcoma by central review, except if the diagnosis was already confirmed by the RRePS (Réseau de Référence en Pathologie des Sarcomes et des Tissus Mous et des Viscères) network.

3.1.2 Relapsed disease after standard chemotherapy.

3.1.3 Patients must have measurable disease (lesion in previously irradiated field could be considered as measurable if progressive at inclusion) defined as per RECIST v1.1 with at least one lesion that can be measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan.

3.1.4 Age ≥12 years.

3.1.5 ECOG performance status ≤1 (see Appendix A).

3.1.6 Life expectancy of greater than 3 months.

3.1.7 Patients must have normal organ and marrow function as defined below:

– absolute neutrophil count	≥1,500/mcL
– lymphocyte count	>1,000/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 × ULN
– AST(SGOT)/ALT(SGPT)	≤3.0 × institutional upper limit of normal
– creatinine	≤1.5 × ULN OR
– creatinine clearance	≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal (Cockcroft formula, see Appendix I).
– hemoglobin	≥9 g/dL
– serum albumin	≥2.8g/dL
– lipase	<2.0 × ULN and no radiologic or clinical evidence of pancreatitis
– urine protein/creatinine ratio (UPCR)	≤1
– serum phosphorus, calcium,	≥ LLN

magnesium, and potassium

3.1.8 Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

3.1.9 The effects of Cabozantinib on the developing human fetus are unknown. For this reason and because tyrosine kinase inhibitors agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (see below) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of Cabozantinib administration.
Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (*e.g.*, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s).

3.1.10 Metastatic or unresectable locally advanced.

3.1.11 Documented disease progression (as per RECIST v1.1) before study entry. For patients with osteosarcoma, this progression will be confirmed by central review on the basis of two CT scan or MRI obtained at less than 6 months in the period of 12 months prior to inclusion.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 In accordance with French Regulatory Authorities: Patients with French Social Security in compliance with the French law relating to biomedical research (Huriet Law 88-1138 and related decrees).

3.2 Exclusion Criteria

3.2.1 The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (*e.g.*, cytokines or antibodies) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.

3.2.2 Prior treatment with Cabozantinib.

3.2.3 Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before the first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.

3.2.4 Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment. Note: Subjects with prostate cancer currently receiving LHRH or GnRH agonists may be maintained on these agents.

3.2.5 The subject has received any other type of investigational agent within 28 days before the first dose of study treatment.

3.2.6 The subject has not recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs.

3.2.7 The subject has a primary brain tumor.

3.2.8 Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 2 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment.

3.2.9 The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 7 days before the first dose of study treatment.

3.2.10 The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (*e.g.*, clopidogrel). Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.

3.2.11 The subject requires chronic concomitant treatment of strong CYP3A4 inducers (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort).

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.12 The subject has experienced any of the following:

- clinically-significant gastrointestinal bleeding within 6 months before the first

dose of study treatment

- hemoptysis of ≥0.5 teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment
- any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment

3.2.13 The subject has radiographic evidence of cavitating pulmonary lesion(s).

3.2.14 The subject has tumor in contact with, invading or encasing any major blood vessels.

3.2.15 The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib.

3.2.16 The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

1. Cardiovascular disorders including:
   a) Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening
   b) Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment
   c) Any history of congenital long QT syndrome
   d) Any of the following within 6 months before the first dose of study treatment:
      - unstable angina pectoris
      - clinically-significant cardiac arrhythmias
      - stroke (including TIA, or other ischemic event)
      - myocardial infarction
      - thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study)

2. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
   a) Any of the following within 28 days before the first dose of study treatment
      - intra-abdominal tumor/metastases invading GI mucosa
      - any evidence of active peptic ulcer disease, patients must be completely recovered
      - any evidence of inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, patients must be completely recovered from these conditions
      - malabsorption syndrome

b) Any of the following within 6 months before the first dose of study treatment:
- abdominal fistula
- gastrointestinal perforation
- bowel obstruction or gastric outlet obstruction
- intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before the first dose of study treatment.

3. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy

4. Other clinically significant disorders such as:

a) active infection requiring systemic treatment within 28 days before the first dose of study treatment

b) serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment

c) history of organ transplant

d) concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment

e) history of major surgery as follows:

i. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment.

ii. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment.

Subjects with clinically relevant ongoing complications from prior surgery are not eligible

3.2.17 The subject is unable to swallow tablets.

3.2.18 The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before treatment. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

3.2.19 The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

3.2.20 The subject has had evidence within 2 years of the start of study treatment of another malignancy which required systemic treatment

3.2.21 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Cabozantinib.

3.2.22 Pregnant women are excluded from this study because Cabozantinib is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Cabozantinib, breastfeeding should be discontinued if the mother is treated with Cabozantinib. These potential risks may also apply to other agents used in this study.

3.2.23 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Cabozantinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.24 Participation to a study involving a medical or therapeutic intervention in the last 30 days.

3.2.25 Prior participation in this study.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the Institut Bergonie by the Study Coordinator. The required forms, Screening and registration, can be found in Appendix D and Appendix E.

Drug will only be used by French sites. The central EU depot/distributor that Exelixis would like to use is Theorem Clinical Research in Germany. The packaging and labeling would occur in Canada, by Bellwyk Packaging Solution, and then these supplies would be transferred to Germany.

A total of 10 French sites will participate in this trial. Exelixis will supply Cabozantinib directly to the French sites through Theorem Clinical Research (TCR) based in Germany. Additional information on the drug distribution process, please see Section 8.1.2.

4.2 Registration Process

4.2.1 Screening

Upon signature of informed consent, screened patient will be entered on study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator.

The **following documents should be faxed** as soon as possible to the Bergonie Institute Data Center:

- Screening form (Appendix D):
    - Institution number
    - Name of the responsible investigator
    - Patient's code (2 letters of name, 2 letters of first name)
    - Patient's birth date (day/month/year)
    - Date of signed consent form

Clinical Trial and Epidemiology Unit – Institut Bergonié
FAX: +33 (0)5 56 33 04 85
From Monday through Friday – From 9.00 am to 5.00 pm
Contact: Sabrina SELLAN-ALBERT (CRA) – Tel: +33 5 56 33 78 05, Mail – s.albert@bordeaux.unicancer.fr
and David JUZANX (Back-up CRA) – Mail: d.juzanx@bordeaux.unicancer.fr

Each site will send to Bergonie Institute within 7 days after the signature of informed consent:

- Pathology request form completed
- 10 unstained slides and/or preferable FFPE (Formalin-Fixed Paraffin-Embedded) block of specimen tumor sampling, obtained anytime during disease development
- Initial pathology report with patient code and date of birth (including macroscopic description) and pathology report of molecular biology if any.

For osteosarcoma only, each site will send to Bergonie Institute for central review before registration:

- Anonymized CD of CT-scan or MRI of two radiological assessments identical obtained at less than 6 months interval within the 12 months prior to inclusion
- Baseline Clinical Subject Profile with the first shipment
- Radiological Referral Form

To complete the registration process, the Coordinator will assign a patient screening number.

Once results of pathological and radiological review will be available, the CRA at Institut Bergonie should inform site by e-mail and return results by fax.

4.2.2 Inclusion

Upon signature of informed consent, eligible patient will be entered on study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator.
The registration form (Appendix E) should be faxed as soon as possible to the Bergonie Institute Data Center with the following information:
- Institution number
- Name of the responsible investigator
- Patient's code (2 letters of name, 2 letters of first name)
- Patient's birth date (day/month/year)
- Eligibility criteria
- Date of signed consent form
- Date foreseen for protocol treatment start

Clinical Trial and Epidemiology Unit – Institut Bergonié
FAX: +33 5 56 33 04 85
From Monday through Friday – From 9.00 am to 5.00 pm
Contact: Sabrina SELLAN-ALBERT (CRA) – Tel: +33 5 56 33 78 05, Mail – s.albert@bordeaux.unicancer.fr
and David JUZANX (Back-up CRA) – Mail: d.juzanx@bordeaux.unicancer.fr

This must be done **before the start of the protocol treatment which should begin within one week (5 days) following registration**.
To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number

The patient study number attributed at the end of the registration procedure identifies the patient and must be reported on all case report forms.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen description					
Agent	***Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
XL 184	*Take without food, and patients should not eat for at least two hours before and one hour after taking it*	*60 mg for patients ≥ 16 years 40mg/m² for patients ≥ 12 years and <16 years* (Chuck *et al*, 2014)	*PO*	*Days 1-28*	*4 weeks (28 days)*

Since dose is based on BSA for patients < 16 years of age, the calculated dose should be round to the nearest tablet size (see Appendix J).

The patient will be requested to maintain a medication diary (Appendix F) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

5.1.1 XL184 - Cabozantinib

Cabozantinib must be taken on an empty stomach. Patients must fast for 2 hours before and 1 hour following each dose of Cabozantinib. Cabozantinib tablets should be swallowed whole with at least 8 ounces of water.

The tablets should not be crushed. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken

later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose. In case of vomiting, patients should be instructed to don't take a new dose.

Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

Patients will be instructed to bring all unused tablets and their medication diary (refer to Appendix F) to each study visit for assessment of compliance.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Cabozantinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.2.1 Concomitant Medications and Therapies

5.2.1.1 Anticancer Therapy

If a subject requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (*e.g.*, palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

5.2.1.2 Other Medications

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the case report forms.

5.2.1.3 Allowed therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically in accordance to standard clinical practice if clinically indicated;

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines);

- Drugs used to control bone loss (eg, bisphosphonates and denosumab) are allowed if started before screening activities but may not be initiated or exchanged during the course of the study and require Sponsor approval;

- Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical;

- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

    - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion;

    - *Therapeutic doses of LMWH* after the first dose of study treatment are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to section 6.

    - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction);

    - For restrictions on oral anticoagulants see Section 5.2.1.4.

- Antacids, H2-blockers, PPIs:

  Co-administration of gastric pH modifying drugs such as PPI, H_2-blockers or antacids is not contraindicated in subjects administered cabozantinib.

5.2.1.4 Prohibited or restricted therapies

The following therapies are prohibited while the subject is on study:

- Any investigational agent or investigational medical device;

- Any drug or herbal product used specifically for the treatment of osteosarcoma and/or Ewing sarcoma;

- Therapeutic doses of oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines);

- Any other systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides) and local anticancer treatment such as surgery, ablation, or embolization.

The following therapies should be avoided if possible, while the subject is on study:

- Palliative external radiation to bone metastasis for bone pain should not be performed while on study. Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints;

- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence and/or progression associated with erythropoietin (Wright 2007);

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;

- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, because this could significantly increase the exposure to cabozantinib;

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

5.2.1.5 Potential Drug Interactions

Cytochrome P450: Preliminary data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the AUC of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (*i.e.*, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). *In vitro* data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate (but not a CYP2C9 or CYP2D6 substrate), based on data from *in vitro* studies using CYP-isozyme specific neutralizing antibodies.

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

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

Because *in vitro* studies only assessed the metabolizing capacity of the CYP3A4, CYP2C9, and CYP2D6 pathways, the potential for drugs that inhibit/induce other CYP450 pathways (*e.g.*, CYP2C8, CYP2C19, CYP2B6, CYP1A2) to alter cabozantinib exposure is not known. Therefore, these drugs should be used with caution when given with cabozantinib.

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (Flockhart 2007; http://medicine.iupui.edu/clinpharm/ddis/table.aspx).

Protein Binding: Cabozantinib is highly protein bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (*e.g.*, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Drugs Associated with QTc Prolongation: Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTc prolongation (see http://www.qtdrugs.org). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs.

Other Interactions: Concomitant use of gastric pH modifying agents (ie. PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered Cabozantinib.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity.

Additional details related to these overall conclusions are provided in the Investigators Brochure for XL184 (cabozantinib).

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

- Necessity for treatment with other anticancer treatment prohibited by the protocol (other than short cycle of palliative radiotherapy for bone pain),
    - Sexually active subjects who refuse to use medically accepted barrier methods of contraception (*e.g.,* male condom, female condom) during the course of the study and for 4 months following discontinuation of study treatment,
    - Women who become pregnant or are breast feeding,
    - Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol, or
    - Significant noncompliance with the protocol schedule in the opinion of the investigator.
    - The minimum dose of study treatment will be 20 mg qd. Subjects who cannot tolerate

20 mg qd will have study treatment discontinued.

5.4 Duration of Follow Up

Patients will be followed every 6 months after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

XL184-Related Adverse Event Management

Subjects will be monitored continuously for AEs throughout the study. **Subjects must be instructed to notify their physician immediately for any and all toxicities**.
Guidelines for the management of AEs (ie, dose interruptions and dose reductions) are presented in the next sections. Each dose reduction of cabozantinib should be to one dose level lower that the current dose. Dose reductions of more than one dose level are acceptable if agreed to by the Investigator. All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to the study treatment.

If study treatment of cabozantinib is restarted after being withheld or interrupted, the subject should be instructed not to make up the missed doses of cabozantinib.

The reason for treatment delay and reduced dose must be recorded on the case report form (CRF).

Dosing may need to be interrupted for AEs considered not related to cabozantinib if this is clinically indicated or if causality is initially uncertain. Study treatment may be resumed at the same dose (or a lower dose per investigator judgment) if the AE is determined not to be related to cabozantinib once the investigator determines that retreatment is clinically appropriate and the subject meets the protocol re-treatment criteria.

Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

Re-escalation to the previous dose, [but not higher than 60 mg/day for patients ≥ 16 years and pediatric dose will not exceed the adult dose (60 mg)] may be allowed at the discretion of the investigator but no sooner than 2 weeks beyond resolution of AEs that led to the dose reduction. Dose re-escalation is not allowed for a drug-related dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

A patient who requires a dose interruption (regardless of the reason for the interruption) lasting > 28 days (counting from the first day when a dose was missed) must discontinue Cabozantinib.

Dose reduction for patients ≥ 16 years*			
	Starting dose level -0	Reduced dose level-1	Reduced dose level-2
XL-184	60 mg QD	40 mg QD	20 mg QD**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Dose reduction below 20 mg is not allowed.			

Dose reduction for patients ≥ 12 years < 16*			
	Starting dose level -0	Reduced dose level-1	Reduced dose level-2
XL-184	40 mg/m² QD	30 mg/m² QD	20 mg/m² QD**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Dose reduction below 20 mg/m² is not allowed.			

Table 6-1. General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events

CTCAE Version 4 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2:	
Grade 2 AEs which are intolerable and cannot be adequately managed	Interrupt cabozantinib treatment or dose reduction. Add supportive care as indicated. • If cabozantinib dosing is interruoted, then upon resolution of the AE to baseline or Grade ≤ 1, or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced.
Grade 3:	
Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Interrupt cabozantinib and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade ≤1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety. All dose modifications should be based on the worst preceding toxicity. Patients are allowed two dose reductions: a dose reduction from 60 mg QD to 40 mg QD, and, if necessary, a dose reduction from 40 mg QD to 20 mg QD. Dose re-escalation is not allowed for a drug-related dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).	

Table 6-2. General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events

CTCAE Version 4 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤1, and resume cabozantinib treatment at a reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until platelet count is ≥100,000/mm^3, and resume cabozantinib treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤1 and temperature to ≤38.0°C and resume cabozantinib treatment at a reduced dose.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Other Grade 4 Hematologic Toxicities	
Grade 4 hematologic toxicities other than anemia	Permanently discontinue study treatment unless determined that the subject is clearly deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor and only with approval by the sponsor.
Grade 4 anemia	Permanent discontinuation for Grade 4 anemia is not mandated. Dose reductions or dose delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed according to institutional guidelines.
ANC, absolute neutrophil count; LLN, lower limit of normal Neutropenia: Grade 1 (LLN ≤ ANC < 1.5 × 10^9/L; Grade 2 (1 × 10^9/L ≤ ANC <1.5 x 10^9/L), Grade 3 (0.5 × 10^9/L ≤ ANC < 1 × 10^9/L), Grade 4 (ANC < 0.5 × 10^9/L). Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated). Thrombocytopenia: Grade 1 (Platelet count <LLN – 75 x 10^9/L); Grade 2 (Platelet count <75.0 – 50.0 x 10^9/L); Grade 3 (Platelet count ≤ 50 - 25 × 10^9/L); Grade 4 (Platelet count < 25 × 10^9/L).	
All dose modifications should be based on the worst preceding toxicity. Patients are allowed two dose reductions: a dose reduction from 60 mg QD to 40 mg QD, and, if necessary, a dose reduction from 40 mg QD to 20 mg QD. Dose re-escalation is not allowed for a drug-related dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).	

Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

Diarrhea
Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson *et al.,* 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The dose modification guidance in Table 6-1 should be followed. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting
Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table 6-1 should be followed.

The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Ondansetron, a 5-HT_3 inhibitor, is not allowed due to QTc prolongation. Other 5-HT_3 antagonists can be used.

Stomatitis and Mucositis
Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic cleansing, and oral rinses (*e.g.*, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

Hepatobiliary Disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases.

Since subjects may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks.. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval..

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (*e.g.*, International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is

determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 × ULN, total bilirubin < 1.5 × ULN, aminotransferases ≤ baseline grade).

Subjects must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2 ×ULN), in the absence of evidence of biliary obstruction (*i.e.*, significant elevation of alkaline phosphatase) or some other explanation of the injury (*e.g.*, viral hepatitis, alcohol hepatitis), as the combined finding (*i.e.*, Hy's Law cases) represents a signal of a potential for the drug to cause severe liver injury.

All subjects who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

Pancreatic Conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general has not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Asymptomatic Lipase or Amylase Elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 or Grade 4 elevations recur, then treatment must be interrupted again until lipase and amylase levels have resolved to Grade ≤1 or baseline and retreatment must be at a reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤1 or baseline and retreatment must be at a reduced dose.

Pancreatitis

Pancreatitis	
Grade 2 and asymptomatic	• Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 2 symptomatic and Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline , cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced at a reduced dose agreed to by the investigator and sponsor but only with sponsor approval.

Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures includes the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (*e.g.*, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral.

Treatment guidelines for PPE related to study treatment are presented in the table below.

In the case of study treatment-related skin changes (*e.g.*, rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
Grade 1	Continue cabozantinib at current dose if tolerable or reduce to the next lower dose if intolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 2 PPE
Grade 2	Reduce cabozantinib dose to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed.. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 3 PPE. If the dose was only reduced but not interrupted, treatment may continue at the reduced dose. If the dose was only interrupted but not reduced, then treatment may be restarted upon resolution to Grade 0 or Grade 1 at one dose level lower.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

Embolism and Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in subjects who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment.. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. 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 Sponsor. Venous filters (*e.g.* vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

Arterial thrombotic events (*e.g.*, transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥160 mm Hg systolic or ≥110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (see next Table below).

Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic) and < 160 mm Hg **or** > 100 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (ie, increase dose of existing medications and/or add new antihypertensive medications) ; • Maintain dose of cabozantinib; • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be interrupted and/or reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg **or** ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Interrupt and/or reduce cabozantinib by one dose level; • Increase antihypertension therapy (ie, increase dose of existing medications and/or add new antihypertensive medications) ; • Monitor subject closely for hypotension; • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 150 systolic or < 100 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) **or** ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications; • Monitor subject closely for hypotension; • When SBP < 150 and DBP < 100, restart cabozantinib treatment at one dose level lower; • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 150 systolic or < 100 diastolic, dose of cabozantinib should be reduced further.
Hypertensive emergency or hypertensive encephalopathy	Discontinue all study treatment

BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure

NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria

Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick should be quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria >3.5 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in the next Table below.

Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1	• No change in treatment or monitoring
> 1 and < 3.5	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once every week. If UPCR is < 1 on two consecutive readings, then UPCR monitoring can revert to protocol specific time points. (The second reading is a confirmatory reading and can be done within 1 week of the first reading.).
≥ 3.5	• Hold cabozantinib immediately and confirm with 24 hour urine protein excretion. • Evaluate for nephrotic syndrome. If present, discontinue cabozantinib treatment permanently, and monitor subject for resolution of nephrotic syndrome. • If proteinuria of ≥ 3.5 g/24 hours is confirmed without diagnosis of nephrotic syndrome, continue to hold cabozantinib and monitor UPCR weekly. If UPCR decreases to < 1.5, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.

UPCR, urine protein/urine creatinine ratio

Guidelines for the Prevention of Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. As preventive measures, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor lesions with cavitations or tumor lesions which invade, encase, or abut major blood vessels. The anatomic location and characteristics of primary tumors or metastases as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity.
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases.
- Underlying medical conditions which affect normal hemostasis (*e.g.*, deficiencies in clotting factors and/or platelet function, or thrombocytopenia).
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis.
- History of clinically significant hemoptysis.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥0.5 teaspoon (2.5mL) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided at a dose agreed to by the sponsor and the investigator. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from cabozantinib treatment.

Rectal and Perirectal Abscess

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and Non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI-perforation/fistula:

- Intra-abdominal tumor/metastases invading GI mucosa.
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis .
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or non-steroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:

- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with drugs that inhibit VEGF pathways. In addition, subjects who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

Wound Healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib.

Treatment with cabozantinib must be interrupted for any wound healing complication which needs medical intervention. Treatment with cabozantinib can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. Cabozantinib should be discontinued in subjects with serious or chronic wound healing complications.

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 3 weeks (5 half lives) prior to elective surgery.

Endocrine Disorders

Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects (see Cabozantinib Investigator's Brochure). Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (*e.g.*, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of subjects. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is required. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

Guidelines for Prevention of Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible,

treatment with cabozantinib should be held for at least 2 weeks prior to a dental procedure and resumed after complete wound healing occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the Sponsor on a case by case basis.

Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors which may contribute to QTc prolongation include

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org).
- Treatment with CyP 3A4 inhibitors (which may increase cabozantinib drug levels)
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).
- Medical conditions which can alter electrolyte status *e.g.*, severe or prolonged diarrhea.

Subjects having any of these additional risk factors while on cabozantinib must have ECGs performed approximately one week after the onset of these factors.

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be withheld and the following actions should be taken:

- Check electrolytes, especially potassium, magnesium and calcium. Correct abnormalities as clinically indicated.
- If possible, discontinue any QTc-prolonging concomitant medications.
- Repeat ECG triplets hourly until the average QTcF is ≤500 msec or otherwise determined by consultation with a cardiologist.

The Sponsor should be notified immediately of any QTc prolongation event.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated according to standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the subject has been thoroughly evaluated, and further treatment has been agreed to by the Sponsor. If any additional study treatment is given (*e.g.*, after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the Sponsor.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

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

7.1.1 CAEPRs for XL184 (cabozantinib)

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

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)***
	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]		

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%)**	
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	
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		

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 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, 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.

7.2 Adverse Event Characteristics [*Following NCI procedure*]

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting [*Following NCI procedure*]

7.3.1 CTEP-AERS

Expedited AE reporting for this study must use AERS (Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into AERS by the original submitter at the site.

7.3.2 Multi-institutional studies.

AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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.

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, 2]

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

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

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Attribution
Endocrine disorders	Hypothyroidism	2	Related
Gastrointestinal disorders	Abdominal pain	2	Related
	Diarrhea	2	Related
	Constipation	2	Related
	Dry mouth	2	Related
	Dyspepsia	2	Related
	Mucositis oral	2	Related
	Nausea	2	Related
	Oral pain	2	Related
	Vomiting	2	Related
General disorders and administration site conditions	Fatigue	2	Related

7.4 Routine Adverse Event Reporting [*Following NCI procedure*]

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through AERS must also be reported in routine study data submissions.**

7.5 Secondary Malignancy [*Following NCI procedure*]

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via AERS. Three options are available to describe the event:

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

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

7.6 Second Malignancy [*Following NCI procedure*]

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.

7.7 Safety Evaluation [*Following Institut Bergonie procedure*]

7.7.1 Description of safety evaluation criteria

The safety evaluation will comprise an evaluation of the patient's general condition (ECOG Appendix A), a physical exam, regular blood tests and the recording of adverse events occurring throughout the study. Toxicity will be evaluated using the NCI-CTCAE scale, version 4 available on website: http://ctep.info.nih.gov. All appropriate treatment areas should have access to a copy of the CTCAE version 4.
In an emergency situation, the patient, his/her friends/family or treating physician will contact the investigator to report an event and/or to discuss the treatments to be implemented.

7.7.2 Definition

7.7.2.1 Adverse event

An adverse event is defined as any untoward medical occurrence which occurs in a patient, a clinical investigation subject. Adverse events include, but are not limited to:

- Abnormal test findings,
- Clinical symptoms and signs,
- Changes in physical examination findings,
- Hypersensitivity,
- Drug abuse,
- Drug dependency,
- Any suspected transmission of an infectious agent via a medicinal product.

As well as signs and symptoms resulting from:

- Drug overdose,
- Drug withdrawal,
- Drug misuse,
- Drug interactions,
- Extravasation,
- Exposure during pregnancy,
- Exposure during breastfeeding,
- Medication error,
- Occupational exposure.

7.7.2.2 Serious adverse event

A serious adverse event is defined as an adverse event regardless of the dose and that:

- results in death (fatal) and/or,
- is life-threatening and/or,
- requires inpatient hospitalization or prolongation of existing hospitalization and/or,
- results in persistent or significant disability/incapacity and/or,
- results in congenital anomaly/birth defect and/or,
- is medically significant.

Medical and scientific judgment is exercised in determining whether an event is an important

medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent, pathogenic or non-pathogenic, is assessed as a serious adverse event with the seriousness criterion important medical event. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. The terms "suspected transmission" and "transmission" are considered synonymous.

Any abnormal laboratory's result resulting as a grade 4 in the CTCAE version 4 will be considered as serious adverse event even if this event is not clinically relevant.

Whether or not corresponding to the above-mentioned criteria, any other adverse event considered as serious by any IMP, any healthcare professional or any investigator should be handled as a serious adverse event.

- ***Death***

Death as such is the outcome of a SAE or the seriousness criteria and should not be used as the SAE term itself. Instead the cause of death should be recorded as the SAE term. When available, the autopsy report will be provided to the Sponsor.

- ***Life-threatening Event***

Any event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- ***Hospitalization or Prolongation of Hospitalization***

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.

Hospitalizations that do not meet criteria for SAE reporting are:

- Reasons described in protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc]. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
- Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE.
- Pre-planned hospitalizations: Any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

7.7.2.3 Non serious adverse event

A non-serious adverse event is an adverse event whose characteristics do not meet the criteria of a serious adverse event.

7.7.2.4 Adverse effect

An adverse effect is any untoward and unintended responses to an experimental drug regardless of the dose.

7.7.2.5 Expected/Unexpected Character

An unexpected adverse event is an event whose nature, severity/intensity or outcome does not correspond to the information shown within the reference document for the study. The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the most updated Investigator's Brochure (IB) for the studied IMP.

In practice, the term "new effect" is sometimes used as a synonymous of "unexpected adverse effect".

7.7.2.6 Intensity criterion

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Event (CTCAE) will be utilized for AE reporting.

The intensity of adverse events not listed in this classification will be assessed using the following descriptors:

- Mild (grade 1): does not affect the patient's usual daily activities,
- Moderate (grade 2): disturbs the patient's usual daily activities,
- Severe (grade 3): prevents the patient's usual daily activities,
- Very severe (grade 4): requires critical care/life-threatening,
- Death (grade 5).

7.7.2.7 New information

A new information is any new safety data that could lead to reevaluate the ratio between the benefits and risks of the research, or that could be sufficiently important to consider modifications of the research documents, the research management or, if need be, the drug utilization.

7.7.2.8 Special considerations

Certain product safety monitoring reports should be forwarded even if there is no associated adverse event. These reports involve circumstances that may increase the patient/consumer's risk of developing adverse events.

These circumstances include:

- medication errors,
- exposure during pregnancy,
- exposure during breastfeeding,
- overdose,
- misuse,
- extravasation,
- occupational exposure.

Some of these special circumstances are considered in more details below.

- ✓ Medications errors: a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

A medication error does not necessarily involve the administration of the product (e.g. the error may have been corrected prior to administration of the product).

Potential medication errors or "near-misses," which are individual reports of information or complaints about product name, labeling, or packaging similarities that do not involve a patient, are also reportable.

- ✓ Exposure during pregnancy: exposure during pregnancy refers to pregnancies where the fetus (from pre-embryo to birth) may have been exposed at a given time during pregnancy to a medicinal product (or a blinded treatment). Even if there is no associated adverse event, exposure during pregnancy must always be reported. It can indeed provide the opportunity to obtain pregnancy outcome important information where appropriate.

Exposure during pregnancy may occur either:

- Through maternal exposure

A female becomes, or is found to be, pregnant either:

- While receiving a medicinal product;
- After discontinuing a medicinal product;
- During or following environmental exposure to a medicinal product (eg, a nurse reports she is pregnant and that she was exposed to chemotherapy drugs via inhalation or after accidentally overturning a bottle).

or

-Through paternal exposure

A male has been exposed to a medicinal product (either due to treatment or environmental circumstances) prior to or around the time of conception and/or is exposed during the partner pregnancy.

- ✓ Exposure during breastfeeding: exposure during breastfeeding occurs where an infant or child may have been exposed through breast milk to a medicinal product during breastfeeding by a female taking the product.

All drug exposure during breastfeeding cases are reported, whether or not there is an associated adverse event.

7.7.3 Serious adverse events and new information notification (responsibility of the investigator)

The investigator will notify the Vigilance Unit without delay about any serious adverse events or new events occurring:

- From the date of the informed consent is signed,
- During the whole patient treatment period as defined by the research,
- Until 30 days after the last dose of the IMP/studied treatments.

- Beyond these periods of time specifics to each IMP, only those SAEs suspected to be related to the IMP or the research (other treatments used, diagnostic procedures, examinations carried out during the research, etc) will be collected without any limitation in terms of deadline.. Nonetheless, the Sponsor will evaluate any safety information related to the clinical trial that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

Type of Event	**Reporting procedure**	**Deadline for reporting to the sponsor**
SAE	SAE Notification form + written report form if necessary	To be reported immediately to the sponsor
New information	Written report form	To be reported immediately to the sponsor
Pregnancy	Pregnancy Notification form + Written report form if necessary	As soon as pregnancy is confirmed

The investigator must complete the "Serious Adverse Event Notification Form" (Appendix G) immediately, in English, and assess the relationship with the study treatment. The form must then be dated, signed and sent by fax to the following address without delay to:

CELLULE DE VIGILANCE (VIGILANCE UNIT) – Institut Bergonié
Fax: +33 5 56 33 04 85
Or contact Sabrina Sellan-Albert (CRA) +33 5 56 33 78 05 – Mail: s.albert@bordeaux.unicancer.fr
Dr Emilie Toulza (pharmacist) +33 5 47 30 60 53 – Mail: e.toulza@bordeaux.unicancer.fr
Head of the Vigilance Unit: Dr Barbara Lortal +33 5 56 33 78 90 – Mail: b.lortal@bordeaux.unicancer.fr

For each event, the investigator will record:
- A description of the event that is as clearly as possible, using medical terminology,
- The date the event started and ended,
- The patient's relevant medical history,
- The steps taken and whether or not corrective treatment was required, whether or not the investigational treatment was discontinued, etc.
- Concomitant medications / therapies,
- The causal link between this event and the trial treatment, disease treated or an intercurrent disease or treatment, or any obligation imposed by the research (a treatment-free period, additional examinations requested as part of the research etc.),
- Clinical course. If the event was not fatal, it should be monitored until recovery, until the patient has returned to his/her previous condition, or until any sequelae have stabilized.

Whenever possible, the investigator must also attach the following with the serious adverse event report:
- A copy of the hospitalization or extended hospitalization report,
- A copy of the autopsy report, if required,
- A copy of all the results of any additional tests performed, including relevant negative results, along with the normal laboratory values,
- Any other document he or she considers useful and relevant.

All these documents must be anonymized. Additional information may be requested (by fax, by telephone or during a visit) by the CRA and/or by the Vigilance Unit using a follow-up request

form.
The investigator is responsible for providing appropriate medical follow-up for patients until resolution or stabilization of the adverse event or until the patient's death. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.
The investigator keeps the documents about the presumed adverse effect so that the information previously sent can be added to if necessary.
The investigator responds to requests for additional information from the Vigilance Unit in order to document the original observation.

7.7.4 Reporting pregnancy cases occurred within the clinical trial

Pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of a female patient or the female partner of a male patient occurring while the patient is on study drug, or within 30 days from the patient's discontinuation visit, are considered immediately reportable events.
The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP is suspected,
- Possible exposure of a pregnant woman (this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMP),
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.
Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Vigilance Unit immediately by facsimile using the Pregnancy Report form (Appendix H).In the case of pregnancy of the female partner of a trial patient, the Investigator will obtain her consent to provide the information in these situations
The Investigator will follow the pregnancy until its outcome, and must notify the Vigilance Unit the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.
For any event during the pregnancy which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly) the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the Vigilance Unit by facsimile within 24 hours of the Investigator's knowledge of the event).
All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug/IMP should also be reported to the Vigilance Unit by facsimile within 24 hours of the Investigators' knowledge of the event.

Whenever possible, the investigator must also attach the following with the serious adverse event report:
- A copy of the hospitalization or extended hospitalization report,
- A copy of the autopsy report, if required,
- A copy of all the results of any additional tests performed, including relevant negative results,

along with the normal laboratory values,
- Any other document he or she considers useful and relevant.
All these documents must be anonymized.
Additional information may be requested (by fax, by telephone or during a visit) by the Vigilance Unit.

7.7.5 Non serious adverse events

TYPE OF EVENT	REPORTING PROCEDURES	DEADLINE FOR REPORTING TO THE SPONSOR
Non-serious AE	Case report/record form	Does not need to be reported immediately

Non-serious adverse events will be reported by the investigator in the patient's CRF and will be followed up until complete resolution.
If an adverse event becomes serious, it should be reported and followed-up as mentioned in the previous reporting procedures.
If the investigator would like to decrease trial treatment dose or temporarily stop study management without respecting protocol procedures, he/she should have previously discussed with the coordinator.
However, symptomatic treatment can be prescribed to manage the adverse event.
Any definitive interruption of the procedure has to be immediately notified to the sponsor. The patient remains in the study and is followed-up according to the procedures described in the protocol.

7.7.6 Vigilance Unit

The Vigilance Unit will analyze each SAE to define:
- The relationship with the study treatment,
- The listedness/expectedness according to the most updated reference safety information of the studied IMP Investigator's Brochure (IB).

7.7.7 Notification and registration of unexpected serious adverse events and new information (responsibility of the sponsor)

The sponsor notifies unexpected serious adverse events and new information to the Regulatory Authorities (in person, or through an organization which has received allowances for this task) according to the usual notification procedures.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 XL184 (cabozantinib) (NSC 761968)

8.1.1 *XL 184 (NSC # 761968)*

Chemical Name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Other Names: Cabozantinib, EXEL-7184, EXEL-02977184

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: $C_{28}H_{24}FN_3O_5.C_4H_6O_5$ **M.W.:** 635.6

Mode of Action: Cabozantinib inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are RET, AXL, KIT, TIE-2, and FLT-3.

How Supplied: Cabozantinib is supplied by Exelixis and distributed by Theorem Clinical Research in Germany. Cabozantinib is available in 20 mg and 60 mg tablet. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. 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 bottle.

Cabozantinib should be dispensed in its original container. Cabozantinib tablets are stable for up to 24 hours when dispensed in an open container, such as in a pill cup, and are stable for up to 7 days when dispensed in a closed container, such as a pharmacy dispensing bottle.

XL184 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

Storage: Store intact bottles at controlled room temperature, 20^0 to 25^0C.

Stability: Stability testing of the intact bottles is on-going. Cabozantinib is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container.

Route of Administration: Oral.

Method of Administration: Take Cabozantinib on an empty stomach, no food 2 hours before and 1 hour after taking Cabozantinib. Do not crush or chew.

Potential Drug Interactions: Cabozantinib is a substrate of CYP3A4. Coadministration of Cabozantinib with medications that are strong inhibitors/inducers of CYP3A4 should be avoided. Examples of strong CYP3A4 inducers are rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, Phenobarbital, and St. John's Wort. Strong CYP3A4 inhibitors are ketoconazole, itraconazole, clarithroumycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications. Avoid grapefruit/ grapefruit juice and Seville oranges including herbal tea while participating in this trial.

Vitro data indicate that Cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Additional details related to these overall conclusions can be found in the investigator brochure.

Cabozantinib is highly protein bound, 99.9%. Use caution when coadministering Cabozantinib with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with Cabozantinib as warfarin is highly protein-bound and has a very narrow therapeutic index.

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

Potential Food Effect
The effect of food on the bioavailability of cabozantinib was evaluated in healthy adult subjects in a Phase 1, open-label, randomized, single-dose, two-treatment, two way crossover study (Study XL184-004). Based on the PK data, a high fat meal did not appear to alter the terminal t1/2 but significantly increased the median tmax. The high fat meal also significantly increased both the cabozantinib Cmax and AUC values. Based on this result, cabozantinib should be taken on an empty stomach (fasting is required 2 hours before and 1

hour after each cabozantinib dose).

Patient Care Implications: Do not take grapefruit/ grapefruit juice or Seville oranges including herbal tea while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. There are many H2-blockers and PPIs available over-the-counter (OTC) such as cimetidine or omeprazole. For dyspepsia or indigestion, use an antacid first, then an H2 blocker if not relief with an antacid. Do not use cimetidine. Co-administration of gastric pH modifying drugs such as PPI, H_2-blockers or antacids is not contraindicate in subjects administered cabozantinib.

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Availability

XL184 (cabozantinib) is an investigational agent supplied to investigators by Exelixis.

XL184 (cabozantinib) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 Agent Ordering

Each participating institution will order Cabozantinib directly from Theorem Clinical Research (TCR) based in Germany (TheoremCSshippingorders@theoremclinical.com). A specific procedure will be provided by the sponsor.

8.1.2.2 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all Cabozantinib using the NCI Drug Accountability Record Form (DARF) (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

Biomarkers have the potential to shape diagnostic strategies and influence therapeutic management. In the future, biomarkers may promote a personalized medicine approach, grouping patients by the molecular signatures of their tumors and of markers in the blood rather than by cancer type. We are concentrating our efforts in identifying predictive biomarkers, which provide information about the likely efficacy of Cabozantinib. To evaluate the pharmacodynamic and mechanistic effects of a drug on the tumor a tumor biopsy is often required.

Preclinical studies have shown that Cabozantinib dramatically altered tumor pathology, resulting in decreased tumor and endothelial cell proliferation coupled with a strong inhibition of phosphorylation of MET. Cabozantinib has also been shown to induce changes in the levels of circulating biomarkers related to its mechanism of action of cabozantinib, including VEGF-A, soluble VEGFR2, and soluble MET.

Optional serial tumor samples (day 1 cycle 1 predose and day 28 postdose in cycle one) will be analyzed in consenting patients for:
• Hematoxylin and eosin staining (H&E).
• Immunohistochemistry (IHC) assessments including, but not limited to the following markers: MET, phospho-MET, CD31 (microvessel density), Ki67.
The analysis will be prioritized based on the amount of material available.
The MET and Phospho-Met antibodies (Tyr1349, Cell Signaling, Danvers, MA antibody (AF276, R&D Systems, Minneapolis, MN) will be used to assess MET and phosphor-MET protein expression on tumor samples. The assay will be evaluated on a semi-quantitative scale in which the percentage of tumor cells staining will be recorded at the following levels: 0 (unstained), 1+ (weak staining), 2+ (moderate staining), and 3+ (strong staining). A negative isotype control will be run on every sample and a positive staining control will be run with each staining run. Derivative scores, such as total percent positive, and maximum staining intensity, will be provided. Cytoplasmic and membrane staining will be evaluated separately.

Plasma samples for pharmacodynamic analysis will be collected on days 1, 15, and 28 of cycle 1 by using the following assays.

Plasma levels of hepatocyte growth factor (HGF)	Human HGF/Scatter: Factor immunoassay kit (R&D Systems, Minneapolis, MN) that detects pro-HGF, rilotumumabbound HGF, and free HGF.
Plasma levels of soluble MET	MSD assay using a biotinylated, affinity-purified, MET ectodomain-specific (soluble MET) capture antibody (R&D Systems, Minneapolis, MN) and an MSD sulfotag-conjugated antibody against the extracellular domain of recombinant human MET (R&D Systems, Minneapolis, MN).
Plasma levels of soluble of VEGFA and soluble VEGFR2	VEGFA and VEGFR-2 ELISA kits (R&D Systems, Minneapolis, MN, USA).

Pharmacodynamic analysis will be primarily based on the population of patients assessable for efficacy endpoints. For the analysis of biomarkers the primary evaluation will be based on the observed change from baseline. Whenever appropriate, the actual change or the log transformed change will be assumed normal distributed and analyzed accordingly. Both actual values and estimated parameters with belonging 95% confidence intervals will be presented in summary tables and graphically.
Whenever normal assumption is not appropriate, data will be analyzed in frequency tables. The study is not designed to establish formal pharmacodynamics data-efficacy relationships. However, exploratory analyses will be performed for the pharmacodynamic and biomarker data to explore pharmacodynamic and clinical effect. Different approaches will be investigated, among these analysis of regression including baseline value and other relevant co-factors, and analysis of repeated measurements including confounding factors and within subject correlation. Biomarker data will be evaluated descriptively and may be analyzed for their correlation with clinical data, imaging parameters and clinical response/safety if feasible. In all cases data

transformation will be applied if relevant to meet model assumptions. This will be investigated graphically.

9.2 Laboratory Correlative Studies

9.2.1 *Whole Blood samples for Pharmacodynamic analysis*

9.2.1.1 Collection of Specimens

Pharmacodynamic of Cabozantinib will be assessed on C1D1 pre-dose, C1D15 and C1D28.
For each patient, blood samples will be collected at predefined time points.

Schedule of blood sampling for BM study

	EDTA
C1D1	XX
C1D15	XX
C1D28	XX

For plasma study, two 4,5 ml EDTA tubes (or one 7 ml EDTA tube) will be taken at each time point.

The sample collection information must be captured on the appropriate CRF page(s).

9.2.1.2 Handling of Specimens

Samples will be centrifugated in the next 15 minutes, at 3100g (4000 rpm) for 15 minutes and 4°c. In case of incapacity to centrifugate in the next 15 minute, samples should be kept cold until handling. The aliquoted samples (3 aliquots) will be annotated with the study name (CABONE), center study ID number (1, 2, 3, 4), patient study ID number, date (dd/mm/yyyy) and the identification (marker ID: HGF, MET, VEGFA and VEGFR2, and time point) and stored at < 80°c until day of shipping.
Pharmacodynamics Methods Guidelines will be provided by the sponsor as a separate document.

9.2.1.3 Shipping of Specimens

The containers containing the samples will be labeled with coded numbers to ensure full compliance with privacy policy. Samples will be grouped in each institution and sent frozen for centralized processing.
Shipping will only be performed by a promoter authorized transporter with respect to good practice.

9.2.1.4 Site Performing Correlative Study

Plasma studies will be performed at Institut Bergonie, Biopathology Department, Bordeaux – France.
Samples will be sent to:

Docteur Julie DUBOIS
Institut Bergonie
Biopathology Department
229 cours de l'Argonne
33076 Bordeaux Cedex, France

9.2.2 *Tumor samples*

9.2.2.1 Collection of Specimen(s)

Tumor biopsies will be performed on consented adult patients at Day 1 of cycle 1 predose and at Day 28 of cycle 1 postdose.

9.2.2.2 Handling and shipping of Specimen(s)

One half of the specimen will be formalin fixed and paraffin embedded [FFPE (Formalin-Fixed Paraffin-Embedded)] and the second half will be fresh frozen at -80°C.
The samples will be labelled with coded numbers to ensure full compliance with privacy policies. Samples will be grouped in each institution and sent for centralized processing with the documents.
All samples will be stored before they are analyzed.
The sample collection information must be captured on the appropriate CRF page(s).

9.2.2.3 Site(s) Performing Correlative Study

All pathological specimens sampling with documents must be sent to:

Marie Louty
Institut Bergonie – Pathology Unit
Protocol CABONE
229 cours de l'Argonne
33076 Bordeaux Cedex, France

9.3 Imaging Studies

FDG-PET can improve patient management by identifying responders early, before tumor size is reduced. Moreover, a reduction in the FDG-PET signal within days or weeks of initiating therapy (e.g., in breast (Avril, 2009), ovarian (Schwarz, 2009) and non–small cell lung (Zander, 2011) significantly correlates with prolonged survival and other clinical end points now used. Several studies performed in Ewing and osteosarcoma patients have shown that changes in tumor 18F-FDG uptake correlate with tumor necrosis in patients treated with chemotherapy (Hawkins, 2005 ; Schulte, 1999 ; Sato, 2008 ; Ye, 2008 ; Hawkins, 2002). We hypothesize that XL184 treatment-induced changes in tumor metabolism may be assessed with FDG-PET and that change in tumor 18F-FDG uptake may correlate with outcome.

All the patients will undergo FDG-PET before C1D1 and C1D28. Patients should be scanned on the same scanner for the baseline and end-of-cycle 1 FDG PET scan to minimize variations in SUV measurements.

PD markers assessed as changes from baseline in imaging, i.e. FDG-PET will be a secondary endpoint.

10. STUDY CALENDAR

Follow-up will be the same for young and adult patients. During treatment, clinical exam and blood analysis will be performed every week during cycle 1, every two weeks during cycles 2-4, and every month thereafter. For each blood analysis, 12 ml will be necessary (hematology and biochemistry), for a total of 48 ml during cycle 1, 24 ml during cycles 2-4 and 12 ml per month thereafter.

As effect of Cabozantinib on bone remodeling was only observed on bone models, no specific bone assessment and follow-up will be performed during this study.

	SCREENING	**CYCLE 1**				**CYCLES 2 à 4**				**CYCLE N**	**End of treatment (30-37 days)**
		D1	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
XL184		X ……..continuous …….X									
Informed consent	X										
Demographics	X										
Medical History	X										
Concomitant treatments	X	X ……X									X
Physical exam	X	X	X	X	X	X		X		X	X
Vital signs[a]	X	X	X	X	X	X		X		X	X
Height	X										
Weight	X	X	X	X	X	X		X		X	X
Performance status	X	X	X	X	X	X		X		X	X
Clinical laboratory test[b]	X	X	X	X	X	X		X		X	X
Urinalysis and UPCR	X	X	X	X	X	X		X		X	X
PT/INR, PTT	X	X				X				X	
TFTs (TSH, free T3, free T4)	X	X				X				X	
ECG[f]	X	X				X				X	X
Toxicity		X ……X									X
Tumor measurement	X	Repeated every 2 cycles (ie. 8 weeks). Documentation (radiologic) must be provided for patients removed from study for progressive disease									
Chest X-ray						X[h]				X[h]	
B-HCG [c] (if indicated)	X	X				X				X	X
Blood samples		X[d]		X[d]	X[d]					X[d]	
PET-FDG	X[g]				**D28**						
Biopsy for translational research	X				X[e]						

a: Heart rate, blood pressure, temperature
b: CBC, differential, platelets, albumin, alkaline phosphatase, SGOT [AST], SGPT [ALT], amylase, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyltransferase (GGT), glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein
c: Serum test 10-14 days and within 24 hours prior to the first dose of XL 184. Pregnancy test must be repeated at least once every month thereafter (serum or urine).
d: on Day 1, Day 15 and Day 28 of cycle 1
e: to be performed on Day 1 of cycle 1 predose and on Day 28 of Cycle 1 postdose on the same scanner for the two evaluation
f: Required in triplicate at baseline. Three ECG should be obtained within 30 minutes but at least 3 minutes apart.
g: to be done within 1 week prior do Day 1 of Cycle 1
h: to be performed at the end of cycle 1, 3, 5 etc.. (every 8 weeks between each tumor evaluation)

Screening evaluation should be done within 28 days prior to 1st dose of study treatment.
Evaluations on C1D1 should be done within 4 days prior to the 1st dose of XL184.
Each other evaluation should be done with an interval of +/- 5 days.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *Lesion in previously irradiated field could be considered as measurable if progressive at inclusion.*

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

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

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-

cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

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

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body

scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.3 Response Criteria

11.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.3.2 Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.3.3 Evaluation of Best Overall Response

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

In this study, only patients with Measurable Disease (*i.e.*, Target Disease) are eligible, and as such, the following definitions apply (RECIST 2009):

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. ***Confirmation required***
CR	Non-CR/Non-PD	No	PR	≥4 wks. ***Confirmation required***
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline ***Confirmation required***
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	

Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.4 Duration of Response

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

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

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

11.1.5 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.6 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to the time of death

11.1.7 Response Review

11.1.7.1 Review process:

Centralized radiological review will be performed for all patients to confirm Disease status at 6 months in comparison with baseline, Week#8 and Week#16
In case of discordance between the local radiologist and the expert reviewer, the judgment provided by the expert reviewer will be retained and used in statistical analyses.

11.1.7.2 Review process schedule:

All tumor evaluations will be sent as soon as there were available.
Patient's information must be anonymized and recorded on a provided imaging CD.

11.1.7.3 Practical implementation:

For each shipment, each media should be accompanied by the Radiological Forms provided by the sponsor.

All CDs must be sent to:

Sabrina SELLAN-ALBERT
Clinical Research Associate
Institut Bergonié – 229 cours de l'Argonne – 33076 Bordeaux Cedex, France
Phone: +33 5 56 33 78 05 – Mail: s.albert@bordeaux.unicancer.fr

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

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 electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 12.1.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

Either the Coordinating Center or the Lead Organization is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3 Collaborative Agreements Language

If the investigational study agent is provided by CTEP under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA), Clinical Trials Agreement (CTA), Agent-CRADA or Clinical Supply Agreement (CSA)] with the Pharmaceutical Company, this section must be included in the protocol. Information on the investigational study agent's Agreement status will be provided in the approved LOI response. If no Collaborative Agreement applies to the investigational study agent, this section should be marked "N/A" and the text below deleted.

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.

13. STATISTICAL CONSIDERATIONS

For each stratum (osteosarcoma and Ewing sarcoma), two statistical analyses plan (SAP), will be produced: one for the final statistical analysis and one for the interim statistical analysis (see section 13.6).
For each stratum, the SAP will be drafted before the inclusion of the first patient.

13.1 Study Design/Endpoints

13.1.1 Osteosarcoma

We rely on a single-arm phase 2 trial based on dual endpoint design (Goffin et al. J Clin Oncol 2008).
The primary efficacy endpoint is a composite endpoint encompassing non-progression and objective response at 6 months.
Non-progression is defined as complete response, partial response or stable disease as defined in section 11.1.3.
Objective response is defined as complete response or partial response as defined in section 11.1.3.

13.1.2 Ewing sarcoma

We rely on a single-arm phase 2 trial based on an optimal two-stage Simon's design.
The primary efficacy endpoint is objective response rate at 6 months.
Objective response is defined as complete response or partial response as defined in section 11.1.3.

13.1.3 Imaging

All patients will undergo FDG-PET before C1D1 and C1D28. We will assess the ability of metabolic tumor response as measured by FDG-PET at the end of one cycle of treatment to predict PFS.

FDG-PET tumor response at C1D28 will be defined following Young et al. (Eur J Cancer 1999) and classified as follows: progressive metabolic disease (PMD), stable metabolic disease (SMD), partial metabolic response (PMR), and complete metabolic response (CMR). The count and proportions of patients for each type of response at C1D28 will be reported.

The ability of PMR at C1D28 to predict PFS will be investigated in exploratory survival analyses. After verification of the underlying hypotheses of the statistical models, multivariate Cox proportional hazards models will be fitted that include both PMR (binary variable) and usual known prognostic factors.

13.2 Sample Size/Accrual Rate

The data from the literature about outcome of patients with advanced Ewing or osteosarcomas are limited. Objective response may not be an appropriate surrogate marker for therapeutic activity in osteosarcoma. Indeed, due to the abundant bone matrix, substantial anti-tumor activity may not result in a marked decrease in overall tumor volume. Moreover, non-progression rate is a worldwide recognized endpoint to assess new investigational agents in advanced sarcoma patients (Van Glabbeke et al. 2002). Median progression-free survival of relapsed osteosarcomas patients with unresectable disease and rechallenged with chemotherapy is about 2 months (Leary et al., 2013).
Recent studies investigating biological agents in Ewing sarcomas have concluded that a response rate < 10% represent only a modest activity (Ho et al., 2011; Pappo et al., 2011)

13.2.1 Osteosarcoma

We rely on a single-arm phase 2 trial based on 2-stage dual endpoint design (Goffin et al. J Clin Oncol 2008). Cabozantinib will be considered promising if either tumor response rate or 6-month non-progression rate is promising.

Hypotheses under Cabozantinib treatment are the following:
- Hypotheses for non-progression at 6 months:
    - 25% non-progression rate (null hypothesis / median PFS of 3 months),
    - 50% non-progression rate (alternative hypothesis / median PFS of 6 months),
- Hypotheses for objective response at 6 months:
    - 5% objective response rate (null hypothesis),
    - 20% objective response rate (alternative hypothesis),

Assuming 41 eligible and assessable patients:

- Stage 1 (21 eligible and assessable patients): Inclusions will continue if either objective response is observed in at least 2 patients or non-progression is observed for 7 patients. Otherwise, the stratum will be terminated early and declared negative.
- Stage 2 (41 eligible and assessable patients): Cabozantinib will be considered worthy of further testing in this indication if at least 5 objective responses (at least 12%), or at least 16 instances of 6-month PFS (at least 39%), were observed among the 41 evaluable patients.

This design yields at least 90% power to detect a true objective response rate of at least 20%. It yields at least 92% power to detect a true 6-month PFS rate of at least 50% (median PFS of 6 months). It yields at least .925 probability of a negative result if the true objective response rate is no more than 5% and the true 6-month PFS rate is no more than 25% (median PFS of 3 months), with approximately .53 probability, at least, of early negative stopping in this case. These last two probabilities are calculated assuming that tumor response rate and 6- month PFS rate are uncorrelated. If they are positively correlated, as is likely, the probabilities will be a bit higher.

Given the disease is rare and the absence of standard treatment in this indication, inclusion will not be suspended after the recruitment of the first 21 patients. Inclusion will be pursued, while

data on the first 21 patients will be analyzed.

In order to account for not evaluable patients (+/- 10%), 45 patients will be recruited.

The anticipated accrual rate is 2-3 patients/month.

13.2.2 Ewing sarcoma

We rely on a single-arm phase 2 trial based on an optimal two-stage Simon's design.

Based on the following hypotheses under Cabozantinib treatment:
- 5% 6-month objective response rate (null hypothesis),
- 20% 6-month objective response rate (alternative hypothesis),
- 5% type I error rate (1-sided),
- 90% power,
a total of 41 patients (eligible and assessable for efficacy – see definitions of study populations below) will be necessary, with 21 recruited to the first stage.

Stage 1: Following the inclusion of the first 21 patients, if 1 or less patient exhibits objective response (complete response, partial response) at 6 months, the study would be terminated early (objective response rate lower than 5%). Otherwise, the second group of 20 subjects will be recruited.

Stage 2: If at the end of recruitment, 5 patients or more exhibit objective response (out of the 41 patients) at 6 months, Cabozantinib would be considered worthy of further testing in this disease and the objective response rate will be considered greater than 5%.

Given the disease is rare and the absence of standard treatment in this indication, inclusion will not be suspended after the recruitment of the first 17 patients. Inclusion will be pursued, while data on the first 17 patients will be analyzed.

In order to account for not evaluable patients (+/- 10%), 45 patients will be recruited.

The anticipated accrual rate is 2-3 patients/month.

13.3 Definition of study populations

13.3.1 Osteosarcoma

13.3.1.1 Eligible population
All patients without major violations of the eligibility criteria are included in this population. In case of violation of the eligibility criteria, the steering committee will assess for each patient, whether the violation is minor or major.

13.3.1.2 Population assessable for efficacy
All patients eligible and who received at least one complete or two incomplete treatment cycles.

13.3.1.3 Population assessable for safety
All patients will be assessable for safety from the time of their first administration of Cabozantinib.

13.3.2 Ewing sarcoma

13.3.2.1 Eligible population
Same definition as for osteosarcoma.

13.3.2.2 Population assessable for the efficacy criteria
Same definition as for osteosarcoma.

13.3.2.3 Safety population
Same definition as for osteosarcoma.

13.4 Stratification Factors

Not applicable

13.5 Analysis of Secondary Endpoints

Endpoints will be analyzed independently for each stratum (osteosarcoma and Ewing sarcoma) following the SAP.

13.5.1 Best overall response

Best overall response is defined in section 11.1.4.3 and will be assessed on the population assessable for efficacy criteria. This endpoint will be described using frequency, percentage and 95% confidence interval (binomial law).

13.5.2 Progression-free survival

Progression-free survival (PFS) is defined in section 11.1.6 and will be assessed on the population assessable for efficacy criteria. PFS will be analysed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses can also be carried out based on Cox's proportional risk method and after checking the risk proportionality hypothesis.

13.5.3 Overall survival

Overall survival (OS) is defined in section 11.1.7 and will be assessed on the population assessable for efficacy criteria. OS will be analyzed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses can also be carried out based on Cox's proportional risk method and after checking the risk proportionality hypothesis.

13.5.4 Safety

Treatment safety will be assessed using the CTCAE version 4 on the safety population. Quantitative variables will be described using mean and standard errors if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be used. Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).

13.6 Interim statistical analysis

13.6.1 Osteosarcoma

An interim statistical analysis will be carried out after the inclusion of the first 21 eligible and assessable patients. The trial will be terminated if no more than 1 objective response (5%), and no more than 6 instances of 6-month PFS (no more than 29%) were observed among the initial 21 patients. Otherwise, the second group of 20 subjects will be recruited. A statistical report will be produced by the statistician of the study. Inclusion will not be suspended during this interim analysis.

No additional interim statistical analysis is foreseen.

13.6.2 Ewing sarcoma

An interim statistical analysis will be carried out after the inclusion of the first 21 eligible and assessable patients. The trial will be terminated if 1 or less patient exhibits objective response. Otherwise, the second group of 20 subjects will be recruited. A statistical report will be produced by the statistician of the study. Inclusion will not be suspended during this interim analysis.

No additional interim statistical analysis is foreseen.

13.7 *For phase 2 protocols only:* Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Cabozantinib.

13.7.2 Evaluation of Efficacy

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be

assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the definition for "Population assessable for efficacy" (see section 13.3) will be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14. QUALITY ASSURANCE AND TRIAL MONITORING

14.1 Monitoring of the trial

14.1.1 Steering committee

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:

- Dr A. Italiano, Co-ordinating Investigator and Chairman of the Commitee,
- Dr BN. Bui, Investigator and medical oncologist,
- Pr S. Mathoulin-Pélissier, Head of the Clinical Research and Epidemiology Unit,
- Dr C. Bellera, biostatistician,
- Dr B. Lortal, Pharmacist
- S Sellan-Albert, Co-ordinating Clinical research assistant

This committee must ensure the following:

- Implementation and regular follow-up of the study
- Patient protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated and the scientific results are checked during or at the end of the trial.

It decides on any relevant amendment to the protocol that is required in order to continue the trial (protocol amendments prior to submission to the EC and the relevant Health Authorities, decisions on whether to open or close research sites, discussion of results and the strategy for the publication of these results). It must inform the sponsor of any decisions taken. Decisions

concerning a major amendment or a change to the budget must be approved by the sponsor.

14.1.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (IDMC) may be created at the request of the relevant Authority, the sponsor or the Steering Committee. The IDMC plays an advisory role for the Sponsor, who has the final decision regarding the implementation of recommendations put forward by the IDMC.

Composition of the IDMC

- This Committee must comprise at least one qualified oncologist, one pharmacologist and one statistician, all of whom will have experience in the monitoring and analysis of clinical trials. One of these members will be appointed as the Trial Rapporteur.
- Each of these members must be unconnected with the trial and cannot, therefore, be one of the trial investigators.
- These members are appointed by the Sponsor in consultation with the trial co-ordinator and the Steering Committee.

Responsibilities of the IDMC

The IDMC is responsible for the following:

- Analyzing preliminary efficacy and safety data,
- Making recommendations on the continuation, early discontinuation (in the case of toxicity or lack of efficacy) or publication of the trial results,
- Drafting the minutes after each meeting and monitoring their confidentiality.

Organization rules of the IDMC will follow the internal procedures of Institut Bergonié.

14.2 Quality assurance

14.2.1 Data collection

The data will be collected on an electronic case report form and directly input via the Internet. Only the investigators and the Investigator's Clinical Research Assistants (CRAs) appointed by the later and duly authorized by the sponsor will be authorized to enter the data.

Data will be handled by an online trial management software on the Internet (Macro, Infermed Company); it will be transferred and monitored remotely in real time.

The study CRA and/or any other person appointed by the sponsor will be available to assist the investigators in carrying out the study and to ensure that the trial is carried out in accordance with the protocol.

The study CRA will contact the investigators regarding the study implementation visit.

All of the necessary data will be collected on an electronic case report form provided by the sponsor. The generic names of the concomitant medication will be given in French.

Corrections made to the original data must be justified. These corrections will be automatically dated and signed by the authorized member of staff via the personalized password allocated at the start of the study.

The case report form will be validated by the investigator or the CRA at the authorized center whenever data is entered.

Laboratory data exceeding normal limit values will be commented upon if they are considered clinically significant. Data other than that requested within the scope of the protocol can be collected as additional data; their interest will be specified.

14.2.2 Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles of GCP (Good Clinical Practice) dated 24 November 2006, the sponsor shall implement a quality assurance system comprising:

- the management and monitoring of the trial in accordance with the procedures stipulated by the Bergonié Institute,
- the quality control of the research site data by the CRA whose role is to:
    - check compliance with the protocol, GCP and current legislation and regulations,
    - check the consent and eligibility of each patient taking part in the trial,
    - check the consistency and coherence of case report form date against the source documents.
    - check that each serious adverse event is reported,
    - monitor the traceability of the study medication (dispensation, storage and drug accountability),
    - check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed. The CRA shall also ensure that the patients have not participated in a trial for which an exclusion period currently applies.
- The possible audit of study centers
- The centralized review of certain protocol criteria.

The check procedures will include:

- Study progression,
- Protocol compliance,
- The updating of information on the Internet site.

The checking of data by comparing the information on the electronic case report form and the original clinical or laboratory data is one of the monitoring procedures. Data will be check as determined in the monitoring plan.

The following will be checked, in particular, for each patient (100% level): patient identification, informed consent (procedure and signature), selection criteria, therapeutic procedure, adverse events, principal response variables. The personal data relating to each patient shall remain confidential. On the electronic case report form or any other form dispatched, the patients will be identified solely by their initials (2/name – 2/surname) and an inclusion number. However, the investigators must keep a list identifying the patients in their folders.

The CRAs responsible for the quality control of this clinical trial are duly appointed by the sponsor for this particular purpose and must have access, with the consent of those involved, to

individual trial participant data required strictly in accordance with this control procedure. The CRAs are subject to professional secrecy under the conditions defined by Articles R 5121-13 of the Public Health's code. The traceability of monitoring visits is guaranteed by a written monitoring report.

The investigators shall undertake to give CRAs direct access to the medical records of each patient in order to allow the CRAs to ensure optimal quality control of the trial. The same applies to health authority representatives.

14.2.3 Handling of missing data

The monitoring of data for adverse events will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis.

14.2.4 Audits

The sponsor, the local authorities or the authorities to which information about this study has been submitted can decide to have an audit. All the documents relating to this study must be available for such an inspection after prior notification.

15. REGULATORY ASPECTS AND ETHICAL CONSIDERATIONS

Clinical Research Management Unit – Institut Bergonié
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The study will be carried out in accordance with:

- The ethical principles of the current version of the "Declaration of Helsinki"
- Good Clinical Practice (GCP): I.C.H. version 4 of 1 May 1996 and decision dated 24 November 2006 (Official Bulletin of 30 November 2006, text 64).
- European Directive (2001/20/EC) on clinical trial procedures.
- Huriet's law (No. 88-1138) dated 20 December 1988, concerning the protection of persons taking part in Biomedical Research with the provisions of the Public Health law (No. 2004-806) of 9 August 2004 and implementating decree No. 2006-477 of 26 April 2006 relating to biomedical research.
- The French law on Data Protection and Civil Liberties, No. 78-17 of 6 January 1978 amended by law No. 2004-801, dated 6 August 2004, concerning the protection of persons with regards to the processing of personal data.
- The application of Circular DHOS/INCA/MOPRC/2006/475 of 7 November 2006: the Sponsor shall undertake to register the Trial and thus make it accessible to the general public, in the INCa (French Cancer Institute) register via the Internet site: www.e-cancer.fr. Each trial published in the INCa register will be sent to the NCI for registering on the following site: www.clinicaltrials.gov. The trial will be registered before the first patient is entered into

the study. The Sponsor is responsible for updating the study data in order to guarantee the reliability of the information available on-line.

- Law no. 2004-800 dated 6 August 2004, concerning bioethics, amended by law No. 2012-387, dated 22 March 2012.

15.1 Clinical trial authorization

This trial is registered under Eudract N° 2014-XXXXXX-XX.

The protocol has been approved by the South West and Overseas Territories III Ethics Committee, Bordeaux. Approval was given on |__|__|/|__|__|/|__|__|__|__|.

The Relevant Authority, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM - French Agency for the Safety of Health Care Products) authorized the clinical trial on |__|__|/|__|__|/|__|__|__|__|.

Any amendments to the protocol concerning study objectives, patient population and principal methods will require an amendment, which must be approved by the EC and l'ANSM. The sponsor will inform the EC and ANSM of expected and/or unexpected serious adverse events in accordance with current regulations and within 30 days after of completion of the trial.

The sponsor will send the summary of the final report to the relevant Authority within one year of completion of the trial.

The sponsor has made a commitment to compliance the Reference methodology for the processing of personal data carried out in biomedical research: Reference methodology MR-001. This commitment of compliance is registred under No 118019 of the 07/11/2006.

15.2 Insurance policy

The Institut Bergonié has taken out an insurance policy with société HDI-Gerling, Tour opus12, 77, Esplanade de la défense, 92914 PARIS LA DEFENSE through an insurance broker, namely Biomédic Insure (Parc d'Innovation Bretagne Sud, CP 142, 56038 Vannes, tel. 02 97 69 19 19) in case compensation is payable to investigators or patients taking part in the study.

15.3 Informing and obtaining consent from patients

The investigator in charge of the patient will provide the latter with relevant information relating to the study objectives, potential benefits and possible adverse events. The study methods will be outlined. The patient can refuse treatment before or at any time during the study, without experiencing any adverse repercussions in terms of his/her subsequent care.

The patient’s written consent will be obtained prior to entry into the study by using the Patient Information Leaflet and Informed Consent Form (appendix 9 to 12). These forms must be combined in the same document in order to ensure that all of the information is given to the trial participant.

The consent form must be personally dated and signed by the trial participant and the investigator. The original will be given to the patient and the second, archived in the investigator’s folder. Upon request, a copy will be sent to the sponsor in a sealed envelope.

15.4 Sponsor's responsabilities

The sponsor of the clinical trial, the Institut Bergonié, will take the initiative for this clinical trial. The Institute will manage the trial and ensure that finance is provided.

The sponsor's main responsibilities are to:

- Take out civil liability insurance,
- Obtain the Eudract No. and register the trial in the European database (European Drug Regulatory Authorities Clinical Trials),
- Obtain clinical trial authorization for the initial project and any amendments from the EC and ANSM; approval by the EC and decision taken by ANSM.
- Notify the relevant authority any suspected unexpected serious adverse reaction (SUSAR),
- Give trial-related information to the site directors, pharmacists and investigators,
- Notify the relevant authority of the trial start and end dates,
- Draft the final trial report and sent the summary to ANSM,
- Send the trial results to the relevant authority, EC and investigators,
- Archive essential trial documents in the sponsor's folder for a minimum period of 15 years after the trial has ended.

15.5 Investigators' responsabilities

The principal investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol that was approved by the ethics committee and the relevant authority (ANSM).

The investigator must not make any changes to the protocol without the written consent of the sponsor or without the ethics committee and the relevant authority having authorized the proposed changes.

It is the responsibility of the principal investigator is:

- to provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,
- to identify the members of his/her team who are participating in the trial and to define their responsibilities,
- to start patient recruitment after authorization has been obtained from the sponsor,
- to ensure that he/she is available for investigators's meeting anf for "monitoring".

It is the responsibility of each investigator:

- to comply with the confidential nature of the trial,

- to obtain informed consent, signed and dated personally by each trial participant, before any screening procedures specific to the trial are carried out,
- to regularly complete the case report forms (CRFs or e-CRFs) for each of the patients enrolled in the trial and to allow the Clinical Research Assistant (CRA) duly authorised by the Sponsor a direct access to source documents so that the latter can validate the data on the CRF or e-CRF,
- to promptly notify the sponsor of any serious adverse event and/or new information occurring during the trial,
- to date, correct and validate corrections on the case report forms (CRFs or e-CRFs) and the Data Clarification Forms (DCFs),
- to accept regular visits CRA and eventually visits of auditors duly authorised by the Sponsor or inspectors of regulatory authorities,
- to inform trial participants of the overall results of the research on first demand.

15.6 Authority to execute the trial

The investigator shall certify that he/she is authorized to enter into this agreement and that the terms and conditions of the protocol and agreement do not conflict with other agreements that the investigator may have entered into with any other party, or any other arrangement agreed by the Institution where the investigator is employed.

15.7 Regulations governing the collection of human biological samples

During the medical procedures to be carried out, samples will be collected for medical purposes. A fraction of these samples will be kept and used for scientific research purposes.

The patient will be informed of this research and provided that he/she approves by signing an informed consent, these samples intended for research will be:

- Initially prepared and stored using a specific technique to preserve them under excellent conditions.
- and secondly, used within the scope of this research.

The preparation, storage and use of these samples will not in any way affect current or future medical care administered to the patient for the purpose of diagnosis or treatment.

The results of this research may, in future, appear in scientific publications. All of the data shall remain anonymous.

Obtaining and using additional samples
This biomarker study is made up of exploratory research that is described in the section "Ancillary Study".

On completion of the trial, provided that the patient agrees and provided that not all of the samples have been used, the said samples can be used for subsequent scientific research purposes without the approval of the Ethics Committee (EC) and the signing of a new consent form by the patients included.

15.8 Fédération des comités de patients pour la recherche clinique en cancérologie (FCPRCC) (Federations of patient committees for clinical research in oncology)

The Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie (FCPRCC) (Federation of Patient COmmittees for Clinical Research in Oncology) was created on the initiative of the Fédération des Centres de Lutte Contre le Cancer (FNCLCC) (Federation of Anti-Cancer Centers) and the Ligue Nationale Contre le Cancer (National Anti-Cancer League) in order to review clinical trial protocols in oncology. This Federation of Patient Committees is co-ordinated by the Office for Clinical and Therapeutic Trials and groups together the League patient committees as well as other health care establishments. The Sponsor undertakes to transmit the protocol to the Federation for review. The Federation undertakes to propose improvements focusing primarily on the quality of the information leaflet, the availability of a treatment and monitoring plan and the suggestion of measures aimed at improving patient comfort.

15.9 Data processing

In accordance with the French Law on Data Protection and Civil Liberties of 06 August 2004 and its implementing decrees, the Sponsor shall follow the methodology of reference MR001 of the Commission Nationale de l'Informatique et des Libertés (French National Commission for Data Protection and Liberties).

Furthermore, if the biomedical research data is computer processed or managed by computerized systems, each Center:

- shall check and document the fact that the computerized systems used in the research comply with requirements drawn up in relation to data integrity, accuracy and reliability, as well as compliance with expected performances (i.e. validation);
- shall implement and ensure the monitoring of standard operating procedures relating to the use of these systems;
- shall ensure that the design of these systems allows for data to be amended such that the amendments are documented and that any item of data input cannot be deleted (i.e. maintaining data and amendment audit trail) ;
- shall implement and ensure the monitoring of a secure system that prevents any unauthorized data access;
- shall update the list of persons authorized to amend the data;
- shall keep appropriate back-up copies of the data;
- shall maintain blind status, where applicable (e.g. during data entry and processing);
- shall ensure that personal data used within the scope of the trial is processed in accordance with the conditions defined by law No. 78-17 dated 6 January 1978 relating to data processing, files and liberties modified by law No. 2004-801 of 6 August 2004 and its implementing regulations.

If the data is converted during processing, it must always be possible to compare the original

data and observations with the data after conversion.

The system used to identify subjects taking part in the trial must not present with any ambiguity and must allow all of the data collected for each of these subjects to be identified whilst maintaining the confidentiality of the personal data, in accordance with law No. 78-17, duly amended.

The archiving data is performed according to the applicable regulations and under the responsibility of investigator. All data and the patient indentification codes will be kept for at least 15 years after the completion or discontinuation of the trial.

16. CONFIDENTIALITY AND OWNERSHIP OF DATA

All of the information communicated or obtained and the data and results generated by the trial legally belong to as their obtaining the Institut Bergonié, which can use this data at its own discretion.
According to article R 5121-13 of the French Public Health Code, investigators and people who will have to collaborate in the trial shall be bound by professional secrecy with regard to the particular nature of the products studied, trial, trial participants, and results. In particularly, all documentation relating to the trial sent to the investigator should be considered confidential information.
Without the consent of the sponsor, the investigator cannot give information about trials at anyone, except the Minister in charge of Public Health, public health medical inspectors, public health pharmacists inspectors, the General Director and inspectors of ANSM.
The trial cannot be the subject of any written or verbal comments without the sponsor's consent.

17. PUBLICATION AND VALORISATION

17.1 Scientific communication

All of the information arising from this study shall be considered confidential (cf. section 12).
All forms of publication must be submitted to the Steering Committee for review and approval prior to publication (allowing at least 15 working days for abstracts and oral presentations, and 45 working days for written publications). The Steering Committee shall check the accuracy of the information submitted (in order to avoid any inconsistency with that submitted to the Health Authorities), and ensure that confidential information is not inadvertently disclosed. It will also provide additional information as required. In any case, the sponsor will control the first publication.
Furthermore, all memos, manuscripts or presentations must comprise a heading referring without fail to the Institut Bergonié, all of the institutions, investigations, co-operating groups and learned societies that have contributed to the implementation of the trial, and listing any organizations that have provided financial support.
For the principal publication, either in French or English, the authors are:

- the study coordinator

- the investigators will be listed on a pro rata basis according to the number of patients recruited
- a representative of the trial statistics unit (in the first 3 positions according to degree of involvement in the preparation of publications)

17.2 Information to patients

According to Article L.1122-1 of the French Code of Public Health Investigator undertakes to inform trial participants of the overall results of the research on first demand.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

<u>Agent Ordering</u>

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

The patient _____ is enrolled on a clinical trial using the experimental agent **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.*

[Agent name] interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

[Use or delete sections below as appropriate.]

XL184 interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is **CYP3A4**. This enzyme breaks down XL184, gradually reducing the level of the active drug in your system.
- Other medicines may affect the activity of the enzyme. XL184 must be used very carefully with these medicines, or you may need to switch to alternate medications.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers of **CYP3A4**."
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.

- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- *[The following are **examples** of text for common over-the-counter medications or supplements that may interact with the study agent.]* Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking *[agent name]*.
    - *[Add other specific medications here, if necessary.]*

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent **XL184 (cabozantinib)**. This clinical trial is sponsored by the NCI. **XL184 (cabozantinib)** interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) 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) interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers of **CYP3A4**."
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX D SCREENING FORM

***CABONE* study**	SCREENING FORM

Fax and email this form to Clinical Trial and Epidemiology Unit (UREC) :
05.56.33.04.85
From Monday through Friday: from 9.00 am to 5.00 pm
Contact : Sabrina SELLAN-ALBERT (CRA) 05.56.33.78.05 / **Mail** : s.albert@bordeaux.unicancer.fr

CENTRE (letters)_____ Centre's number |__|__|

Investigator's Name_____

Fax |__|__| |__|__| |__|__| |__|__| |__|__| Phone |__|__| |__|__| |__|__| |__|__| |__|__|

PATIENT	
Name |__|__|	Surname |__|__|
Date of birth	|__|__| |__|__| |__|__|__|__|
Date of signed consent patient	|__|__| |__|__| |__|__|__|__|
Version	|__|.|__|
Does the patient accept to participate at the optional study?	❑ No ❑ Yes
Date of signed optional consent form	|__|__| |__|__| |__|__|__|__|
Version	|__|.|__|
OSTEOSARCOMA / EWING SARCOMA **Histology**: Reviewed in the RRePS Network: ☐ YES : send only the anonymized pathology report with this form ☐ NO : Central review needed *	
Warning : *Send CD of CT-scan or MRI of two radiological assessments within 7 days for radiological central review (see radiology procedure)* *and pathological specimen if necessary* (see pathology procedure)*	

To be filled by the coordinator centre

Date of registration (DD/MM/YYYY) .....|__|__| |__|__| |__|__|__|__|

Patient's screening number for this study .....|__|__|

Pathological central review needed: Yes ☐ No ☐

Version 1.0- 21/11/2014

APPENDIX E INCLUSION FORM

CABONE **study**	INCLUSION FORM

Fax and email to Clinical Trial and Epidemiology Unit (UREC) :

05 56 33 04 85

From Monday through Friday: from 9.00 am to 5.00 pm

Contact : Sabrina SELLAN-ALBERT (CRA) 05.56.33.78.05 / **Mail :** s.albert@bordeaux.unicancer.fr

CENTER (letters) _____ Centre's number |__|__|

Investigators' name _____

Fax |__|__| |__|__| |__|__| |__|__| |__|__| Phone |__|__| |__|__| |__|__| |__|__| |__|__|

PATIENT		
Name	|__|__|	Surname |__|__|
Date of birth		|__|__| |__|__| |__|__|__|__|
Date of signed consent patient		|__|__| |__|__| |__|__|__|__|
Version		|__|.|__|
Screening number		|__|__|
Does the patient accept to participate at the optional study?		❑ No ❑ Yes
Date of signed optional consent form		|__|__| |__|__| |__|__|__|__|
Version		|__|.|__|

All inclusion criteria have been respected?	❑ NO	❑ YES
If no, derogation request made to sponsor?	❑ NO	❑ YES
Date foreseen for protocol treatment start	|__|__| |__|__| |__|__|__|__|	
Date of inclusion request:	|__|__| |__|__| |__|__|__|__|	

To confirm inclusion, **signed investigator** :

To be filled by the coordinator center

Date of inclusion (DD/MM/YYYY) _____|__|__| |__|__| |__|__|__|__|

Inclusion Number _____ **|__|__|__|**

Name of the person who performed the inclusion: _____
Signature :

Version 1.0- 21/11/2014

APPENDIX F PATIENT MEDICATION DIARY

PROTOCOLE

CABONE

Carnet patient

De Mme/Mr.....
Cycle N° I_I_I

Madame, Monsieur,

Dans le cadre de votre participation à l'étude *CABONE*, il est nécessaire d'avoir des informations sur le suivi de votre traitement par XL-184

Vous trouverez dans ce carnet un tableau à compléter chaque jour, et nous vous remercions d'y noter :

- ✓ la date, et le nombre de comprimés pris par jour
- ✓ d'annoter un commentaire si nécessaire (effets secondaires par exemple)
- ✓ l'indication de non prise du XL-184 s'il y a lieu en cochant la case correspondante et en complétant d'un commentaire la raison.

N'oubliez pas de remettre ce livret à l'Infirmier(e) de Recherche Clinique, Attaché(e) de Recherche Clinique ou Pharmacie hospitalière lors de votre prochain rendez-vous.

Nous vous remercions de votre précieuse collaboration.

Notice d'utilisation du médicament à l'étude

- ✓ 1 prise par jour en dehors des repas
- ✓ Etre à jeun, au moins 2 heures avant et 1 heure après la prise

En cas d'oubli

- Ne pas prendre la dose, et ne pas doubler la dose suivante

En cas de vomissements

- Ne pas reprendre la dose, et ne pas doubler la dose suivante

Conservation du traitement

- o Conservation à température ambiante inférieure à 25°C.
- o Ne pas utiliser après la date de péremption figurant sur la boite

Date		Heure	XL-184 Nombre de comprimés	Non pris	Commentaires
J1	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J2	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J3	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J4	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J5	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J6	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J7	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J8	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J9	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J10	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J11	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J12	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J13	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J14	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J15	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J16	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J17	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J18	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J19	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J20	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J21	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J22	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	

J23	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J24	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J25	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J26	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J27	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J28	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J29	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	
J30	___/_____/___		__| comp de 20mg __| comp de 60mg	☐	

Nombre de comprimés pris |__|__|comprimés de 20 mg et |__|__|comprimés de 60 mg

Retour |__|__|comprimés de 20 mg et |__|__|comprimés de 60 mg

Commentaires du patient (observance): _____

_____

Date: Signature:

Commentaires du personnel de recherché (observance) : _____

_____

Date: Signature:

APPENDIX G SERIOUS ADVERSE EVENT NOTIFICATION FORM

Serious Adverse Event Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**ACRONYM**	EUDRACT/ ID-RCB N°:**2014-XXXXXX-XX**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	SITE N°:
DATE OF THIS REPORT: |___|___|_____|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|___|	FINAL REPORT ☐

1. PATIENT IDENTIFICATION

INCLUSION N°: \|_____\| SURNAME (3 LETTERS): \|___\| 1ST NAME (2 LETTERS): \|___\| DATE OF BIRTH: \|___\|___\|____\|

TREATMENT ARM: \|__\| DOSE LEVEL (PHASE I STUDY): \|__\|

GENDER: F ☐ M ☐ WEIGHT (KG): \|___\| HEIGHT (CM): \|___\| BODY SURFACE AREA (M^2): \|__\|.\|___\|

2. INFORMATION ON EVENT

DATE OF ONSET: \|___\|___\|____\| TOXICITY (NCI–CTC GRADE): 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS *OR MAIN SYMPTOM*: **only one diagnosis or one symptom** (except for linked symptoms) .....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN (INCLUDING RELEVANT TEST/LAB DATA): .....

.....

.....

3. SERIOUSNESS CRITERIA

- ☐ DEATH, DATE OF DEATH: .....\|__\|__\|____\|
- ☐ LIFE-THREATENING
- ☐ REQUIRING/PROLONGING HOSPITALIZATION (> 24H) :
  DATE OF ADMISSION: .....\|__\|__\|____\|
- ☐ PERSISTENT/SIGNIFICANT DISABILITY/INCAPACITY
- ☐ CONGENITAL DISORDER/BIRTH DEFECT
- ☐ MEDICALLY RELEVANT

4. OUTCOME

- ☐ ONGOING EVENT
- ☐ UNKNOWN OUTCOME
- ☐ RECOVERED WITHOUT SEQUELAE, ☞ DATE \|__\|__\|____\|
- ☐ RECOVERED WITH SEQUELAE, ☞ DATE \|__\|__\|____\|
  SPECIFY SEQUELAE: .....
- ☐ DEATH RELATED TO THIS EVENT, ☞ DATE \|__\|__\|____\|
- ☐ DEATH UNRELATED TO THIS EVENT, ☞ DATE \|__\|__\|____\|
  CAUSE OF DEATH: .....
  OR CAUSE UNKNOWN ☐
- ☐ AUTOPSY: YES ☐ NO ☐

IF PATIENT WAS HOSPITALIZED: DATE OF END OF HOSPITALIZATION: \|__\|__\|____\|
OR PATIENT STILL HOSPITALIZED AT TIME OF THIS REPORT ☐

FOR IMP TRIALS ☞ COMPLETE **SECTION 5** FOR RADIOTHERAPY TRIALS ☞ COMPLETE **SECTION 6** FOR OTHER NON IMP TRIALS ☞ COMPLETE **SECTION 7**

5. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S), including combined RADIOTHERAPY / SURGERY...) ..... TICK IF NA ☐

INVESTIGATIONAL PROCEDURE(S) INDICATE THE INTERNATIONAL COMMON DENOMINATION OF THE IMP & OTHER COMBINED	ROUTE	SAE CYCLE NUMBER	DATES		DOSE & UNIT			
			DATE OF FIRST ADMINISTRATION/USE (1ST DAY OF 1ST CYCLE)	DATE OF LAST ADMINISTRATION/USE BEFORE SAE	LAST DOSE ADMINISTERED BEFORE SAE		CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION	
					DOSE	UNIT	DOSE	UNIT
1.			|__|__|____|	|__|__|____|				
2.			|__|__|____|	|__|__|____|				
3.			|__|__|____|	|__|__|____|				
4.			|__|__|____|	|__|__|____|				
5.			|__|__|____|	|__|__|____|				
6			|__|__|____|	|__|__|____|				
7.			|__|__|____|	|__|__|____|				

UNBLINDING : YES ☐ NO ☐ NA ☐

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN STOPPED?
☐ YES N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| ☐ NO ☐ NA

DID THE EVENT DISAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) IS STOPPED?
☐ YES ☐ NO ☐ NA

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN REINTRODUCED?
☐ YES N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| ☐ NO ☐ NA

DID THE EVENT REAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) REINTRODUCTION?
☐ YES ☐ NO ☐ NA

Serious Adverse Event Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**ACRONYM**	EUDRACT/ ID-RCB N°:**2014-XXXXXX-XX**	COUNTRY:
SPONSOR IDENTIFICATION N°:	**INVESTIGATOR SITE :**	**SITE N°:**
DATE OF THIS REPORT: |___||___||_____|	**INITIAL REPORT ☐** **FOLLOW-UP REPORT N°**|___|	**FINAL REPORT ☐**
INCLUSION N°: |_____| SURNAME (3 LETTERS): |____| 1ST NAME (2 LETTERS): |___| DATE OF BIRTH : |___||___||_____|		

6. RADIOTHERAPY ..... TICK IF NA ☐

TECHNIQUE	FIELD(S)	DATES		DOSE (GY)	
		DATE OF FIRST ADMINISTRATION	DATE OF LAST ADMINISTRATION	LAST DOSE ADMINISTERED BEFORE SAE (GY)	CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION (GY)
		|__|__|__|_____|	|__|__|__|_____|		
		|__|__|__|_____|	|__|__|__|_____|		
		|__|__|__|_____|	|__|__|__|_____|		
		|__|__|__|_____|	|__|__|__|_____|		

MACHINE (SPECIFY IF POSSIBLE TRADE NAME / MODEL/SERIAL NUMBER): .....

.....

HAS RADIOTHERAPY BEEN STOPPED?	HAS RADIOTHERAPY BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER RADIOTHERAPY IS STOPPED?	DID THE EVENT REAPPEAR AFTER RADIOTHERAPY REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER: .....

7. MEDICAL DEVICE or NON MEDICINAL PRODUCT, METHOD or ACTION ..... TICK IF NA ☐

DEVICE / Non Medicinal Product, Method or Action	DATES OF USE
COMMON DENOMINATION :	START DATE: |__|__|__|_____|
TRADE NAME (IF EC MARKING) :	STOP DATE: |__|__|__|_____|
MODEL :	VERSION (INCLUDED SOFTWARE) :
SERIAL NUMBER :	AND/OR BATCH NUMBER :
INDICATION OF USE FOR THE PATIENT :	

HAS DEVICE OR ONE (OR SEVERAL) PRODUCTS(S), METHOD(S) OR ACTION(S) BEEN STOPPED?	HAS DEVICE OR ONE (OR SEVERAL) PRODUCT(S), METHOD(S) OR ACTION(S) BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER STOP?	DID THE EVENT REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER, SPECIFY: .....

Serious Adverse Event Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**ACRONYM**	EUDRACT/ ID-RCB N°:**2014-XXXXXX-XX**		COUNTRY:
SPONSOR IDENTIFICATION N°:	**INVESTIGATOR SITE :**		**SITE N°:**
DATE OF THIS REPORT: |___|___|_____|	**INITIAL REPORT ☐**	**FOLLOW-UP REPORT N°**|___|	**FINAL REPORT ☐**
INCLUSION N°: |_____|	SURNAME (3 LETTERS): |____|	1ST NAME (2 LETTERS): |___|	DATE OF BIRTH : |___|___|_____|

8. CONCOMITANT DRUG(S) – (EXCLUDE THOSE USED TO TREAT REACTION)

CONCOMITANT DRUG	ROUTE	START DATE	STOP DATE	ONGOING	INDICATION
1.		FROM |__|__|__|	TO |__|__|__|	☐	
2.		FROM |__|__|__|	TO |__|__|__|	☐	
3.		FROM |__|__|__|	TO |__|__|__|	☐	
4.		FROM |__|__|__|	TO |__|__|__|	☐	

9. OTHER RELEVANT HISTORY (E.G. DIAGNOSTICS, ALLERGIES, PREGNANCY WITH LAST MONTH OF PERIOD, ETC…)

.....

.....

.....

10. ASSESSMENT: IN YOUR OPINION **(INVESTIGATOR),** THIS EVENT IS RELATED TO (TICK ONLY ONE BOX):

☐ IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S) INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE IMP NUMBER(S) (SEE SECTION 5 OF THE FORM): N°|_| N°|_| N°|_| N°|_| N°|_| N°|_| N°|_|
☐ INVESTIGATIONAL RADIOTHERAPY,
☐ INVESTIGATIONAL MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION

IF NOT RELATED TO EITHER INVESTIGATIONAL MP / RADIOTHERAPY / SURGERY, NMP, OR MD, **PLEASE SPECIFY** (TICK ONLY ONE BOX)

☐ PROTOCOL
☐ CONCOMITANT TREATMENT(S), SPECIFY: .....
☐ CONCOMITANT DISEASE(S), SPECIFY: .....
☐ OTHER, SPECIFY: .....

11. SAE NOTIFICATED BY:

NAME:
FUNCTION:
ADDRESS:
PHONE: ..... FAX: .....
E-MAIL: .....
DATE |___| / |___| / |_____|

SIGNATURE: .....

INVESTIGATOR

NAME:
DEPARTMENT:

DATE |___| / |___| / |_____|

SIGNATURE: .....

SPONSOR ONLY (DO NOT FULFIL THIS PART)

SPONSOR IDENTIFICATION NUMBER:.....
DATE OF RECEIPT: |___| / |___| / |_____| DATE OF THIS REPORT: |___| / |___| / |_____|

ASSESSMENT(Tick only one box):

1 ☐ INVESTIGATIONAL **MP** (INCLUDING COMBINED RADIOTHERAPY / SURGERY)
☐SPECIFY THE NUMBER(S)° N° |_| N° |_| N° |_| N° |_| N°|_| N°|_| N°|_|
2 ☐ INVESTIGATIONAL **RADIOTHERAPY,**
3 ☐ INVESTIGATIONAL **MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION**

☐IS IT A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (**SUSAR**)?
YES ☐ NO ☐

IF NOT RELATED TO EITHER 1, 2 OR 3, PLEASE SPECIFY (TICK ONLY ONE BOX)

4 ☐ PROTOCOL
5 ☐ CONCOMITANT TREATMENT(S)
6 ☐ CONCOMITANT DISEASE(S), SPECIFY .....
7 ☐ OTHER, SPECIFY .....

DATE |___| / |___| / |_____| NAME ..... SIGNATURE : .....

APPENDIX H PREGNANCY NOTIFICATION FORM

Pregnancy Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**ACRONYM**	EUDRACT/ ID-RCB N°:**2014-XXXXXX-XX**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	**INVESTIGATOR SITE :**	**SITE N°:**
DATE OF THIS REPORT: |__|__|/|__|__|/|__|__|__|__|	**INITIAL REPORT ☐** / **FOLLOW-UP REPORT N°**|__|__|	**FINAL REPORT ☐**

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____|

SURNAME (3 LETTERS): |___| 1ST NAME (2 LETTERS): |___| DATE OF BIRTH (DD/MM/AAAA): |____||____||____|

TREATMENT ARM: |___| DOSE LEVEL (ONLY FOR PHASE I STUDIES): |___|

GENDER: FEMALE ☐

MALE ☐

2. INFORMATION ON PREGNANT

THE PREGNANT IS: THE PATIENT ☐

A PATIENT PARTNER ☐ ☞ SPECIFY INITIALS: |___| DATE OF BIRTH (DD/MM/AAAA): |____||____||____|

DATE OF LAST MENSTRUAL PERIOD (DD/MM/AAAA): |____||____||____|

ESTIMATED DATE OF DELIVERY (DD/MM/AAAA): |____||____||____|

WAS THE PATIENT USING CONTRACEPTION? YES ☐ NO ☐

DESCRIBE ALL RELEVANT TREATMENTS ADMINISTERED TO THE PREGNANT AND HER PARTNER IF APPLICABLE (DATE AND DOSE OF INVESTIGATIONAL DRUGS AND CONCOMITANT TREATMENTS): .....

.....

.....

.....

.....

PARENTS RELEVANT MEDICAL HISTORY:

MOTHER: .....

.....

.....

FATHER: .....

.....

.....

3. FOLLOW-UP INFORMATION

FOLLOW-UP INFORMATION CAN BE OBTAINED FROM:

DOCTOR: .....

INSTITUTION: .....

ADDRESS: .....

E-MAIL: .....

PHONE: ..... FAX: .....

4. INVESTIGATOR

NAME: .....

DEPARTMENT: .....

PHONE: .....

FAX: .....

E-MAIL: .....

DATE (DD/MM/AAAA): |__|/|__|/|____|: SIGNATURE: .....

APPENDIX I COCKCROFT FORMULA

$$\text{Creatinine clearance (ml/min)} = \frac{[(140\text{-age (years)}) \times \text{weight (Kg)}]}{72 \times \text{serum creatinine (mg/dl)}} \times G^{1}$$

[1]G (Gender) = 0.85 if Female; 1 if Male

Reference: *Cockcroft, DW, Gault, H. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41 [84].*

APPENDIX J DOSING TABLE FOR PATIENTS < 16 YEARS OF AGE

Dose Level 0: 40 mg/m²		
BSA (m²)	Calculated dose	No. of tablet
1.2 – 1.5	40 mg	2 x 20 mg
> 1.5	60 mg	1 x 60 mg

Dose Level 1: 30 mg/m²		
BSA (m²)	Calculated dose	No. of tablet
1.2 – 1.5	20 mg	1 x 20 mg
> 1.5	40 mg	2 x 20 mg

Dose Level 2: 20 mg/m²		
BSA (m²)	Calculated dose	No. of tablet
1.2 – 1.5	Stop treatment	Stop treatment
> 1.5	20 mg	1 x 20 mg