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A Phase 1/2 Study of Neoadjuvant Cabozantinib in Combination with Radiation Therapy for Sarcomas of the Extremities

Investigational Product	**Cabozantinib**
Protocol Number:	**RG1003562 (CC10051)**
Study Phase:	**1/2**
IND Number:	**146,712**
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Original v1.0:	September 21, 2019
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Principal Investigator	**dd/mm/yyyy**
Lee Cranmer, MD, PhD, FACP	
Printed Name of Principal Investigator	
Institution Name: University of Washington	
By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Exelixis representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT	Cabozantinib, an oral receptor tyrosine kinase inhibitor
INDICATION	Soft tissue sarcomas of the extremities, which are to be treated with radiation therapy
TITLE	A Phase I/II Study of Neoadjuvant Cabozantinib in Combination with Radiation Therapy for Sarcomas of the Extremities
PROTOCOL NUMBER	RG1003562 (CC10051)
PHASE OF DEVELOPMENT	1/2
STUDY OBJECTIVES	**Primary Objective(s)** • Phase I: To determine if administration of cabozantinib is safe and feasible in combination with neoadjuvant radiation therapy. • Phase II: To assess the proportion of subjects alive and free of both local and distant disease recurrence (and progression after incomplete resection) one year after treatment initiation. **Secondary Objective(s)** • Rate of pathologic response. • Rate of surgical excision with negative margins. • Response rate (complete, partial, overall) of the combination therapy prior to surgery, as defined by RECIST 1.1 criteria. • Pattern of and time to local vs. distant recurrences. • Relapse-free and overall survival at various time points from study entry. • Safety and tolerability of combined treatment regimen, including the rate of discontinuation during the cabozantinib monotherapy component of the study. **Exploratory Objective(s)** • Comparison of pre- and post-treatment specimens to identify changes in activation of molecular pathways associated with MET genetic profiles associated with treatment response and with relapse-free survival.

	• Evaluation of pre- and post-treatment specimens for mutational status of signaling pathways, including MAP-Kinase and AKT/m-TOR pathways. • Explore changes in the immune microenvironment induced by this neoadjuvant treatment, in comparison to matched specimens obtained from the University of Washington pathology archives. • Radiomic studies to identify predictors of treatment response and relapse-free survival.
STUDY ENDPOINTS	**Primary Endpoints** • Phase I: Recommended Phase 2 dose (RP2D) of cabozantinib in combination with radiation • Phase II: Rate of relapse at 12 months after treatment initiation. **Secondary endpoints** • Rate of pathologic response. • Rate of surgical excision with negative margins. • Response rate (complete, partial, overall) of the combination therapy prior to surgery, as defined by RECIST 1.1 criteria. • Pattern of and time to local vs. distant recurrences. • Relapse-free and overall survival at various time points from study entry. • Safety and tolerability of combined treatment regimen. • Rate of treatment discontinuation prior to neoadjuvant radiation therapy. **Exploratory endpoints** • Comparison of pre- and post-treatment specimens to identify changes in activation of molecular pathways associated with MET genetic profiles associated with treatment response and with relapse-free survival. • Assessment of mutational status of signaling pathways, including MAP-Kinase and AKT/m-TOR pathways. • Assess changes in infiltration of immune cell subsets (CD4, CD8, myeloid) in the immune microenvironment induced by this neoadjuvant treatment, in comparison to matched specimens obtained from the University of Washington pathology archives. • Radiomic studies to identify predictors of treatment response and relapse-free survival, when comparing pre-treatment imaging with imaging prior to surgery (after completion of radiotherapy and concurrent cabozantinib).

SAMPLE SIZE ESTIMATE	**Phase I/Dose Escalation:** Expected 6, but up to 12 subjects to identify the MTD. Subjects enrolled to Phase 1 who withdraw for reasons other than toxicity during the dose-limiting toxicity (DLT) period will be determined to be not evaluable and will be replaced. **Phase II/Dose Expansion**: 34 additional subjects For sample size determination, we assume the following: Null hypothesis: 1-yr RFS=75% Alternative hypothesis: 1-yr RFS=0.90 Alpha=0.1 (one-sided) Beta=0.1 (power=90%) Total accrual=40 evaluable subjects. Anticipate accrual of 6 evaluable subjects from phase I component of study. 34 subjects to accrue in phase II portion of study. Assuming 10% non-evaluable rate, 44 subjects would be accrued to the efficacy component of the study to yield 40 evaluable subjects. Subjects enrolled to Phase 2 who withdraw for toxicity during the initial lead-in cycle will be determined to be not evaluable and replaced.
DURATION OF TREATMENT AND STUDY PARTICIPATION	The study is expected to take approximately 36 months from first subject enrolled to last subject follow-up, including approximately 12 months of enrollment period, an estimated 5 months of treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AUC	area under the time-concentration curve
BSA	body surface area
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
CBC	complete blood count
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
DLT	dose-limiting toxicity
DSMC	Data safety monitoring committee
DNA	deoxyribonucleic acid
DCR	disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
CRF	electronic case report form
EOS	end of study
EOT	end of treatment
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	investigational new drug
IP	investigational product

IRB	Institutional Review Board
mg	Milligram
mL	Milliliter
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	partial response
PTEN	protein tyrosine phosphatase
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-Free Survival
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
TBL	total bilirubin level
ULN	upper limit of normal

Abbreviation or Term	Definition/Explanation
Study Day 1	First day that protocol-specified IP is administered to the subject.
End of Treatment	The date of the last dose of cabozantinib therapy.
End of Treatment Visit	The date when safety assessments and procedures are performed after the last treatment, which should occur within 1 week (±3 days) after the last dose of cabozantinib.
End of Study	Either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol, whichever is later.
Follow-up Period	Follow-up period is the on-study time period after the EOT Visit. All subjects that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for disease recurrence. Follow up will continue approximately every 12 weeks (±2 weeks), until either one (1) year has elapsed since initiation of cabozantinib therapy (C1D1), death, withdrawal of consent, disease recurrence, or the study closes, whichever is the earliest. This will include a physical exam and imaging assessment. Thereafter, subjects who will be followed every 6 months (+/- 1 month) until 3 years have elapsed since initiation of cabozantinib therapy (C1D1), end-of-study, death, or withdrawal of consent, whichever is earliest. This evaluation may be made by review of publicly available information, record review and/or telephone contact.
Primary Analysis	For this study will occur once all data for primary and secondary endpoints is collected.
Efficacy Analysis Dataset	This includes all subjects treated with at least one dose of cabozantinib at the recommended phase 2 dose, concurrently with neoadjuvant radiation therapy.
Full Analysis Set	All enrolled subjects who receive at least 1 dose of cabozantinib (treated population). Subjects enrolled to Phase 1 who withdraw for reasons other than toxicity during the DLT Period will be considered not evaluable and will be replaced.

Per-protocol Analysis Set	All enrolled subjects who do not have any prospectively defined protocol violations. Subjects enrolled to Phase 1 or Phase 2 who are unable to tolerate cabozantinib monotherapy will not be considered evaluable for the Phase 1 or 2 component of the study and will be replaced. Subjects enrolled to Phase 1 who withdraw for reasons other than toxicity during the DLT Period will be considered not evaluable and will be replaced.
Progression-free survival	The time from the first dose date to the first observation of a disease progression or death due to any cause.
Overall survival	The time from the first dose date to the date of death due to any cause.

1. INTRODUCTION

1.1. Soft Tissue Sarcoma

1.1.1. Epidemiology

Soft-tissue sarcomas (STS) are mesenchymally derived cancers, with an estimated incidence of 13,040 new cases and 7,370 deaths in the United States in 2018[1]. Their impact is made greater by the relatively young age population affected by them: this magnifies the impact of these diseases in terms of years-of-life lost versus more common cancers affecting older subjects. STS are also characterized by great heterogeneity: at least 173 histologic entities are classified as STS[2]. The combination of these factors has hindered progress in the management of these conditions. Sarcomas remain an underserved area in oncology, as recognized by the National Cancer Institute's "Roadmap for Sarcoma Research"[3].

Soft tissue sarcomas are the subject of a staging system proposed by the American Joint Commission on Cancer[4]. This incorporates data regarding the tumoral grade (a measure of proliferative rate), tumor size, tumor depth, presence of nodal involvement, and presence of distant metastases. These data yield a staging classification from I (earliest disease) to IV (most advanced). Long-term survival segregates strongly by stage, from 90% 5-year survival for those with stage I disease, to less than 20% for those with stage IV disease.

1.1.2. Standard Treatment

The therapy of non-metastatic sarcomas is dominated by surgery. In certain cases, definitive radiation therapy may be used, such as in subjects who are not candidates for surgery, or for whom the cosmetic or functional results of surgery are unacceptable. Surgery may be supplemented by adjuvant or neoadjuvant radiation therapy[5]. For certain subtypes of sarcomas (osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma), the use of chemotherapy, administered prior to or after definitive local therapy with surgery or radiation, has demonstrated survival benefits. For most other types of sarcomas, the benefits of chemotherapy are unclear[5].

For unresectable or metastatic STS, treatment is palliative[5]. Systemic chemotherapy remains the backbone of treatment. Surgery and/or radiotherapy may be useful to relieve symptoms, or, in a limited number of cases with uni- or oligo-metastatic disease, to provide definitive control. In subjects with unresectable disease, the life expectancy is limited, with median survival of approximately 12-18 months[6,7].

In treatment of primary disease, the surgical status of the tumoral margins (the presence of viable tumor at the edge of the resection specimen and the distance from the resection margin to the tumor) is an important indicator of outcome. Several systems exist for classifying the marginal status of tumors. One of the more widely used classifies tumor resection status into R0 (complete resection of grossly/macroscopically evident tumor, with no evidence of residual microscopic disease at the margins of resection); R1 (complete resection of grossly/macroscopically evident tumor, but with microscopically evident disease at the margins of resection); and R2 (gross/macroscopically evident disease remains after attempted resection).

Marginal status is a key factor in the primary treatment, with positive margins being associated with increased risk of local recurrence and sarcoma-specific death[8]. Risk of distant metastasis of disease is not, however, determined by the extent of surgery, as demonstrated by a study of amputation for primary treatment of extremity sarcomas[9]. In multivariable Cox analysis, the probability of distant metastasis was determined by tumor size and histologic grade, rather than the type of local surgery (amputation versus limb-sparing procedure) undertaken to control the primary tumor. Limb-sparing procedures lead to improved functional outcomes versus amputation, but do not alter anticipated survival[10].

1.1.3. Use of radiotherapy in adjuvant and neo-adjuvant therapy

While the traditional approach to soft tissue sarcoma surgery was amputation (in the extremities) or radical surgery in other locations, more conservative approaches, such as limb-sparing approaches in STS of the extremities, have been adopted in recent decades[11,12]. This has been facilitated by the widespread adoption of combined modality therapy, in which subjects with resectable or potentially resectable disease receive combination therapy with both surgery and radiation therapy. Radiation therapy to the resection site may be administered post-operatively (known as “adjuvant” therapy”) or pre-operatively (known as “neoadjuvant” therapy).

No clear difference in efficacy is apparent between neoadjuvant and adjuvant use of radiotherapy[11,12,13,14]. However, pre-operative approaches allow use of lower doses of radiotherapy and smaller radiation fields[15]. While associated with higher rates of complication in subsequent tumor surgery wound healing, pre-operative therapy yields lower rates of long-term complications attributable to radiation therapy[16]. This observation is consistent with the known radiobiology of late radiation toxicity, which exhibits a threshold effect[17]. Small increases in radiation dose may be associated with marked increases in toxicity. An increase in dose from a total of 50 Gy typically given neoadjuvantly to 60-66 Gy administered adjuvantly may explain the increase in late toxicity with adjuvant radiotherapy[14,15,18.]

Two randomized trials comparing adjuvant (post-operative) radiation therapy to no adjuvant therapy have been reported[19,20]. In one study, a limb-sparing surgical procedure combined with adjuvant radiotherapy was compared to amputation of the affected extremity[19]. All subjects also received post-operative chemotherapy. This was administered concurrently with radiotherapy in those undergoing limb-sparing procedures. Local recurrence rates at the site of resection were higher in the group undergoing limb-sparing procedure (80% vs 0% at 5 years), although the study was quite small, with only 43 subjects enrolled. No difference in disease-free or overall survival was reported.

The second study randomized subjects undergoing a limb-sparing procedure to receive adjuvant radiation therapy (n=70) or no additional local therapy (n=71) [19]. For those with high histological grade, chemotherapy was administered concurrently with radiation. Local recurrence rates were suppressed, irrespective of histologic grade, with overall local recurrence of 1% in those treated with post-operative radiotherapy versus 24% in those not receiving radiotherapy. In the subset with high-grade tumors, no difference in metastatic disease-free or overall survival was evident based on radiotherapy assignment status.

These studies have some limitations[19,20]. Both studies had relatively small sample sizes, especially the earlier study enrolling only 43 subjects, and both included chemotherapy in addition to post-operative radiotherapy. Local control was superior in both studies when radiation was included. No survival difference was observed based on administration of radiotherapy, implying that local control did not necessarily determine survival. The possibility of synergism between chemotherapy and radiation therapy was not addressed, nor were issues of toxicity. Neoadjuvant radiotherapy has not been compared to surgery alone.

The combination of surgery with either post-operative or pre-operative radiation therapy, the latter being the subject of this proposal, is quite effective in achieving local control of disease. One randomized study compared pre- and post-operative radiotherapy in treatment of extremity soft tissue sarcomas, with the primary endpoint of toxicity[21]. Among the 186 subjects evaluable for secondary efficacy measures, there was no difference in rate of local control, development of regional/distant relapse, and progression-free survival (log rank p=0.70, 0.79 and 0.83, respectively). Survival for post-operatively treated subjects was inferior (median follow-up=3.3 year; 85% alive pre-operative vs. 72% post-operative, log rank p=0.0481). This was due to an increased number of deaths due to sarcomas and to non-malignant causes in the post-operative group.

A large retrospective analysis of 1225 sarcoma subjects treated over 39 years at a single major center supports these observations[13]. Neither treatment sequence with respect to radiation therapy and surgery nor receipt of adjuvant chemotherapy was associated with local control, metastatic recurrence, disease-free survival, or disease-specific survival. Tumor size and tumor grade were associated with all three of these efficacy outcomes, with large, high-grade tumors being unfavorable.

1.1.4. Use of chemotherapy in adjuvant and neo-adjuvant therapy

Administration of systemic chemotherapy in the primary treatment of STS could have several theoretical benefits. First, chemotherapy may have a direct effect on the existing primary tumor, allowing complete resection with negative margins (an R0 resection). The ability to achieve a negative marginal status is independently associated with local control, disease-free survival and disease-specific survival[8,13]. Second, chemotherapy may be able to eradicate micrometastatic disease prior to it becoming clinically apparent (and generally ineradicable with current systemic therapies). This is perhaps best exemplified by the experience with sarcomas of childhood, osteosarcoma, Ewing's sarcoma and rhabdomyosarcoma[22]. Finally, systemic therapy, given during or in the vicinity of radiation therapy, may enhance the effects of radiation therapy.

The use of peri-operative chemotherapy has been assessed in a number of randomized trials, which have been the subject of meta-analyses[23,24]. Specifically, these analyses include randomized trials employing anthracycline-based chemotherapy, primarily doxorubicin. Doxorubicin was administered alone, or in combination with other chemotherapy agents. In both analyses, anthracycline-based chemotherapy was associated with improvement in risk of local, distant, and overall relapse. Neither analysis indicated a survival benefit associated with doxorubicin therapy. The analysis of Pervaiz and colleagues indicated that the combination of

doxorubicin and ifosfamide appeared to be associated with a survival benefit, estimated at an 11% reduction in risk of recurrence[23].

A large study of adjuvant therapy in soft-tissue sarcomas with doxorubicin and ifosfamide was recently reported[25]. This study enrolled 351 subjects. Neither relapse-free nor overall survival was improved by administration of chemotherapy. Subgroup analysis suggested benefit in those with large, high-grade tumors. An earlier randomized trial from the Italian Sarcoma Group suggested that subjects with large, high grade tumors might benefit from peri-operative chemotherapy[26]. Participation was limited to those subjects with tumors at least 5 cm in maximal dimension and high histologic grade. This study demonstrated an improvement in disease-free survival at two years, the primary endpoint of the study (72% chemotherapy versus 45% control, p=0.003). Although an initial survival benefit was reported, this secondary outcome was not maintained with continued follow-up[27].

A retrospective study of French sarcoma subjects also identified tumor grade as a key factor in identifying benefit from adjuvant chemotherapy[28]. In multivariable Cox regression analysis, adjuvant chemotherapy was associated with improved survival in those with grade 3 (high), but not grade 2 (intermediate) tumors. Subject age, tumor size, and the presence of bone or neurovascular invasion were adverse in both grade 2 and 3 subjects, while anatomic site was a prognostic factor only in those with grade 3 tumors.

Only one randomized study of neoadjuvant chemotherapy has been reported[29]. This study enrolled subjects with high-risk sarcomas, defined as the following groups: those greater than 8 cm in maximal dimension; those of intermediate (grade II) or high (grade III) histologic grade; grade II/III locally recurrent tumors; and grade II/III tumors inadequately treated within 6 weeks of randomization and requiring further surgery. Eligible subjects were randomized to receive three pre-operative cycles of chemotherapy with doxorubicin and ifosfamide or no chemotherapy. After surgery, subjects with selected high-risk features received adjuvant radiation therapy.

This study was initially intended to allow feasibility assessment as part of a lead-in to a phase III assessment of the regimen. The primary endpoint of the proposed phase III was detection of a 15% improvement in 5-year survival. This would have a required enrollment of 269 subjects. The study was closed due to slow accrual after enrollment of 134 evaluable subjects (67 per arm). No improvement in disease-free or overall survival was observed. The authors concluded that the negative results of this admittedly underpowered trial argued against a major survival benefit for the regimen. Nevertheless, the results did not exclude the proposed 15% benefit that the phase III trial would have been powered to detect.

At least four factors have been cited as possible reasons for the failure of peri-operative chemotherapy to improve outcome in subjects with primary soft tissue sarcomas[27]. First, sarcomas represent a diverse group of related, but distinct, disease entities. This may increase population heterogeneity, reducing the power of trials. Combined with the reasonable size of the population available for participation, this may make detection of beneficial effects difficult with trials of the size that can reasonably be generated.

Second, the efficacy of local treatment with surgery and/or radiotherapy may also be improving over time, such as by the introduction of new radiotherapy techniques[27]. This may produce better primary treatment results, making assumptions regarding anticipated treatment outcomes less reliable. Power calculations based on earlier studies may therefore overestimate the relapse rate in the control group. This again can lead the trials to be underpowered for their endpoints.

Third, even using presently known criteria, there is heterogeneity with respect to the populations that are enrolled in trials[27]. Two trials and a retrospective cohort analysis cited previously suggested that larger, high-grade tumors are most likely to benefit from peri-operative chemotherapy[25,26, 28]. Host factors may also be important in determining outcome.

Fourth, most trials to date have been based on the use of anthracycline-based chemotherapy[27]. Although this class of drug has activity in sarcomas, there may be some sarcoma subtypes that are more or less sensitive to anthracycline effects[5]. Furthermore, sarcoma subtypes have been identified which demonstrate non-responsiveness to cytotoxic chemotherapy but were previously included in clinical trials. The exclusion of those subtypes, such as gastrointestinal stromal tumors (previously classified as a type of leiomyosarcoma), from trials of cytotoxic agents is important. Such sarcoma subtypes would not respond to cytotoxic agents and would statistically minimize differences between intervention and control groups. This further depresses the power of studies already struggling under the disease heterogeneity and relatively small pool of eligible subjects.

1.1.5. Use of chemoradiotherapy in adjuvant and neo-adjuvant therapy

Several studies have evaluated the use of neoadjuvant protocols combining pre-operative radiotherapy with chemotherapy. One study assessed a regimen of three cycles of pre-operative doxorubicin, ifosfamide and dacarbazine ("MAID") chemotherapy, with radiation therapy. Subjects with positive surgical margins received additional post-operative radiation, and subjects received an additional three cycles of post-operative MAID therapy[30]. Subjects enrolled had intermediate or high-grade (grade II or III) tumors at least 8 cm in maximal dimension. The treatment group of 48 subjects was compared to 48 historical controls, 12 of whom had received some form of adjuvant chemotherapy. Controls were subjects from the same institution who were matched with respect to tumor size, grade, age at diagnosis, and era of treatment.

While the primary endpoint was not explicitly stated, positive margins were observed in 15% (7/48) of the experimental treated subjects at the time of surgery versus 19% (9/48) of the matched controls. There was no difference in the rate of local control between the two groups. Distant metastasis-free, disease-free and overall survival however heavily favored the group treated with the MAID regimen. The non-randomized nature of the study implies that the results must be taken with caution.

This regimen was assessed again in a retrospective review of subjects treated more recently at the same institution[31]. No control group was presented in this analysis. Surgical margins were positive in 11% of resection specimens. Local and distant metastasis-free rate at 5 years was 91 and 64%. The authors attempted to identify factors associated with clinical outcomes using Cox

analysis but were unable to identify any factors in the dataset analyzed. Again, it is difficult to evaluate the value of this chemoradiotherapy treatment regimen due to lack of an adequate control group.

A prospective study from a single center evaluated pre-operative administration of doxorubicin, followed by a 10-day regimen of radiotherapy, in subjects to undergo sarcoma resection[32]. 75 subjects were enrolled in the study. Tumors were greater than 5 cm in 66% of the subjects and intermediate- or high-grade (grade II/III) in 71%. In 11% (8/75), surgical margins were positive for residual sarcoma. Subjects with positive margins had 5-year local control of only 50%, versus 97% for those with negative margins. Tumor grade and tumor stage (reflecting tumor size, depth and anatomic extent of involvement) were associated with the risk of death in multivariable Cox analysis. Wound complications occurred in 11 (15%) of the 75 subjects, including 3 subjects requiring re-operation. Like the studies above, interpretation of this one is hampered by lack of a control group.

A retrospective analysis examined results of 112 subjects treated with various neoadjuvant chemoradiotherapy regimens, neoadjuvant radiation, or with surgery alone[33]. All three treatment groups had high rates of margin negativity at the time of surgery (86-91%). For all subjects, there was no difference in rate of local control rate, distant metastasis free survival or overall survival. For those with primary tumors greater than 5 cm, overall survival was superior when the radiation-treated groups were compared to those treated only with surgery. However, only 7 subjects treated with surgery alone fell into this group.

A great deal of work has been undertaken, primarily using the anthracycline doxorubicin alone and in combinations (especially with ifosfamide), to evaluate the value of peri-operative cytotoxic therapy in soft tissue sarcomas. Use of this drug in peri-operative setting is problematic. While this drug is among the most active as monotherapy for sarcomas, it can cause a dose-dependent cardiomyopathy[5]. This limits the lifetime dose of the drug, as excessive amounts can cause treatment-refractory heart failure. Doxorubicin can also be associated with enhancement of radiation-associated skin toxicity[34]. In the absence of proven peri-operative benefit, use of doxorubicin alternatives would be sensible: this would reserve the agent for treatment of metastatic disease in those later developing metastatic disease and avoid the risk of cardiotoxicity in the subjects who did not have recurrent disease. Further, the results cited earlier indicating that tumoral biology is a key determinant of outcome suggest that agents exploiting sarcoma and radiation biology might be very desirable to explore in combination regimens of radiotherapy and systemic therapy.

Even if a subject is ultimately cured of the condition, treatment can have lifelong impact. Surgery remains the mainstay of treatment. Due to the relatively advanced condition that subjects often present with, surgery to render subjects disease-free is often cosmetically and functionally disfiguring. While rehabilitation is a key component of the treatment process, it cannot entirely solve the deficits consequent to proper sarcoma treatment.

Radiation therapy (RT) is a critical component of optimal sarcoma therapy. While occasionally used as definitive therapy, RT is more often used in coordination with surgery. Administered neoadjuvantly or adjuvantly, RT improves local control, and may allow tumors initially considered unresectable to be removed successfully. Although based on retrospective analysis,

recent data from one group suggest that peri-operative RT may also convey a survival benefit. This remains to be confirmed by additional analyses.

Surgery combined with radiation therapy provides excellent local disease control, providing definitive local control in about 85-90% of subjects. Results with high-risk tumors are less successful. "High-risk" tumors are those that are large (generally greater than 5 cm in maximal dimension), high histologic grade, and/or located in surgically challenging positions. Further, these therapies do not address the major reason for the ultimate failure of treatment in most cases: distant metastasis. Approaches to improve local control and simultaneously address distant treatment failure are needed. Systemic therapy approaches may be most useful for this.

Up to now, peri-operative systemic therapy of sarcomas has demonstrated clear benefit only in sarcomas associated with childhood: osteosarcoma, Ewing's sarcoma, and rhabdomyosarcoma. In these diseases, this therapy has both a local control and distant control advantage, leading to marked improvements in survival over local therapy alone. Similar benefits have not been demonstrated through use of current agents in the majority of STS.

Systemic, peri-operative therapy of most STS is reserved for those with high-risk tumors likely to pose difficulties in complete surgical extirpation. Combination therapy, typically with Adriamycin and ifosfamide (a regimen known as "AIM"), yields a significant response rate (estimated ORR about 26%). A treatment response may improve the quality of subsequent local therapy with surgery and radiation therapy. Whether such therapy impacts control of distant micro-metastatic disease is unclear.

AIM poses several problems in this setting:

i) While it has the highest documented response rate of any general STS regimen, it is still only 26%. Benefit can only be determined empirically. Thus, subjects must suffer the significant toxicity and logistical complexity of the regimen in exchange for, more likely than not, no discernible benefit.

ii) Adriamycin, an important component of the regimen, is incompatible with concurrent RT. Thus, any possible synergism to be derived from concurrent chemoradiotherapy is lost.

iii) Traditionally, peri-operative systemic therapy regimens have been derived from those with previously demonstrated activity in the metastatic setting. In the metastatic setting, a clear survival benefit for AIM therapy over Adriamycin monotherapy has been excluded. Clear evidence of survival benefits for Adriamycin-based, peri-operative systemic therapy is lacking, despite significant efforts. If such benefit exists, it is modest, at best.

iv) If effects on distant disease are a major focus of peri-operative systemic therapy, then Adriamycin monotherapy might be considered. However, response rates for Adriamycin monotherapy are only about 10%. Administration of Adriamycin monotherapy as an alternative to AIM in the

peri-operative setting would sacrifice one of the few documented benefits of multi-agent therapy with AIM: its increased response rate.

v) AIM is relatively toxic therapy. Subjects must be in good physical condition with good performance status and end-organ function to be considered for this therapy. Due to either disease status or co-morbidities, subjects may not be able to receive AIM therapy.

New approaches to peri-operative systemic therapy of STS are desperately needed.

1.2. Cabozantinib Background

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases (RTKs). It is provided as both capsules and tablets, but the two formulations are not interchangeable. Cometriq® (cabozantinib capsules, 140 mg) was approved by the United States Food and Drug Administration (FDA) on 29 November 2012 for the treatment of subjects with progressive, metastatic medullary thyroid cancer (MTC). On 21 March 2014, cabozantinib capsules were approved by the European Commission for the treatment of adult subjects with progressive, unresectable locally advanced or metastatic MTC. Cabometyx™ (cabozantinib tablets, 60 mg) was approved by FDA on 25 April 2016 for subjects with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy and by the European Commission on 09 September 2016 for the treatment of advanced RCC in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy.

The targets of cabozantinib include several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely MET (hepatocyte growth factor [HGF] receptor), vascular endothelial growth factor receptor 2 (VEGFR2, also known as KDR), AXL, and RET. Other recognized targets of cabozantinib include ROS1, TRKA, TRKB, TYRO3, MER, two additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely-related RTKs KIT and FLT-3. In vivo pharmacodynamic activity of cabozantinib against MET, VEGFR2, AXL, and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis and tumor invasiveness and metastasis.

In nonclinical toxicology studies of cabozantinib in rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, adrenal, and reproductive tract tissues, and secondary changes were observed in bone and pancreas. Cabozantinib tested negative in bacterial and mammalian cell genotoxicity assays in vitro. In reproductive toxicity studies, cabozantinib was embryotoxic in rats, produced fetal soft tissue changes in rabbits, produced fetal external malformations in rats, and decreased fertility in male and female rats. The metabolite present at highest concentrations in humans administered cabozantinib, EXEL-1644, was negative in an in vitro bacterial genotoxicity bioassay and caused no systemic tissue toxicity in rats. In a 2-year rat carcinogenicity study, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes. No clinical cases of pheochromocytoma have occurred to date. No carcinogenic

signal was observed in a rasH2 transgenic mouse model following cabozantinib dosing for 26 weeks.

1.3. Rationale for Combination of Cabozantinib with Radiation Therapy for High-Risk Soft Tissue Sarcoma of the Extremities

Given the established benefit of combination surgery and radiation therapy, systemic agents that increase the therapeutic index of radiotherapy in this relatively radio-resistant class of tumors would be desirable. This would be most important in cases where surgical excision is likely to be complex. In addition, agents that might treat pre-existing micro-metastatic disease would also be desirable.

Targeting the MET oncogene represents a strategy to achieve some of these goals in the sarcoma setting. MET dysregulation appears to be important and frequent in the STS pathogenesis, including in clear cell sarcoma[35], synovial sarcoma[36], leiomyosarcoma[37], pleomorphic sarcoma[37,38,39], rhabdomyosarcoma[40,41], angiosarcoma[38], epithelioid[36], Ewing's[42], and alveolar soft part sarcoma[43]. A phase II study was conducted with the MET inhibitor tivantinib, enrolling 47 subjects, primary with alveolar soft part sarcoma and clear cell sarcoma[44]. These diseases were targeted due to their association with microphthalmia transcription factor (MiTF). MiTF proteins lead to transcriptional activation of the MET gene. Among those with alveolar soft part sarcoma (n=27), median progression-free survival was 5.5 months. At least three studies are in progress to assess the activity of the MET inhibitor cabozantinib in advanced sarcomas (See ClinicalTrials.gov: NCT01755195, NCT01979393, NCT02867592). None of these seek to assess administration of the agent in combination therapy regimens or with neoadjuvant intent.

MET inhibitors also have documented radiosensitizing effects. Pre-clinical studies demonstrating such effects have been undertaken in non-small cell lung cancer[45,46] and prostate cancer[47]. Several mechanisms have been invoked for these radiosensitizing effects. These include: prevention of radiation-induced MET expression via the ATM-NFκB pathway, thereby preventing MET-mediated cell invasion; and anti-apoptotic effects[48] and down-regulation of the ATR-CHK1-CDC25 pathway[49]. Critically, the latter mechanism enhances radiosensitivity in p53-deficient cells, a common circumstance in sarcomas.

This trial will examine cabozantinib in combination with radiotherapy in the neoadjuvant setting. Because of concerns regarding potential toxicities of the combination of a multi-targeted tyrosine kinase inhibitor like cabozantinib with radiotherapy (such as fistula formation[50]), this study will be restricted to those with sarcomas of the extremities. Fistula formation has also been reported in studies of cabozantinib monotherapy[51]. The subject population to be enrolled will include all sarcoma subjects for whom neoadjuvant radiation to the extremities followed by surgical resection is planned.

The results of this study may help to determine whether concurrent administration of cabozantinib and radiotherapy is feasible, and whether there is preliminary evidence of activity in this class of tumors. Correlative studies will utilize specimens that are available pre-treatment, at the time of resection, and at recurrence, if recurrence occurs. These studies will investigate changes in molecular pathway activation during therapy; correlates of response or

lack thereof; and alterations in the immune microenvironment induced by this therapy. In addition, these studies will investigate radiomic metrics correlating with treatment response and relapse-free survival.

1.4. Rationale for Starting Dose Selection

Cabozantinib is presently approved for the treatment of advanced renal cell carcinoma that has progressed despite prior anti-angiogenic therapy and hepatocellular carcinoma (HCC) that has been previously treated with sorafenib[51]. Recommended dose is 60 mg daily. The drug is available in 20 mg tablets. Dose reductions to 40 mg and 20 mg daily are possible in response to toxicity in the currently approved setting. Below 20 mg daily, the drug is discontinued in the currently approved setting.

In this study, we propose to initiate treatment using a 21-day dosing schedule. The following dose levels will be assessed:

Dose Level	Daily Dose of Cabozantinib
-1	20 mg Daily
0	**40 mg Daily**
+1	60 mg Daily

Dose level +1 is the presently approved target dose of cabozantinib[51]. Based on the reported half-life of the drug (99 hours[51]), dose reductions below 40 mg daily would be reasonable to consider, if the initial 40 mg daily dosing is not tolerated. These would result in lower steady state concentrations of the drug. Since one of the primary endpoints is to assess the radiosensitizing effects of cabozantinib, it would still be reasonable to explore doses that are less than would be administered when the drug is being used as monotherapy, if the full dose is not tolerable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

- Phase I: To determine if administration of cabozantinib is safe and feasible in combination with neoadjuvant radiation therapy.
- Phase II: To assess the proportion of subjects alive and free of both local and distant disease recurrence (and progression after incomplete resection) one year after treatment initiation.

2.1.2. Secondary Objective(s)

- Rate of pathologic response.
- Rate of surgical excision with negative margins.
- Response rate (complete, partial, overall) of the combination therapy prior to surgery, as defined by RECIST 1.1 criteria.
- Pattern of and time to local vs. distant recurrences.
- Relapse-free and overall survival at various time points from study entry.
- Safety and tolerability of combined treatment regimen, including the rate of discontinuation during the cabozantinib monotherapy component of the study.

2.1.3. Exploratory Objective(s)

- Comparison of pre- and post-treatment specimens to identify changes in activation of molecular pathways associated with MET genetic profiles associated with treatment response and with relapse-free survival.
- Evaluation of pre- and post-treatment specimens for mutational status of signaling pathways, including MAP-Kinas and AKT/m-TOR pathways.
- Explore changes in the immune microenvironment induced by this neoadjuvant treatment, in comparison to matched specimens obtained from the University of Washington pathology archives.
- Radiomic studies to identify predictors of treatment response and relapse-free survival.

2.2. Endpoints

2.2.1. Primary Endpoints

- Phase I: Recommended Phase 2 dose of cabozantinib in combination with radiation
- Phase II: Rate of relapse at 12 months after treatment initiation.

2.2.2. Secondary endpoints

- Rate of pathologic response.
- Rate of surgical excision with negative margins.
- Response rate (complete, partial, overall) of the combination therapy prior to surgery, as defined by RECIST 1.1 criteria.
- Pattern of and time to local vs. distant recurrences.

- Relapse-free and overall survival at various time points from study entry.
- Safety and tolerability of combined treatment regimen.
- Rate of treatment discontinuation prior to neoadjuvant radiation therapy.

2.2.3. Exploratory endpoints

- Assessment of changes in activation of molecular pathways associated with MET genetic profiles associated with treatment response and with relapse-free survival.
- Assessment of mutational status of signaling pathways, including MAP-Kinas and AKT/m-TOR pathways.
- Assessment of changes in infiltration of immune cell subsets (CD4, CD8, myeloid) in the immune microenvironment induced by this neoadjuvant treatment, in comparison to matched specimens obtained from the University of Washington pathology archives.
- Radiomic studies to identify predictors of treatment response and relapse-free survival, when comparing pre-treatment imaging with imaging prior to surgery (after completion of radiotherapy and concurrent cabozantinib).

3. STUDY DESIGN

This is an open label, dose-finding, single-arm, prospective phase 1/2 study to identify the recommended dose of cabozantinib given orally, once daily, in a 21-day cycle, plus radiation therapy in subjects with high-risk soft tissue sarcoma of the extremities.

The study will be conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practices (GCPs).

3.1. Dose-finding Phase 1 Portion of the Study:

Dose levels of cabozantinib will be tested in cohorts of 3 subjects each using the 3+3 dose-finding design.

Table 1. Dose Levels of Cabozantinib

Dose Levels	Daily Dose of Cabozantinib
-1	20 mg daily
0	**40 mg daily**
+1	60 mg daily

In the dose-finding Phase 1 portion of the study, subjects will receive one week of therapy at the planned starting dosage as monotherapy prior to initiation of radiotherapy. Starting at Cycle 1 Day 8, subjects will initiate therapy concurrently with radiation therapy. Subjects enrolled to phase 1 who withdraw prior to initiation of radiation therapy for any reason, or during the DLT period for reasons other than toxicity will be considered non-evaluable and will be replaced. A window of + 7 days is permitted for initiation of RT in relation to C1D8. It is recommended that subjects begin treatment on a Monday due to radiation scheduling, however this is not mandatory. At least 7 days must pass between C1D1 and initiation of radiation therapy.

In the dose-finding Phase 1 portion of the study, dose levels of cabozantinib will be tested in cohorts of 3 subjects each using the 3+3 dose-finding design, with the starting dose of 40mg once daily, with potential dose escalation to 60 mg, or de-escalating to 20 mg daily. The daily dose of cabozantinib will not be increased to more than 60 mg per day. The DLT period will include all subjects enrolled to the phase 1 component of the study. The DLT period is defined as beginning on C1D8 and continuing until 28 days after completion of concurrent radiation therapy and cabozantinib. If no dose-limiting toxicity (DLT) is observed at the starting dose in the first 3 subjects, the next dose cohort would enroll subjects at 60 mg. If 1 DLT is observed any dose cohorts in the first 3 subjects, then additional 3 subjects will be enrolled at that dose level. If ≤1 of 6 subjects experience a DLT at the starting dose or higher, enrollment would continue to the next higher dose level. The first 3 subjects of each cohort must complete their DLT period prior to expanding the cohort to include additional subjects to ensure a second DLT is not seen in the first 3 subjects. If ≤1 of 6 subjects experience a DLT at the starting dose or higher, enrollment would continue to the next higher dose level.

If ≥2 subjects experience a DLT at dose level higher than the starting dose, enrollment will be discontinued for that dose cohort and the previous dose level would be declared the maximum

tolerated dose (MTD). If ≥2 subjects experience a DLT at the starting dose of 40 mg once daily (and any lower dose level), further enrollment at that dose level will be discontinued and cabozantinib will be reduced to the next planned dose level.

If a subject is considered Not Evaluable due to withdrawal for reasons other than toxicity during the DLT Period, they will be replaced.

The MTD of cabozantinib is the highest dose level at which ≤1 of 6 (or 0 out of 3) subjects experienced a DLT, thus a target DLT rate of roughly 17%. It is possible that the MTD is not reached in this study (e.g., if no DLT observed in the first 3 subjects at 60 mg daily). Recommended Phase 2 dose (RP2D) is identified based of the totality of safety and efficacy data. Once the dose-finding portion of the study is concluded and RP2D is identified, subjects receiving a lower dose may be allowed to receive cabozantinib at the RP2D, based on the investigator judgment.

3.2. Dose Expansion Phase 2 Portion of the Study:

The dose-expansion Phase 2 will be conducted using an open-label, single stage design. Subjects enrolled in the Phase 1 dose-escalation component of the study at the RP2D level and meeting all inclusion/exclusion criteria for the Phase 2 component of the study will be included for efficacy and safety evaluation in the Phase 2 efficacy component of the study.

Subjects enrolled to the dose-expansion Phase 2 portion of the study will receive one week of cabozantinib monotherapy at the RP2D prior to initiating radiation therapy. Starting at Cycle 1 Day 8, subjects will initiate therapy concurrently with radiation therapy. Subjects enrolled to phase 2 who withdraw prior to initiation of radiation therapy will not be considered evaluable and will be replaced. A window of + 7 days is permitted for initiation of RT in relation to C1D8. It is recommended that subjects begin treatment on a Monday due to radiation scheduling, however this is not mandatory. At least 7 days must pass between C1D1 and initiation of radiation therapy.

3.3. Study Duration, End of Study, End of Treatment, End of Treatment Visit, Follow-up Period

The study is expected to take approximately 60 months from first subject enrolled to last subject follow-up, including approximately 36 months of enrollment period, an estimated 5 months of treatment (or until treatment is no longer tolerated).

End of Treatment (EOT) for a subject is defined as the date of the last dose of cabozantinib. End of Treatment Visit for a subject is when safety assessments and procedures are performed after the date of the last dose of cabozantinib.

30-Day Follow-Up for a subject is defined as 30 days (+/- 1 week) after the last dose of cabozantinib. This visit will include safety assessments.

Follow-up period is the on-study time period after the EOT Visit.

The End of Study (EOS) defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol, whichever is later.

4. STUDY POPULATION

4.1. Number of Subjects

Phase 1: Up to 12 subjects to identify the MTD, but the MTD may be reached with as few as 5 subjects. Subjects enrolled to Phase 1 or Phase 2 who are unable to tolerate cabozantinib monotherapy will not be considered evaluable for the Phase 1 or 2 component of the study and will be replaced. Subjects enrolled to Phase 1 who withdraw for reasons other than toxicity during the DLT Period will be considered not evaluable and will be replaced.

Phase 2: An anticipated 34 subjects will accrue in Phase 2 of study.

Assuming a 10% drop-out/non-evaluable rate, 44 total subjects would be accrued to the efficacy component for the study to yield 40 evaluable subjects. Subjects enrolled to Phase 2 who withdraw prior to initiation of radiation therapy will be determined to be not evaluable and replaced.

4.2. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all the following criteria are met:

1. Subjects, ≥18 years old, must have a histologically confirmed diagnosis of sarcomas of the extremities (which may include gluteal muscle involvement) for which neoadjuvant radiation therapy followed by surgical resection is a planned intervention.
    a. Subjects whose bowel cannot be completely protected from radiation exposure due to primary tumor location (e.g., proximal lower extremity) will be excluded.
2. Subjects must have one or more measurable target lesions by RECIST v1.1, assessed via CT scan or MRI.
3. At the time of study enrollment, subjects must have a tumor burden that is judged to be surgically resectable.
4. Subjects must have adequate organ function and blood chemistry and blood count parameters:
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 GI/L) without granulocyte colony-stimulating factor support in the last 28 days.
    b. White blood cell count ≥ 2500/mm^3 (≥ 2.5 GI/L).
    c. Platelets ≥ 100,000/mm3 (≥ 100 GI/L) without transfusion in the last 28 days.
    d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion in the last 28 days.
    e. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤ 3 x upper limit of normal (ULN).
        i. ALP ≤ 5 x ULN is permitted in subjects with documented bone metastases (Phase 1 only).
    f. Total bilirubin ≤ 1.5 x ULN (for subjects with Gilbert's disease ≤ 3 x ULN).
    g. Serum albumin ≥ 2.8 g/dl.
    h. Serum creatinine ≤ 2.0 x ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation:

Males: (140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)

Females: [(140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85

i. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol).

5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
6. Male or non-pregnant and non-breast feeding female:
    a. Females of child-bearing potential (FOCBP) must agree to use highly effective contraception without interruption from initiation of therapy and continue until 4 months (120 days) after last dose of study therapy. FOCBP must have a negative serum pregnancy test (β -hCG) result at screening and agree to ongoing pregnancy testing during the study, and at the end of study treatment. A highly effective method of contraception is defined as one that results in a low failure rate (that is, <1% per year), when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomized partner (APPENDIX 1 - WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION).
    b. Male subjects must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study (APPENDIX 1 - WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION).
7. Life expectancy of >3 months, as determined by the investigator.
8. Ability to understand and sign informed consent.
9. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

4.3. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Receipt of any type of cytotoxic, biologic, or other systemic anticancer therapy (including investigational) for the investigational diagnosis.
2. Receipt of any prior radiation therapy for the investigational diagnosis.
3. Known central nervous system (CNS) metastases.
4. Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel). Allowed anticoagulants are the following:
    - Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted.
    - Low-dose low molecular weight heparins (LMWH) are permitted.

- Anticoagulation with therapeutic doses of LMWH is allowed in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. Subjects with hemoptysis, central nervous system hemorrhage or gastrointestinal hemorrhage within the last 6 months prior to treatment are excluded.

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

    - Cardiovascular disorders:

        i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.

        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.

        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose. Uncontrolled serious medical or psychiatric illness.

    - Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

        i. The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.

        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose.

        iii. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.

    - Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 12 weeks before first dose.

    - Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.

    - Lesions invading or encasing any major blood vessels.

    - Other clinically significant disorders that would preclude safe study participation.

        i. Serious non-healing wound/ulcer/bone fracture.

ii. Uncompensated/symptomatic hypothyroidism.

iii. Moderate to severe hepatic impairment (Child-Pugh B or C).

6. Major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. Complete wound healing from major surgery must have occurred at least 30 days before first dose, and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
7. Corrected QT interval calculated by the Bazett's formula (QTc) > 480 ms per electrocardiogram (ECG) within 28 days before first dose of study treatment.
    - Note: If a single ECG shows a QTc with an absolute value > 480 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTc will be used to determine eligibility.
8. Pregnant or lactating females.
9. Inability to swallow tablets.
10. Previously identified allergy or hypersensitivity to components of the study treatment formulations.
11. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy.
12. Concurrent use of medications (especially those interacting with CYP3A417) that potentially interact unsafely with cabozantinib which cannot be discontinued or substituted
13. Subjects with a sarcoma which has other, defined treatments or biology distinctly different from those of soft tissue sarcomas in general. Including, but not limited to, Ewing's sarcoma, rhabdomyosarcoma, gastrointestinal stromal tumors, Kaposi's sarcoma, Wilms' tumor.
14. Transfusion of blood product or G-CSF support factor within the last 28 days.
15. Recent infection requiring systemic anti-infective treatment that was completed ≤14 days prior to enrollment (except for uncomplicated urinary tract infection or upper respiratory tract infection).

5. TABLE OF EVENTS

The schedule of assessments in Table 2 outlines the specific time points for study assessments.

Table 2. Schedule of Assessments

Assessments [a]	Baseline Screening [b]	Treatment Phase Cycle 1-3			Treatment Phase Cycle 4+	End of Treatment (EOT) Visit [d]	30 Day Safety Follow-Up[p]	Survival Follow-up
		D1	D8 [c]	D15 [c]	D1		(+/- 7 d)	
Informed Consent	X							
Medical History	X							
Hepatitis and HIV Screen [e]	X							
Urinalysis w/micro	X	X	X	X	X	X		
Urine Protein / Creatinine Ratio [q]	X							
TSH, Free T4	X	X			X	X		
Pregnancy Test [f]	X	X			X	X		
LVEF (echo or MUGA)	X							
12-lead ECG	X	X			X	X	X	
Physical Exam/ECOG	X	X	X	X	X	X	X	
Vital Signs, height, and weight [g]	X	X	X	X	X	X	X	
CBC/Diff/Blood Chem [e]	X	X	X	X	X	X	X	
Lipid Panel [m]	X	X			X	X		
Tissue Sample [n]	X[n]					X[n]		
Imaging [h]	X	Every 12 weeks (±2 week).						
Cabozantinib [i]		Daily						
Radiation Therapy [r]		Administered per SOC. Radiation therapy to initiate within +7 days of C1D8.						
AE/Con Med Assessment [j]	X	Continuous from C1D1 through 30-day follow-up.						
Long Term Follow-up [k]								X

[a] All treatment visits are allowed to occur in a window of ±3 days unless otherwise specified.

[b] Baseline screening visit will be done within 28 days prior to enrollment.

[c] Day 8 and Day 15 visit is only in Cycle 1-3. Cycle 4+ will have visits on Day 1 only.

[d] End of Treatment (EOT) Visit should be within 7 days of last study treatment (±3 days).

[e] Baseline HIV and Hepatitis screening to include HIV, HBV sAg, HBV cAb, and HCV Ab. See Table 3 for full Analyte Listing for CBC and chemistry panels.

[f] For all female subjects of childbearing potential (see Inclusion 6), a serum pregnancy test will be done at all indicated timepoints. Pregnancy tests conducted after screening will be recorded in the source documentation only.

[g] Height is measured only at screening. Vitals signs to include respiration rate, temperature, systolic/diastolic blood pressure, and pulse.

[h] Baseline scans should be done within 28 days prior to enrollment, preferably as close to C1D1 as possible. Repeat imaging should be completed every 12 weeks from C1D1 (+/- 2 weeks) for one year after initiation of protocol therapy based on the date of the C1D1 visit, or until disease recurrence/progression, withdrawal of consent, death, or end of study (whichever comes first) regardless of missed or out of window doses. MRI may be used if CT is contra indicated for a subject. The same mode of imaging at screening must be used consistently throughout the study. Baseline imaging must include CAP and the affected extremity. If subjects do not have disease in the A/P, imaging moving forward after baseline may omit those areas.

[i] Cabozantinib will be administered daily. Subjects will complete a daily drug diary during treatment, to be reviewed on Day 1 of each cycle. Subjects with at least stable disease at the first post-RT imaging timepoint may continue to receive cabozantinib therapy for a maximum of 6 cycles, with treatment ending at least 28 days prior to any scheduled surgery, including dental surgery.

[j] Prior and concomitant medications, as well as any recent procedures should be documented at baseline. Prior medications/procedures include any medications or procedures completed ≤ 28 days prior to informed consent.

[k] Follow up will continue to monitor disease status by imaging assessment of, at minimum, CT Chest and the affected extremity approximately every 12 weeks (±2 weeks), until either one (1) year has elapsed since initiating cabozantinib therapy based on the date of the C1D1 visit, death, withdrawal of consent, disease recurrence, or the study closes, whichever is the earliest. Thereafter, subjects will be followed for survival every 6 months (+/- 1 month) until 3 years have elapsed since initiating cabozantinib therapy based on the date of the C1D1 visit, disease recurrence, end-of-study, death, or withdrawal of consent, whichever is earliest. This evaluation may be made by review of publicly available information, record review and/or telephone contact.

[m] Lipid panel should be fasting.

[n] Optional tissue samples will be collected from archival tissue. Pre-treatment tissue should have been collected within 12 months prior to initiating protocol therapy. End of Treatment tissue samples may be collected from surgical resection, if applicable. If there is no surgical resection for any reason, end of treatment tissue samples will not be collected. No biopsies will occur solely for research collection.

[p] 30 Day Follow-Up visit must occur 30 days from the date that the subject was last administered cabozantinib therapy. This visit has a window of +/- 7 days.

[q] If urine protein/creatinine ratio is abnormal, a 24-hour urine collection should be collected for repeat UPC Ratio.

[r] Radiation therapy may not be initiated prior to Cycle 1 Day 8. Radiation therapy must initiate within +7 days of the Cycle 1 Day 8 visit. All treatment plans for subjects that are not treated at the main study site will be submitted for review to the Sponsor-Investigator at least 1 week prior to the subject starting radiotherapy. It is recommended that outside treatment plans are received and reviewed as part of study eligibility and screening review. Review and approval of treatment plans for subjects receiving radiotherapy locally must be reviewed and approved by a radiation oncologist sub-investigator prior to initiation of radiotherapy.

6. PROCEDURES

6.1. Screening Evaluations

This study will be conducted at the University of Washington, Seattle, USA. Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related procedures are performed. The subject identification number will be assigned. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

Before subjects may be entered into the study, Exelixis requires a copy of the sites' written IRB/IEC approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable. A signed and dated Institutional Review Board (IRB) approved informed consent form (latest approved version) must be obtained from each subject prior to performing any study-specific procedures. All subjects or legally acceptable representatives must personally sign and date the consent form before commencement of study-specific procedures. Adverse events are to be collected for a subject once they have signed the informed consent.

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be obtained ≤28 days prior to enrollment, unless otherwise indicated. Baseline imaging should be obtained as close to initiation of protocol therapy as possible.

The following procedures are to be completed during the 28-day screening period, after signed informed consent has been obtained, designated in the Schedule of Assessments found in Table 2.

- Demographics (if allowed by local regulations, date of birth, sex, race, and ethnicity)
- Physical examination (including physical exam, medical/cancer history, ECOG performance status assessment)
- Prior/concomitant medications and procedures evaluation: all medications taken, and procedures completed within ≤28 days prior to signing of informed consent
- Vital signs (height [screening only], weight, temperature, sys/dias blood pressure, respiration rate, and pulse)
- 12-lead Electrocardiogram single tracing
- Left ventricular ejection fraction (LVEF, by echocardiogram or MUGA)
- Adverse event assessment
- Local Laboratory Assessments: blood chemistry, complete blood count (CBC) + differential, complete urinalysis with microscopic evaluation, urine protein/creatinine ratio (UPCR), pregnancy test (women of child-bearing potential), HIV, hepatitis B surface antigen, hepatitis C antibody, fasting lipids, thyroid function

- CT or MRI must be done within the 28-day screening period, but preferably should be done as close to enrollment as possible
- Archival tissue collection (optional)

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and/or in/on the electronic case report form (eCRF). Subjects should initiate treatment within 14 days of being enrolled to the study (28-day screening window from date of consent to enrollment date, plus up to an additional 14 days from enrollment date to C1D1 [total elapsed time from initiating screening to initiating therapy may not exceed 42 days]).

6.2. Treatment Period

A subject is considered on treatment on study day 1 when the IP, cabozantinib, is first administered. Subjects should initiate treatment within 14 days of being enrolled to the study. Cabozantinib is to be administered after all other protocol-specified pre-dose assessments have been performed during each visit that it is required. Subjects will continue therapy until completion of planned course of treatment, disease progression, or unacceptable AEs. Subjects should be instructed to immediately inform the principal investigator (PI) of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

6.2.1. Duration of Treatment

One week of neoadjuvant therapy with cabozantinib will be administered prior to initiation of radiotherapy. Initiation of radiation therapy should occur within +7 days of C1D8.

Typically, RT regimens for neoadjuvant treatment of STS are 5-6 weeks, though may vary based on institutional preference. Typically, an interval of 4-6 weeks exists between completion of RT and time of surgery. Subjects with at least stable disease at the first post-RT imaging timepoint may continue to receive cabozantinib therapy for a maximum of 6 cycles, with treatment ending at least 28 days prior to any scheduled surgery, including dental surgery.

6.2.2. Day 1 Assessment

The following assessments will be performed on Day 1 of each cycle, unless otherwise specified:

- Physical examination
- Concomitant medication and procedures evaluation
- Vital signs (weight, temperature, sys/dias blood pressure, respiration rate, and pulse)
- ECOG performance status
- CBC, differential
- Clinical chemistry panel including fasting lipid panel and thyroid function tests
- Serum pregnancy test (women of child-bearing potential only)
- ECG

- Urinalysis with microscopic evaluation
- Adverse Event assessment

All Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

6.2.3. Day 8 Assessment

The following assessments will be performed on Day 8 of Cycles 1-3 only:

- Physical evaluation
- Vital signs (weight, temperature, sys/dias blood pressure, respiration rate, and pulse)
- Urinalysis with microscopic evaluation
- Concomitant medication and procedures evaluation
- ECOG performance status
- CBC, differential
- Clinical chemistry panel (Day 8 assessments do not include fasting lipid or thyroid studies)
- Adverse Event assessment

6.2.4. Day 15 Assessment

The following assessments will be performed on Day 15 of Cycles 1-3 only:

- Physical evaluation
- Vital signs (weight, temperature, sys/dias blood pressure, respiration rate, and pulse)
- Concomitant medication and procedures evaluation
- ECOG performance status
- CBC, differential
- Urinalysis with microscopic evaluation
- Clinical chemistry panel (Day 15 assessments do not include fasting lipid or thyroid panel)
- Adverse Event assessment

Table 3. Analyte Listing

Chemistry	Hematology	Urinalysis	Other Labs
Sodium	WBC	Specific gravity	Pregnancy test (WOCBP only)
Potassium	RBC	pH	HIV
Bicarbonate	Hemoglobin	Blood	HBV sAg
Chloride	Hematocrit	Protein	HBV cAb
Total protein	MCV	Glucose	HCV Ab
Albumin	MCH	Ketones	Total Cholesterol
Calcium	MCHC	Microscopic	HDL
Glucose (fasting)	RDW		LDL
BUN	Platelets		Triglyceride
Creatinine	Differential:		TSH, Free T4
Total bilirubin	-Neutrophils		
Alkaline phosphatase	-Lymphocytes		
AST (SGOT)	-Monocytes		
ALT (SGPT)	-Eosinophils		
Amylase	-Basophils		
Lipase			
GGT			
Lactate Dehydrogenase			

6.2.5. Disease Assessment

Disease status will be assessed by CT or MRI scan. At baseline, imaging must include chest, abdomen, and pelvis (CAP), in addition to pertinent area of the extremity being treated (per institutional guidelines). If no disease is present in the abdomen/pelvis, these areas may be excluded from repeat imaging. Image preparation and evaluation will follow the specifications provided in the RECIST version 1.1. The same modality (CT or MRI) must be used at screening and throughout the study.

CT/MRI scans to be performed at the following frequency:

- ≤28 days prior to enrollment
- Followed by every 12 weeks (± 2 weeks) from C1D1 for 12 months after initiation of protocol therapy (based on the date of C1D1) until disease recurrence, withdrawal of consent, end of study, completion of protocol participation, or death – whichever occurs first.

An unscheduled scan for suspected disease recurrence/progression may be performed at any time at investigator discretion.

6.3. End of Treatment Visit Assessment

The EOT Visit is a safety follow-up visit that is to be performed within 7 days (+/- 3 days) after the last dose of cabozantinib. All efforts should be made to conduct this visit. If it is not possible to conduct the EOT Visit, documentation of efforts to complete the visit should be provided.

The following procedures will be completed at the EOT Visit as designated in the Schedule of Assessments in Table 2.

- Physical examination
- Concomitant medication and procedures evaluation
- Vital signs (weight, temperature, sys/dias blood pressure, respiration rate, and pulse)
- ECOG performance status
- CBC, differential
- Clinical chemistry panel including fasting lipid panel and thyroid function tests
- Serum pregnancy test (women of child-bearing potential only)
- ECG
- Urinalysis with microscopic evaluation
- Adverse Event assessment
- Archival tumor collection (optional, for subjects undergoing clinical surgical resection)

6.4. Follow-up Period for Survival and Initiation of Anticancer Therapy

Adverse events will be monitored through 30 days after the subject's last dose of investigational product.

6.4.1. 30 Day Follow-Up Visit Therapy

The 30 day follow up visit should be completed 30 days after the subject's last dose of cabozantinib therapy (+/- 1 week).

The following procedures will be completed at the 30 day follow-up visit, as designated in the Schedule of Assessments in Table 2.

- Physical examination
- Concomitant medication and procedures evaluation
- Vital signs (weight, temperature, sys/dias blood pressure, respiration rate, and pulse)
- ECOG performance status
- Clinical chemistry panel including fasting lipid panel and thyroid function tests
- ECG
- Adverse Event assessment

6.4.2. Long Term Follow-Up

Disease status and any subsequent anticancer therapy information status will continue to be monitored. All subjects that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase. Follow up will continue to monitor disease status approximately every 12 weeks (±2 weeks), until either one (1) year has elapsed since initiating cabozantinib therapy based on the date of C1D1, death, withdrawal of consent, disease recurrence, or the study closes, whichever is the earliest. This will include a physical exam and imaging assessment.

Thereafter, subjects will be followed for survival every 6 months (+/- 1 month) until 3 years have elapsed since initiating cabozantinib therapy based on the date of C1D1, disease recurrence, end-of-study, death, or withdrawal of consent, whichever is earliest. This evaluation may be made by review of publicly available information, record review and/or telephone contact.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Cabozantinib

7.1.1. Cabozantinib Dosage, Administration, and Schedule

Subjects will receive cabozantinib orally at a (starting) dose of 40 mg once daily.

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. 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 (e.g., if a subject is scheduled to take their dose at 8AM but misses it, they may take that missed dose any time before 8PM that day). If a subject vomits the dose after taking it, skip the dose and resume the next dose at the regularly scheduled time.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges, and their products should be avoided by subjects taking cabozantinib.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in 7.1.2 below.

Table 4 - Dose Levels for Cabozantinib

Dose Levels	Cabozantinib in mg
-1	20 mg daily
0	**40 mg daily**
+1	60 mg daily

7.1.2. Cabozantinib Dose Modification and Stopping Rules

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- The assigned starting dose for cabozantinib is 40 mg/day. The dose level may go to -1 as seen in Table 4. Further dose reductions beyond 20 mg daily are not permitted.
- Dose modification criteria for cabozantinib are shown in Table 5 and 6. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.

- Dose reductions or interruptions may also occur in the setting of lower grade toxicity if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued.

Dose interruptions for reason(s) other than treatment-related AEs (e.g., surgical procedures, upper respiratory infection, common cold) can be longer than 6 weeks per the discretion of the investigator.

Guidelines for the management of specific AEs are provided in Section 10.2.2.

Table 5 - Dose Modifications of Cabozantinib

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
60-mg cabozantinib oral qd*	40-mg cabozantinib oral qd	20-mg cabozantinib oral qd
40-mg cabozantinib oral qd	20-mg cabozantinib oral qd	No further dose reductions
20-mg cabozantinib oral qd**	No further dose reductions	No further dose reductions

**qd, once daily*
***Cabozantinib will be discontinued if a qd dose of 20-mg cabozantinib daily (minimum dose) is not tolerated*

Table 6 - Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE v.5.0 Grade	Recommended Guidelines for Management [a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.

Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 10.2.2.

[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

7.2. Radiation Therapy

Subjects will receive planned radiation as part of standard clinical care. The typical pre-operative radiotherapy dose will range from 5000 – 5040 cGy delivered with conventional fractionation (180 – 200 cGy per fraction). Other details of the radiation treatment, such as scheduling, are to be completed per institutional standard, at the discretion of the treating radiation oncologist. Radiation oncologists seeking further guidance in radiation planning (i.e. RTOG Consensus Sarcoma Target Volume Definitions) may refer to Appendix 2.

7.2.1. Simulation

Subjects will be immobilized in a safe and reproducible position to allow accurate delivery of radiotherapy. Understanding that the anatomic considerations for immobilization may vary depending on the location of the tumor, a variety of immobilization devices may be used including: vacuum-bags, Alpha Cradles, thermoplastic casts, customized molds. Aquaplast molds are recommended for reliable immobilization of distal extremities (hands or feet).

Positioning for immobilization will also be chosen to minimize radiation dose to non-target critical structures (for instance, a contralateral limb, torso, pelvis, head, etc).

CT Simulation will be performed for all subjects. When possible, appropriate diagnostic studies will be fused with the simulation CT to aid in target delineation (MRI T1 contrast-enhanced and T2 sequences, PET CT). Administration of IV contrast during simulation is optional at the discretion of the treating radiation oncologist. If IV contrast is administered, the density of the contrast should be overridden on the planning scan to provide more accurate dose calculation. Alternately a separate non-contrast scan can be obtained and used for dose calculation and planning.

7.2.2. Planning

Treatment will be delivered using 3D conformal radiotherapy, IMRT, or proton therapy. CT based planning is required. Target expansion guidelines are to follow protocol-defined parameters regardless of treatment modality.

IMRT is the preferred radiotherapy technique and anticipated to be the most likely treatment modality for extremity tumors that approximate critical structures (bone, lymphatics) or involve a significant portion of the circumference of the extremity (with IMRT utilized to reduce lymphedema risk).

For peripheral tumors that do not approximate critical structures, 3D conformal radiotherapy may be appropriate.

Proton therapy may be utilized for tumors that approximately critical structures that cannot be adequately protected using 3D conformal radiotherapy or IMRT.

Normal structure dose constraints:

Long bones (i.e. femur, radius, ulna, humerus, etc):

- Max dose 5500 cGy
- Mean dose < 3700 cGy.
- 5000 cGy line should not cover the entire circumference of a long bone unless the tumor encases said bone.

Femoral neck (right or left):

- Max dose 5000 cGy
- Mean dose < 4500 cGy

Every effort should be made to avoid treating the entire circumference of a limb to avoid risk of lymphedema.

Skin:

- Skin will be defined as a 5mm rind
- V2000 cGy (volume of skin receiving 2000 cGy) should be < 50%
- Max dose to the skin surface should be kept below 3000 cGy when possible.
- However, if the PTV extends close to the skin surface then PTV coverage will be prioritized over the skin dose constraint.
- The use of bolus is discouraged unless it is used to ensure coverage of tumor that invades to the surface of the skin (as in fungating tumors).

Other normal anatomy should follow standard QUANTEC dose constraints.

7.2.3. Prescription Guidelines

The targets will be specified as:

- GTV_5000 or GTV_5040: This is the gross tumor seen on CT as well as MRI T1 contrast enhanced images. Fusion of MRI and CT is recommended when possible.

- CTV_5000 or CTV_5040: This target includes the gross tumor and an additional margin to account for microscopic disease. This is defined as the GTV with a 3 cm longitudinal margin and 1.5 cm radial margin. All edema concerning for tumor involvement as identified on T2 weighted MRI should be included in the CTV. CTV borders can be trimmed at anatomic barriers to tumor spread such as bone, the edges of a muscle compartment, other fascial planes, or skin surface.
- PTV_5000 or PTV_5040: This is a 5mm expansion of the CTV to account for setup error and organ motion. The PTV does not extend beyond the skin surface. Daily image guidance (IGRT) through cone beam CT or kilovoltage imaging should be performed. If daily IGRT is not feasible, the use of an expanded PTV margin may be utilized on a per-subject basis per approval by the delegated radiation oncologist investigator.

PTV coverage guidelines (5000 cGy in 25 fractions):

- Minimum dose: 4650 cGy, and at least 95% of the PTV_5000 receives 4750 cGy
- Maximum dose: 5650 cGy, and no more than 15% of PTV_5000 receives > 5500 cGy.
- If PTV_5000 extends to the skin surface but there is no direct tumor involvement at the skin surface, then a PTV eval can be created as a copy of PTV_5000 subtracted 3mm beneath the skin surface. PTV eval can then be used to evaluate target coverage.

PTV coverage guidelines (5040 cGy in 28 fractions):

- Minimum dose: 4687 cGy, and at least 95% of the PTV_5040 receives 4788 cGy
- Maximum dose: 5695 cGy, and no more than 15% of the PTV receives > 5544 cGy.
- If PTV_5040 extends to the skin surface but there is no direct tumor involvement at the skin surface, then a PTV eval can be created as a copy of PTV_5040 subtracted 3mm beneath the skin surface. PTV eval can then be used to evaluate target coverage.

7.2.4. Treatment Delivery

Treatment will be delivered daily, typically Monday through Friday, over 25-28 fractions. Use of bolus is discouraged unless tumor directly involves the overlying skin surface.

7.2.5. Treatment Interruption and Dose Modifications

Treatment interruptions should be minimized. Any treatment interruption of > 3 days (not including holidays or weekends) must be reported to the Sponsor-Investigator.

7.2.6. Quality Assurance

Subject specific treatment plan QA measurements are required for IMRT and proton treatment plans. Secondary monitor unit calculations are required for all 3D conformal treatment plans.

All treatment plans for subjects that are not treated at the main study site will be submitted for review to the Sponsor-Investigator at least 1 week prior to the subject starting radiotherapy. It

is recommended that outside treatment plans are submitted and reviewed as part of study eligibility and screening. Review and approval of treatment plans for subjects receiving radiotherapy locally must be reviewed and approved by a radiation oncologist sub-investigator prior to initiation of radiotherapy. DICOM plan data is preferred but a printed or electronic copy of the plan document is also acceptable.

8. STUDY DRUG MANAGEMENT

8.1. Description of Study Drugs

8.1.1. Cabozantinib Packaging, Labeling, and Storage

At the study site, all study medication will be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) and inventoried in accordance with applicable Washington state and federal regulations.

Subjects will need to be instructed to store the IP at controlled room temperature, away from direct sunlight or appliances/items that give off heat and to not store the study drug in a hot, unventilated car for a long period of time.

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. The 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets, and doses of 60-mg will comprise of three 20-mg tablets. The components of the tablets are listed in the table below.

Refer to the Pharmacy Manual for details on storage and handling of cabozantinib.

Table 7 - Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w[a]
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes HPMC 2910/Hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

[a] weight fraction, expressed in percentage; HPMC, hydroxypropyl methylcellulose

8.1.2. Study Treatment Accountability

The investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding the date, lot number, and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all

unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

9. SAFETY

9.1. Adverse Events and Laboratory Abnormalities

9.1.1. Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can arise from any use of the drug (e.g. off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in this protocol. All untoward events that occur after informed consent through 30 days after the decision to discontinue study treatment are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits and includes the new onset of or increase in pain during this period.

Seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade and adverse event term will be defined by the current version of the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

For management of Adverse Events and Serious Adverse Events, refer to Section 10.

9.1.2. Serious Adverse Events (SAEs)

The SAE definition and reporting requirements are in accordance with the International Conference of Harmonisation (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is defined as any untoward medical occurrence that at any dose:

- Result in death;
- Is life-threatening (i.e., in the opinion of the investigator, the AE places the subject at risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires subject hospitalization or results in prolongation of an existing hospitalization;
    - Note: While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral

hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an ER visit for hematuria that results in a diagnosis of cystitis and discharge home on oral antibiotics). SAEs must, however, be reported for any surgical complication resulting in prolongation of the hospitalization.

- Results in persistent or significant disability or incapacity:
  - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):
  - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed. Examples of IMEs include 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 product dependency or product abuse.

9.1.3. Relationships to Study Treatment

Assessment of the relationship of the AE to the study treatment by the investigator is based on the following two definitions:

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship. Unrelated and unlikely related AEs should be documented as not related.
- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment. Possibly and probably related AEs should be documented as related.

9.1.4. Serious Adverse Event Reporting

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this must be documented on an SAE Report Form or in an electronic database and include the following:

(i) all SAEs that occur after starting cabozantinib and through 30 days after the decision to discontinue study treatment and

(ii) any SAEs assessed as related to study treatment or study procedures, from the time of informed consent, even if the SAE occurs more than 30 days after the decision to discontinue study treatment.

All SAEs that are assessed by the Sponsor-Investigator as related to drug or study procedure and all pregnancy/lactation reports regardless of outcome must be sent to Exelixis within one (1) business day of the Sponsor-Investigator's knowledge of the event. The reports must be sent to drugsafety@exelixis.com or fax 650-837-7392.

- The Sponsor-Investigator will perform adequate due diligence regarding obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business day of the Sponsor-Investigator's receipt of the new information. Upon Exelixis request, the Sponsor-Investigator will query for follow-up information.

9.1.5. Regulatory Reporting

The treating Sub-Investigator or Sponsor-Investigator will assess the expectedness of each related SAE. The current cabozantinib Reference Safety Information (Appendix K of the most recent approved Investigator Brochure) will be used as the reference document for assessing the expectedness of the event regarding cabozantinib. All serious, unexpected, suspected adverse drug reactions (SUSARs) will be reported to FDA by the Sponsor-Investigator as required by 21 CFR 312.32:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form).
- Exelixis, upon review, reserves the right to upgrade the Sponsor-Investigator assessment of an SAE for their own safety data and reporting purposes based on Exelixis assessment. This assessment will be communicated to the Sponsor-Investigator.
- The Sponsor-Investigator shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.
- The Sponsor-Investigator is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the sponsor of a clinical trial. The Sponsor-Investigator shall provide a copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.
- Exelixis will provide relevant product safety updates and notifications, as necessary.

9.2. Other Safety Considerations

9.2.1. Laboratory Data

All laboratory data required by this protocol and any other clinical investigations should be reviewed per standard clinical practice. Formal source documentation by the investigator of clinical significance for each abnormal laboratory value will not be collected. Grade 1 laboratory abnormalities will not be considered an Adverse Event unless a clinical intervention is taken to directly treat that lab abnormality, or if that lab abnormality results in a modification, delay, or discontinuation of study drug. All lab abnormalities Grade 2 or higher, regardless of clinical significance or intervention, will be captured as AE/SAE as appropriate, and recorded on the subject-specific adverse event log.

9.2.2. Pregnancy/Lactation Exposure

If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. Pregnancy (in subject or partner) or lactation exposure, although not an SAE, should be reported to Exelixis. Forms will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

9.2.3. Follow-Up of Adverse Events

Any related SAEs or any AEs assessed as related that led to treatment discontinuation, including clinically significant abnormal laboratory values that meet these criteria, ongoing 30 days after the decision to discontinue study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs still ongoing 30 days after the decision to discontinue study treatment. This does not apply to subjects who screen-fail. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

10. MANAGEMENT OF TOXICITY AND COMPLICATIONS

10.1. Guidelines for Management of Potential Adverse Events

Subjects will be monitored for AEs from the time of signing informed consent through 30 days after the date of the last dose of cabozantinib treatment. Subjects will be instructed to notify their physician immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.5.0.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption for cabozantinib.

10.2. Cabozantinib Related Toxicity

10.2.1. Dose-Limiting Toxicity

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of the safety profile of cabozantinib, refer to the cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (e.g., transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic AEs (e.g., deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks during treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

Determination and attribution of DLT are critical for determining the RP2D for this study. The DLT period will include all subjects enrolled to the phase 1 component of the study who receive cabozantinib in combination with radiation therapy. The DLT period is defined as beginning on C1D8 and continuing until 28 days after completion of concurrent radiation therapy and cabozantinib. Cabozantinib is anticipated to have systemic effects at sites distant from that receiving neoadjuvant radiation treatment. It may also interact loco-regionally at the site of radiation administration. However, as the objective of this study is to assess the impact of the cabozantinib/radiotherapy combination, only those effects in the region subject to radiation therapy are considered pertinent and will be considered DLT.

DLT are defined as any Grade 3 or greater AE, occurring in the region subject to radiation therapy, at least possibly related (per investigator attribution) to concurrent radiation therapy and cabozantinib therapy. Toxicities with a clearly identified and documented alternative explanation may be deemed non-DLT. Toxicities which are clearly identified and documented as related to cabozantinib therapy only or radiation therapy only may be deemed non-DLT. Only toxicities observed in the region subject to radiation therapy will be considered DLT.

Toxicities that are Grade 3 or greater that meet the following will always be considered DLT:

1. Occur after the initiation of concurrent cabozantinib/radiation therapy until 28 days after completion of radiation therapy;
    a. Involve the region of a subject's body that is receiving concurrent radiation therapy; and
    b. Are of a degree or character inconsistent with anticipated radiation effects.

Dose modification guidelines are outlined in Table 5, Table 6, and Table 8 for clinically significant toxicities that are deemed to have a relation to cabozantinib. Clinically significant toxicities that are deemed to have a relationship to radiation therapy only will be managed per standard institutional practice, additional information is available in Section 10.3.

10.2.2. Adverse Event Management Algorithms

Table 8 - Management Guidelines for Adverse Events Possibly Related to Cabozantinib

System/Organ	Adverse Event	CTCAE Grade v5.0	Dose modification Algorithm
Skin/Mucosa	Palmar-plantar Erythrodysesthesia Syndrome	Grade 1	If PPES is clinically insignificant and tolerable, cabozantinib may be continued at current dose, otherwise reduce by one dose level. Urea 20% cream twice daily and Clobetasol 0.05% cream once daily to be reassessed at least weekly. If PPES does not improve, or worsens after 2 weeks, follow intervention guidelines for grade 2.
		Grade 2	Cabozantinib treatment may be continued if PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
		Grade 3+	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

	Stomatitis and/or Mucositis	Any Grade	No change in cabozantinib treatment. Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for 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 and non-irritating cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.
Lab Abnormalities	Proteinuria	UPC Ratio ≤ 1 mg/mg (≤ 113.1 mg/mmol)	No change in cabozantinib treatment or monitoring
		For UPC Ratio >1 and <3.5 mg/mg (>113.1 and <395.9 mg/mmol)	Consider confirming with a 24-h protein assessment within 7 days No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein >2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg.

			Consider interrupting cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose interruption. Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
		UPC Ratio ≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24 h urine protein. If ≥ 3.5 mg/mg on repeat UPCR, continue to interrupt cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
		Nephrotic Syndrome	Discontinue cabozantinib.

	Elevated Aminotransferases (ALT/AST)	Grade 3 or 4	Interrupt cabozantinib treatment if ALT/AST elevations are also accompanied by progressive elevation of total bilirubin and/or elevations of coagulation tests. Transaminases should be monitored weekly if elevated to Grade 3+, in combination with total bilirubin and coagulation tests. Cabozantinib should be discontinued if hepatic dysfunction does not resolve to Grade 1 or better within two weeks of interrupting therapy. Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation (such as initial findings of cholestasis and obstructive disease, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury) can indicate drug-induced liver injury (DILI) and study drug should be permanently discontinued.
Cardiac Toxicity	Hypertension	Grade 2 (Systolic 140-159 or	Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications.

		Diastolic 90-99)	Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic If subject is symptomatic interrupt cabozantinib treatment
		Grade 3 (Systolic ≥ 160 or Diastolic ≥ 100)	Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per investigator discretion Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic Re-start cabozantinib treatment at the most tolerable dose only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
		Grade 4	Permanently discontinue cabozantinib
	Arterial Thromboembolic Events	Any Grade	Discontinue cabozantinib.
	ECG QTc (QT Corrected)	Grade 3	Perform two additional ECGs not less than 3 minutes apart, within 30 minutes after the initial ECG. If the average of the QTcF of the three ECGs

	Interval Prolonged		is >500ms, interrupt cabozantinib treatment. Symptomatic subjects should be hospitalized for a thorough cardiology evaluation. Regardless of symptom presentation, check magnesium, potassium, and calcium levels, correcting as clinically indicated. Repeat ECG triplicates hourly until average QTcF is <500ms, or otherwise determined by consultation with cardiologist or appropriate expert. Cabozantinib treatment should be interrupted for a minimum of 1 week following the return of the QTcF to <500ms. Cabozantinib treatment may be resumed at one dose level reduction. Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then may return to the regularly defined timepoints. If there are development of prolonged symptoms that are the result of QT interval prolongation or if a recurrence of QTcF prolongation occurs after reinitiation of treatment at a reduced dose, cabozantinib should be permanently discontinued.
		Grade 4	Discontinue cabozantinib.
Gastrointestinal Disorders	Diarrhea	Grade 1-2 lasting < 48h	Continue with study treatment and consider dose reduction Initiate treatment with an antidiarrheal agent (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) Dietary modifications (e.g., small lactose-free meals, bananas and rice) Intake of isotonic fluids (1-1.5 L/day) Re-assess after 24 hours:

			• Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval • Diarrhea not resolving: Continue/resume antidiarrheal treatment and hold cabozantinib therapy until diarrhea resolves to Grade 1 or Baseline
		Grade 2 lasting >48h, Grade 3	Interrupt study treatment Rule out infection (e.g., stool sample for culture) Administer antibiotics as needed (e.g., if fever or Grade 3-4 neutropenia persists > 24 h) Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist
		Grade 4	Permanently discontinue cabozantinib
	Fistula, perforations, bowel	Any Grade	For any grade perforation of any organ, GI leak, or any fistula, discontinue cabozantinib.

	obstruction, intra-abdominal and pelvic abscesses		For any grade bowel obstruction requiring medical intervention, delay cabozantinib until obstruction resolves completely, and then resume cabozantinib at the previous dose. For obstruction requiring surgery delay cabozantinib until full recovery from surgery, then resume cabozantinib at the previous dose.
Other	Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	Permanently discontinue cabozantinib
	Nervous System Disorders (Other)	Any Grade	Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.
	Non-CNS, Non-Pulmonary bleeding	Grade 2	Delay cabozantinib until ≤ grade 1, then resume with one dose level reduction.
		Grade 3 or 4	Permanently discontinue cabozantinib
	Fistula, perforations, bowel obstruction, or wound dehiscence	Any Grade	For any grade perforation of any organ, GI leak, or any fistula, discontinue cabozantinib. For any grade bowel obstruction requiring medical intervention, delay cabozantinib until obstruction resolves completely, and then resume cabozantinib at the previous dose. For obstruction requiring surgery delay

			cabozantinib until full recovery from surgery, then resume cabozantinib at the previous dose. For wound dehiscence requiring medical or surgical intervention discontinue cabozantinib. Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.
	Wound healing and surgery	Any Grade	Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place. Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.
	Hemorrhage	Any Grade	Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood counts and physical

			examination while on study. The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Subjects enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur. Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).
	Thromboembolic event	Any Grade	Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment. Low molecular weight heparins are the preferred management for thrombotic events. Oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

	Osteonecrosis	Any Grade	Osteonecrosis of the jaw (ONJ) occurred in <1% of subjects treated with cabozantinib. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib treatment. Advise subjects regarding good oral hygiene practices. Withhold cabozantinib treatment for at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold cabozantinib for development of ONJ until complete resolution.
	Infections and/or Infestations	Any Grade	Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (e.g., after myelosuppressive anticancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices. Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until adequate healing has taken place.
	Blood and Lymphatic System Disorders	Any Grade	Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

			Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.
	Fatigue	Any Grade	Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited.
	Weight Loss	Any Grade	Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a protocol.
	Electrolyte Disorders	Any Grade	Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

	Endocrine Disorders	Any Grade	Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.
	Angioedema	Any Grade	Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with attention to maintaining an open airway.
	Other Non-Hematologic Grade 3 or 4 Toxicity	Grade 3 or 4	For other grade 3 or 4 non-hematologic toxicity not described above, (excluding nausea, vomiting, and diarrhea; unless refractory to anti-emetics and/or antidiarrheals) and considered at least possibly related to treatment, delay cabozantinib treatment until toxicity improves to ≤ grade 1, then resume treatment with one dose level reduction.

10.2.3. Cabozantinib Dose Reinstitution and Reescalation

If the subject recovers from his or her toxicities to CTCAE v.5.0 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted as outlined in Table 5 and 6.

Subjects receiving a dose of 20 mg daily may be restarted at the same dose if deemed safe at the discretion of the Sponsor-Investigator or treating Sub-Investigator. Subjects unable to tolerate a dose of 20 mg daily should discontinue study treatment.

10.2.4. Dose re-escalation is not permitted. Overdose

Any overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting within one (1) business day to Exelixis.

10.3. Radiation Therapy Related Toxicity

The expected toxicities related to radiation therapy may vary in relation to the site of irradiation. The most commonly observed toxicities include fatigue (Grade 3), and skin toxicities (Grade 3) such as rash, color changes, burning, blistering, or desquamation. Skin toxicities should be managed by radiation-oncology staff utilizing standard of care protocols.

The radiation oncologist may list expected toxicities for a given radiation treatment prior to administration of radiation treatment in the subject's medical record. Strict prospective quality assurance of all radiation plans will be performed prior to initiation of radiotherapy, per institutional standards, to minimize risk of serious toxicity.

Toxicities of radiation should be treated according to standard institutional practices, including the prescription of steroids, if appropriate. Subjects will continue study treatment if steroids are used to treat radiation-associated toxicity.

11. CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, must be reported on the eCRF. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 11.2.

Concomitant therapies are to be collected from enrollment/randomization through the EOT Visit. Therapy name including indication, dose, frequency, route, start date and stop date will be recorded on each subject's CRF(s).

11.1. Permitted Medications and Procedures

The investigator must be informed as soon as possible about any medication taken from the time of screening until the 30 Day Follow-Up visit. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the CRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheas, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. WBC growth factors may be administered at the discretion of the investigator, consistent with institutional guidelines.

Extreme precaution must be taken with contraceptives (either combined or progesterone only), as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins.

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g., ASCO or ESMO guidelines).
- Bisphosphonates can be used to control bone loss or hypocalcemia if the benefit outweighs the risk per the investigator's discretion.
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- 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* at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 6 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.

- *Therapeutic doses of LMWH* after first dose of study treatment are allowed if clinically indicated (e.g., 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 10.2.2.
- 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 (e.g., due to kidney dysfunction).
- For restrictions on oral anticoagulants see Section 11.2.

Potential drug interactions with cabozantinib are summarized in Section 11.3.

11.2. Prohibited Medications and Procedures

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the study will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the Sponsor-Investigator and Exelixis can approve such use.

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Oral anticoagulants (e.g., 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 non-protocol systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

The following therapies should be avoided until study treatment has been permanently discontinued or until otherwise specified:

- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin.
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., 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, as this could significantly increase the exposure to cabozantinib.

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 11.3.

11.3. Potential Drug Interactions with Cabozantinib

Cytochrome P450: 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 area under the plasma concentration-vs-time curve (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 and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, 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. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% 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., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided 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.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) 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).

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest 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. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

12. STATISTICAL CONSIDERATIONS

12.1. Safety Analysis

The safety analysis set includes all treated subjects.

Safety and tolerability will be monitored through continuous reporting of treatment-emergent and TRAEs, AEs of special interest, laboratory abnormalities, and incidence of subjects experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of IP due to an AE. All AEs will be recorded by the investigator from the time the subject signs informed consent until 30 days after the last dose of IP. Adverse events will be graded by NCI CTCAE v5.0.

Physical examination, vital signs, laboratory assessments (e.g., serum chemistry, hematology), and ECOG performance status will be monitored. All SAEs (regardless of relationship to IP) will be followed until resolution or sequelae. Local laboratory analysis will be performed as per study schedule.

12.2. Efficacy Analysis

Assessment of the primary efficacy analysis will take place in real time. Based on anticipated accrual of 40 evaluable subjects, if 9 or more have relapsed or died due to any cause (unless clearly documented as unrelated to investigational diagnosis, e.g., car accident) at or before one year after cabozantinib initiation, then the study will be closed to further accrual, and data will simply be collected on the remaining subjects, as specified in the protocol.

12.3. Exploratory Analysis

Appropriate specimens will be collected in anticipation of the exploratory/correlative studies. Analysis will be undertaken once provision for conduct of planned analyses is made.

12.4. Sample Size Considerations

Phase 1: up to 12 subjects to identify the MTD, but the MTD may be reached with as few as 5 subjects.

Phase 2: For sample size determination, we assume the following:

- Null hypothesis: 1-yr relapse-free survival (local and distant) =75%
- Alternative hypothesis: 1-yr relapse-free survival (local and distant) =90%
- Alpha=0.1 (one-sided).
- Beta=0.1 (power=90%)

Total accrual=40 evaluable subjects.

Anticipate accrual of 6 evaluable subjects from phase I component of study. Therefore, 34 evaluable subjects to accrue in phase II portion of study. Subjects who withdraw for reasons other than toxicity during the DLT Period will be determined to be not evaluable and will be replaced.

Subjects are evaluated for efficacy assessment if they receive at least one dose of cabozantinib in combination with neoadjuvant radiation therapy.

Assuming a 10% drop-out/non-evaluable rate, 44 total subjects would be accrued to the efficacy component for the study to yield 40 evaluable subjects.

From the perspective of efficacy, this study is intended as a screening study of activity. Thus, avoiding a type II error (rejecting the proposed regimen as inactive, when it is an active regimen) is a major consideration. This study is not intended to provide definitive evidence of activity. Therefore, a type I error (false positive) is not considered as critical. For these reasons, we have chosen to increase the power of the study to 90% (minimizing type II errors), while relaxing constraints regarding type I. Specifically, we use a one-sided alpha of 0.10 for rejection of the null hypothesis. Use of a one-sided value is justified based on the high efficacy for *local* control of soft tissue sarcoma provided by the combination of surgery and neoadjuvant radiation therapy (~90%). It is not anticipated that distant disease control would be worsened by addition of cabozantinib to neoadjuvant radiation therapy.

An early stopping rule for accrual to the efficacy component of the study is to be undertaken. If 9 (nine) or more evaluable subjects are found to have died or demonstrated disease recurrence at or before 1 (one) year after cabozantinib initiation, then the efficacy component of the study will be discontinued. This assumes of a binomial probability for the primary endpoint, with a target probability of 0.90 for evaluable subjects to be alive and disease-free at one-year after initiation of cabozantinib therapy. When 9 subjects demonstrate failure with respect to the primary endpoint (disease recurrence or death from any cause), then the upper bound of the 95% confidence interval for the binomial probability distribution would no longer encompass the target probability of 0.90 (31/40=0.775, 95%CI:0.62-0.89). At this point, the study would be considered negative with respect to the primary endpoint, and further accrual will be discontinued.

12.5. Primary Analysis

This will occur once all data for primary and secondary endpoints is collected.

13. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

13.1. Discontinuation from Investigational Product or Study

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, any of the following conditions require discontinuation of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study
- Specific conditions described in the Management of Adverse Events Section 10.2.2;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the study and for 4 months after discontinuation of study treatment;
- Women who become pregnant or are breastfeeding;
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the principal investigator;
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;
- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator

13.2. Sponsor-Investigator Decision to Withdraw or Terminate Subject's Participation Prior to Study Completion

The Sponsor-Investigator can decide to withdraw a subject(s) from Investigational Product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Exelixis' Investigational Product and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism.

14. REGULATORY OBLIGATIONS

14.1. Informed Consent

The Sponsor-Investigator is responsible for preparing the informed consent document to be used at the study site. Updates to the template are to be communicated formally in writing from the investigator to Exelixis. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or the IP is administered.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

14.2. Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Exelixis before recruitment of subjects into the study and shipment of Exelixis IP.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Exelixis, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval [IRBs only]/renewal [IRBs and IECs] throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Exelixis.

This study is being conducted under a United States Investigational New Drug application.

14.3. Subject Confidentiality

The Sponsor-Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Exelixis.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For SAEs reported to Exelixis, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Exelixis (e.g., signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

14.4. Protocol Amendments

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the Sponsor-Investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (e.g., change in monitor or change of telephone number).

14.5. Termination of the Study

Both Exelixis and the Sponsor-Investigator reserve the right to terminate the study according to the study contract. The Sponsor-Investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Exelixis. At any time, the study may be terminated by the -Sponsor-Investigator, the FDA, the IRB, or by Exelixis. Should this be necessary, Exelixis and the Sponsor-Investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the Sponsor-Investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the Sponsor-Investigator shall cease enrolling subjects into the study and shall discontinue conduct of the study as soon as is medically practicable.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data Quality Assurance

Accurate and reliable data collection will be ensured by verification and crosscheck of the eCRFs against the investigator's records by the study monitor (source document verification) to the extent described the Fred Hutch/UW Cancer Consortium Data and Safety Monitoring Plan and the Sarcoma Group Standard Operating Procedure 005 *Clinical Trial Monitoring and Follow-Up* and by the maintenance of a drug–dispensing log by the investigator or designee.

15.2. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy; and the laboratories, as well as copies of CRFs or CD-ROM.

15.3. Data Management

Data will be collected via electronic medical record and subject shadow chart and entered into RedCAP. These data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.4. Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (in Table 2, the investigator can search publicly available records (where permitted) to ascertain survival status.

This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

15.5. Sample Storage and Destruction

Tumor samples collected according to the Schedule of Assessments in Table 2 can be analyzed for any of the tests outlined in the protocol, for any tests necessary to minimize risks to study subjects, and in any other method determined to be appropriate by the Sponsor-Investigator to evaluate a primary, secondary, or exploratory endpoint. Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study.

The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer; but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an

ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of cabozantinib.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the subject, the investigator is to ensure that any remaining blood or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed.

The Sponsor-Investigator is responsible for the destruction of the sample(s) at the request of the subject through the Investigator, at the end of the storage period, or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Study Monitoring

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

16.2. Audits and Inspections

In accordance with ICH GCP, this study may be selected for audit by the US Food & Drug Administration for inspection of site facilities (e.g., pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should understand that source documents for this study must be made available, after appropriate notification, to qualified health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

17. STUDY DOCUMENTATION AND RECORD-KEEPING

17.1. Investigator's Files and Retention of Documents

The Sponsor-Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) the investigator's study file, and (2) subjects' clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, any other records required under the Protocol, and other appropriate documents and correspondence.

Subjects' clinical source documents include the subjects' hospital/clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, electroencephalogram, X-ray, pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The investigator must keep these two categories of documents on file for at least the latest of (a) 2 years following the marketing application approval date for the study treatment in the indication being investigated, or (b) 2 years after the investigation is completed or discontinued, or (c) for a period of time consistent with local regulatory requirements, whichever is longest. After that period, the documents may be destroyed subject to local regulations.

17.2. Source Documents and Background Data

Upon request, the Sponsor-Investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

17.3. Case Report Forms

For enrolled subjects, all and only data from the procedures and assessments specified in this protocol and required by the eCRFs should be entered on the appropriate eCRF. Data from some procedures required by the protocol, such as physical examinations and laboratory results, will be recorded only on the source documents and will not be transcribed to eCRFs. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care and may not be required for eCRF entry.

For each subject enrolled, the eCRF must be completed and signed by the PI or authorized delegate from the study staff.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the eCRFs and in all required reports.

18. PUBLICATIONS

The Sponsor-Investigator holds the primary responsibility for publication of the study results; provided that the Sponsor-Investigator will provide Exelixis with a copy of any proposed publication or release: (a) for abstracts, slide presentations or posters, at least five (5) business day prior to submission (in the case of abstracts) or first public presentation (in the case of slide presentations and posters); and (b) at least thirty (30) days in advance of first submission and each subsequent submission in the case of manuscripts and also comply with any provisions regarding publication that are agreed to between the University of Washington and Exelixis, Inc. in the Clinical Trial Agreement related to this study.

Public presentation of data in any form will be thoroughly de-identified to ensure confidentiality.

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20. APPENDIX 1 - WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

20.1. Definitions

20.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.

20.2. Contraception Guidance for Females of Childbearing Potential

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 4 months after last treatment. Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of < 1% per year when used consistently and correctly.[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable

Highly Effective Methods That are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of

Ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in related to the duration of the study and the preferred and usual lifestyle of the participant.
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests as specified in study calendar.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

[a] *Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.*

Less Than Highly Effective Contraceptive Methods That are User Dependent

Failure rate of > 1% per year when used consistently and correctly.
- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

20.3. Contraception Guidance for Males of Childbearing Potential

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 4 months after last systemic dose.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 4 months after last systemic dose.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 4 months after last systemic dose.

- Refrain from donating sperm for the duration of the study treatment and for 4 months after last systemic dose.

21. APPENDIX 2 – GUIDELINES REGARDING RADIATION THERAPY

Radiation needs may vary considerably from subject to subject. There is significant flexibility regarding potential radiation regimens.

Radiation needs may vary considerably from subject to subject. Treatments for an individual subject may deviate from the standard approach described below at the discretion of the radiation oncology investigator.

Tumors targeted for treatment with radiotherapy should be discussed with Dr. Ed Kim, co-investigator and radiation oncologist for this trial prior to initiating therapy. A gross tumor volume (GTV) should be delineated based on radiographic appearance on radiation planning CT and relevant diagnostic imaging. Clinical Target Volume (CTV) should include the GTV and sites of potential tumor involvement based on consensus guidelines (i.e. RTOG Consensus Sarcoma Target Volume Definitions), adjusted per discretion of treating physician. For extremity sarcomas, the CTV should include the "reactive zone" as seen on T2-weighted MRI sequences. Longitudinal margins of 3cm and radial margins of 1.5 cm will be utilized in most cases, per institutional standards (adjusting for normal barriers to tumor growth such as bone, muscle compartments, and fascial planes). A planning target volume (PTV) of at least 5mm is recommended to account for tumor motion. The PTV expansion may be individualized based on the anatomic location, subject immobilization, and (if relevant) motion-management strategy chosen.

Image guidance (typically cone-beam CT) may be utilized prior to each treatment to verify accurate targeting and sparing of normal tissue.

The RTOG Contouring Atlas can be found here:
https://www.rtog.org/CoreLab/ContouringAtlases/RTOGExtremitySoftTissueSarcomaAtlas.aspx