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The world's childhood cancer experts

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

April 8, 2019

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

Dear Ms. Kruhm,

The study committee for **ARST1321**, *Pazopanib Neoadjuvant Trial in Non- Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS): A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib (NSC# 737754, IND# 118613)*, has provided Amendment 7 for CTEP review.

This amendment is being submitted in response to a Request for Amendment (RA) from Dr. Fernanda Arnaldez dated February 20, 2019. In this amendment, the CAEPR has been migrated from CTCAE version 4.0 to 5.0 terminology. There is no new or modified risk information for pazopanib. Revisions to the protocol and consent documents are detailed in the pages below.

The ARST1321 study team looks forward to approval of this amendment. Please contact me with any questions or concerns.

Sincerely,

Tiffany Liu, MS, MA, Protocol Coordinator (for)

Aaron Weiss, DO, ARST1321 Study Chair
Douglas Hawkins, MD, COG Soft Tissue Sarcoma Disease Chair
Peter Adamson, MD, Children's Oncology Group Chair

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

In accordance with the above discussion, the following specific revisions have been made to the protocol.

#	Section	Page(s)	Change
1.	Title Page	1	Updated version date and amendment number.
2.	Study Committee	8	Updated study committee member's contact information
3.	6.1	82-86	Inserted revised CAEPR for pazopanib (Version 2.8, January, 21, 2019). This CAEPR has been migrated from CTCAE version 4.0 to 5.0 terminology. There is no new or modified risk information for pazopanib.

Activated: 07/07/14
Closed:

Version Date: 04/08/2019
Amendment: #7

CHILDREN'S ONCOLOGY GROUP and
NRG ONCOLOGY

ARST1321

Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS): A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib (NSC# 737754, IND# 118613)

An Intergroup NCTN Phase II/III Study

This trial is part of the national NCI Clinical Trials Network (NCTN) program which is sponsored by the National Cancer Institute (NCI). The trial will be conducted by the network of NCTN researchers, led by the COG and NRG Oncology

NCI Supplied Agent: Pazopanib (NSC# 737754, IND# 118613)
IND sponsor for Pazopanib: DCTD, NCI

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NRG / NRG Oncology
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG
Canadian Cancer Trials Group

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT	NSC#	IND#
Dexrazoxane	169780	Exempt
Doxorubicin	123127	Exempt
Filgrastim	614629	Exempt
Ifosfamide	109724	Exempt
Mesna	113891	Exempt
Pazopanib	737754	118613
Pegfilgrastim	725961	Exempt

IND sponsor for pazopanib; DCTD, NCI

SEE SECTIONS 14 AND 15 FOR SPECIMEN SHIPPING ADDRESSES.

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ABSTRACT

The non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise 4% of all childhood malignancies and less than 1% of all adult malignancies. Intermediate- and high-risk NRSTS account for about 40% of the population. Despite multi-modality therapy, survival rates for these patients are approximately 50% and 15%, respectively. The chemotherapy backbone of ifosfamide and doxorubicin (ID) is considered to be the most active and among the most commonly used regimens in NRSTS but radiographic response rates and outcomes remain poor for those with large, high-grade tumors and those with unresectable or metastatic disease. Further, the lack of homogeneous chemotherapy sensitivity across all subtypes suggests a more histologic-specific approach to NRSTS treatment may be needed.

Certain tyrosine kinases have been found to be expressed and dysregulated in a range of NRSTS subtypes. Multi-targeted tyrosine kinase inhibitors (TKIs), such as pazopanib, have the ability to target multiple signaling pathways that may be disrupted in many NRSTS. The therapeutic approach for this study builds on ARST0332 and RTOG 0630 by adding pazopanib to standard chemotherapy and radiotherapy. This study will first determine the feasibility of adding a TKI in combination with radiation or chemoradiation in pediatric and adult patients newly diagnosed with unresected intermediate- and high-risk NRSTS. Subsequently, it will compare the rates of near complete pathologic response (> 90% necrosis) of (1) preoperative pazopanib plus chemoradiation versus preoperative chemoradiation alone for potentially resectable > 5 cm, Grade 2 or 3 intermediate to high risk chemotherapy-sensitive adult and pediatric NRSTS, and (2) pazopanib plus preoperative radiotherapy versus preoperative radiotherapy alone for potentially resectable intermediate to high risk adult and pediatric NRSTS. It has not been well established whether a significant change in the size of the tumor mass, as determined by RECIST, is a meaningful surrogate of patient outcome in NRSTS. Treatment-induced pathologic necrosis may be a more reliable surrogate of response and predictor of outcome, particularly with the use of targeted therapies, and will be the primary response endpoint used for this study.

This joint study represents a unique and unprecedented opportunity to advance the treatment of both pediatric and adult NRSTS. The study will evaluate the feasibility of standardizing the use of preoperative radiotherapy, with high quality MRI image fusion, consensus clinical target volume definition, and accurate delivery using image guidance technology (IGRT) across both pediatric and adult NRSTS. The study will also benefit from a larger number of NRSTS patients available to explore a common biological targeted therapy in both pediatric and adult populations. The correlative studies will collect the largest sample of pediatric and adult NRSTS to understand the similarities and differences between pediatric and adult NRSTS and potentially identify other actionable targets for future development.

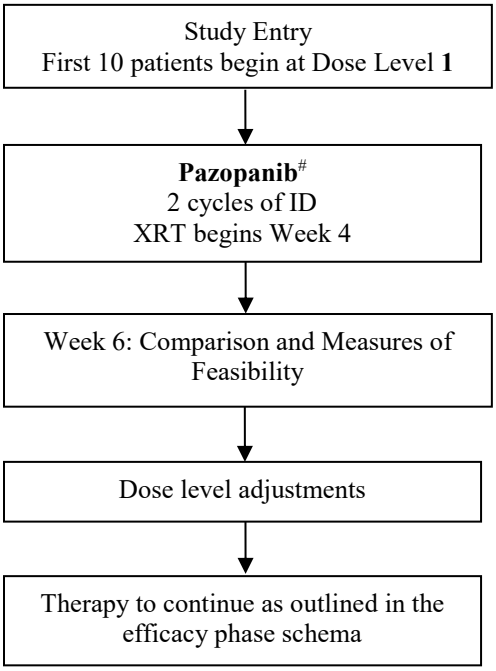
EXPERIMENTAL DESIGN SCHEMAS

DOSE FINDING PHASE

During the dose-finding phase, patients will be non-randomly assigned to treatment with pazopanib.

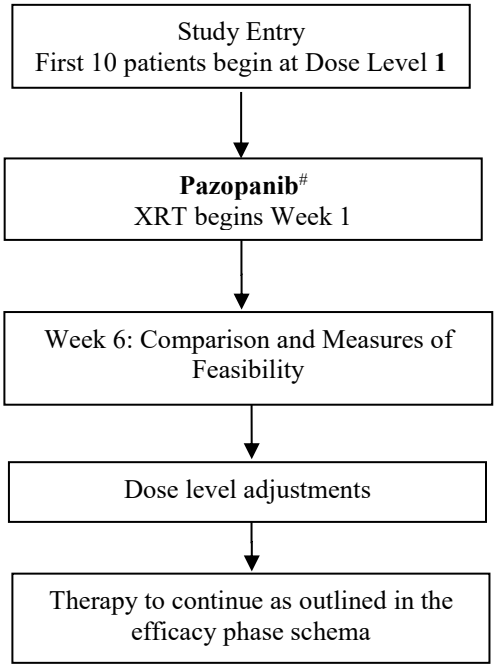
Chemotherapy Cohort (Regimen A)

The Chemotherapy Cohort dose-finding phase is closed and dose level 1 has been found as the MTD, effective May 2015.



Non-Chemotherapy Cohort (Regimen C)

The Non-Chemotherapy Cohort dose-finding phase is closed and dose level 2 has been found as the MTD, effective with Amendment #3A.

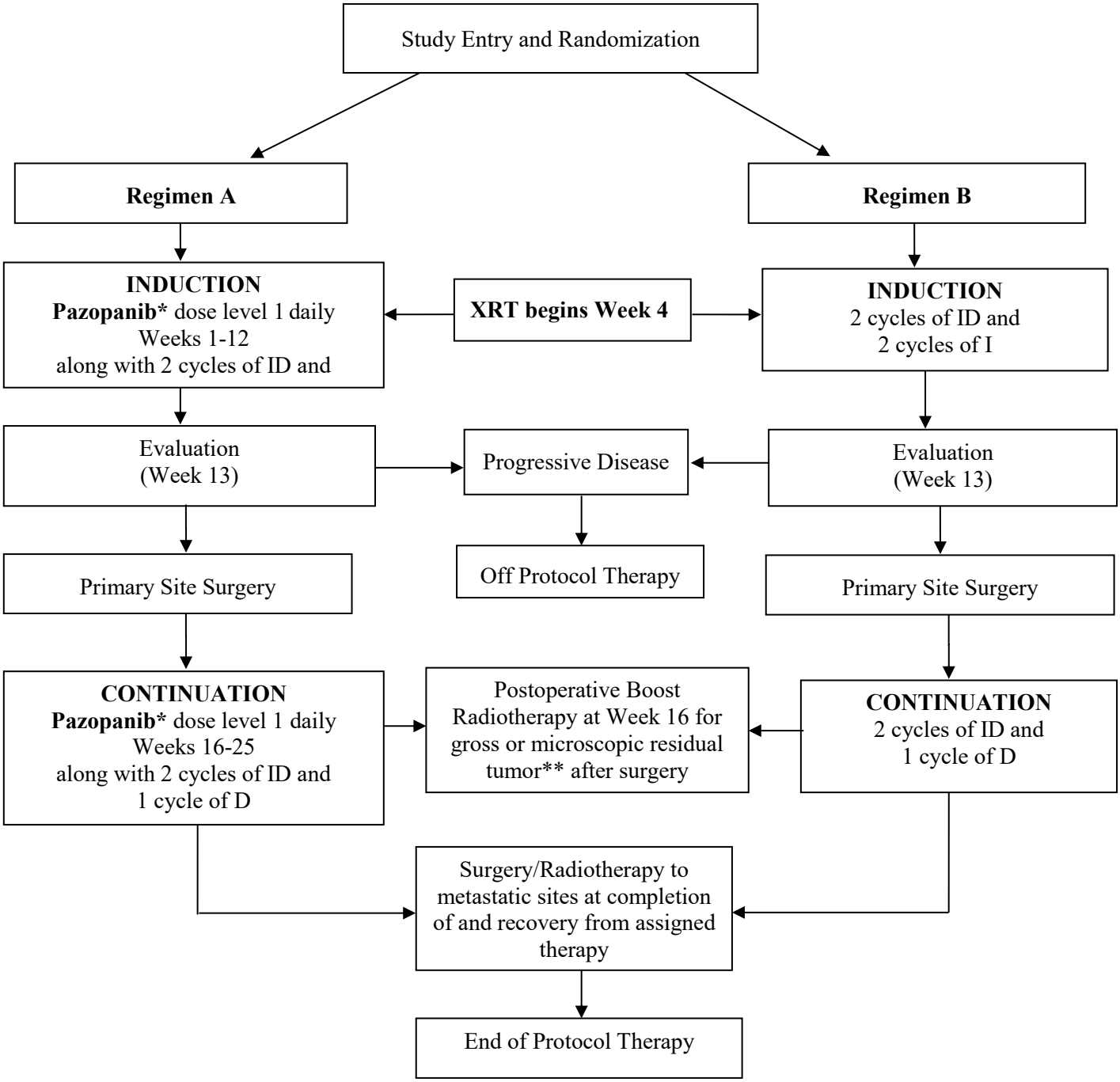


#Pazopanib (Tablet formulation, PO once daily)

Dose Level	Pediatric Dose	Adult Dose
0	275 mg/m^2	400 mg
1	350 mg/m^2	600 mg
2	450 mg/m^2	800 mg

I: Ifosfamide, 2.5 grams/m^2/dose IV on Days 1, 2, 3 (7.5 grams/m^2/cycle)
D: Doxorubicin, 37.5 mg/m^2/dose IV on Days 1, 2 (75 mg/ m^2/cycle)
One cycle of ID is 21 days.

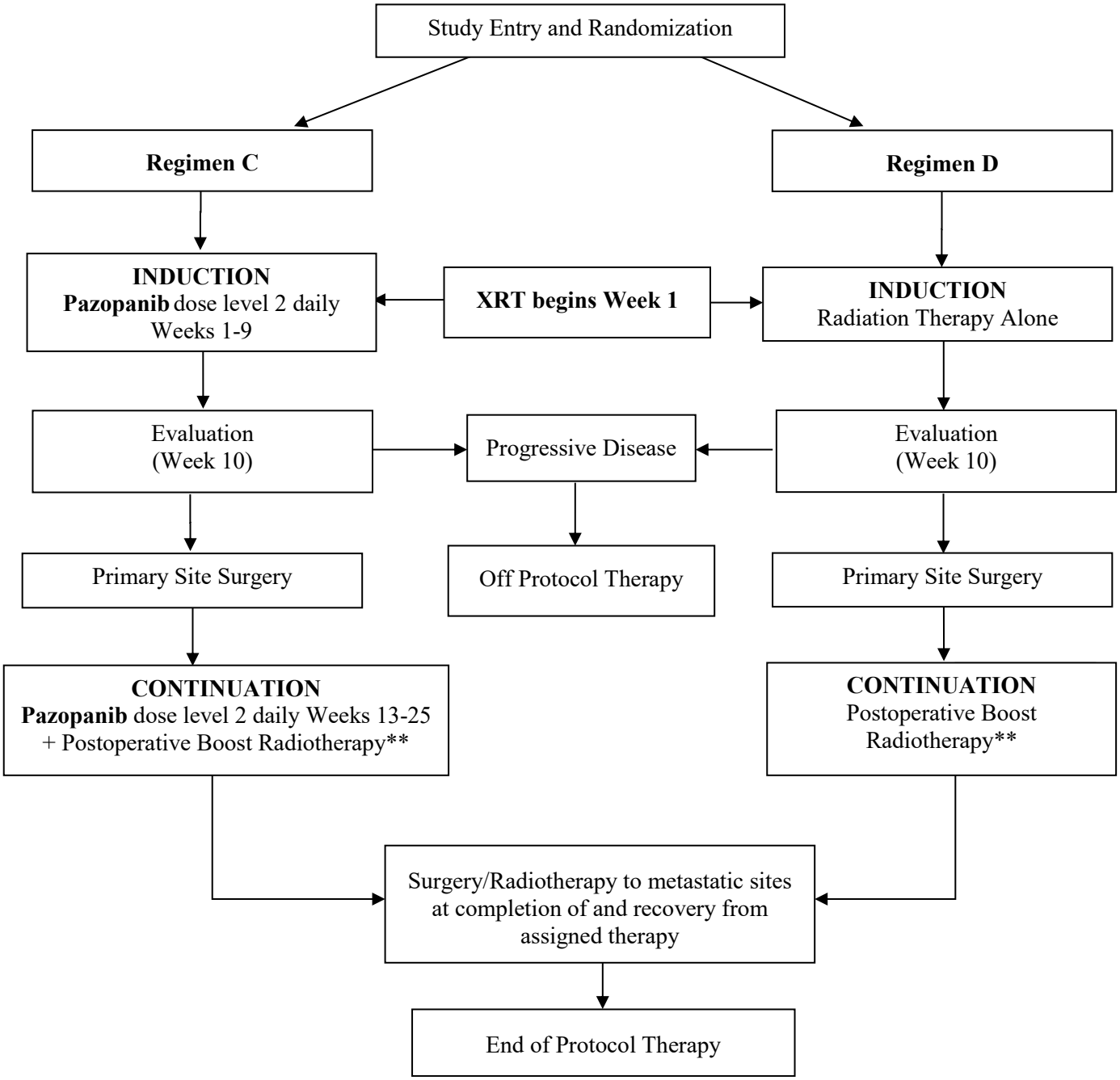
EFFICACY PHASE- CHEMOTHERAPY COHORT



*Pazopanib is to be held pre- and post-surgery.
I = Ifosfamide; D = Doxorubicin. Each cycle lasts 21 days.
** Postoperative boost radiotherapy is required for gross residual disease and is optional for positive margins.

EFFICACY PHASE- NON-CHEMOTHERAPY COHORT

The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.



* Pazopanib is to be held pre- and post-surgery.
** Postoperative boost radiotherapy is required for gross residual disease and optional for positive margins.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1 To identify the dose of pazopanib that is feasible when given in combination with radiation or chemoradiation in pediatric and adult patients newly diagnosed with unresected intermediate- and high-risk NRSTS.

1.1.2 To compare the rates of near complete pathologic response (> 90% necrosis) with the addition of pazopanib to preoperative chemoradiation versus preoperative chemoradiation alone for potentially resectable > 5 cm, Grade 2 or 3 intermediate to high risk chemotherapy-sensitive NRSTS in the Phase II portion of the study for this cohort.

1.1.3 To compare the rates of near complete pathologic response (> 90% necrosis) with the addition of pazopanib to preoperative radiotherapy versus preoperative radiotherapy alone for potentially resectable intermediate to high risk adult and pediatric NRSTS in the Phase II portion of the study for this cohort (using a Phase II decision rule to go onto the Phase III portion of the study).

1.1.4 To compare the rates of event-free survival (EFS) with the addition of pazopanib to preoperative radiotherapy versus preoperative radiotherapy alone for localized intermediate to high risk adult and pediatric NRSTS in the Phase III portion of the study for this cohort if the Phase II decision rule is passed.

1.2 Secondary Objectives

1.2.1 To estimate the rates of local failure, regional failure, distant metastasis free survival, disease-free survival, and overall survival with the addition of pazopanib to preoperative chemoradiation or preoperative radiation in intermediate to high risk adult and pediatric NRSTS.

1.2.2 To compare the pattern of recurrence (local, regional and distant) between preoperative chemoradiation or radiation with the addition of pazopanib for adult and pediatric NRSTS.

1.2.3 To define the toxicities of ifosfamide and doxorubicin chemotherapy and radiation when used in combination with pazopanib in intermediate to high risk adult and pediatric NRSTS.

1.2.4 To define the toxicities of preoperative radiotherapy when used in combination with pazopanib in intermediate to high risk adult and pediatric NRSTS.

1.3 Exploratory Aims

1.3.1 To gain insight into the disease biology of childhood and adult NRSTS through analysis of actionable mutations and whole genome sequencing.

1.3.2 To determine if microvessel density and circulating tumor DNA predict response to pazopanib and outcome.

1.3.3 To determine the effect of pazopanib on doxorubicin exposure in children and adults with NRSTS.

1.3.4 To evaluate change in FDG PET maximum standard uptake value (SUV_{max}) from baseline to Week 10 or 13 in patients with unresected tumors and to correlate this change with pathologic response and EFS.

1.3.5 To compare the rate of response by standard imaging and pathologic assessment to determine which correlates better with local tumor control, distant tumor control, EFS, and overall survival.

2.0 BACKGROUND

2.1 Pediatric NRSTS

NRSTS comprise 4% of all childhood malignancies affecting at least 500 children under the age of 20 years in the United States each year.[1] Few prospective studies of pediatric NRSTS have been conducted.[2-4] Low-risk patients, which account for about 60% of the population, have an excellent long-term survival.[5,6] However, high doses of radiotherapy are required for certain subsets of these patients, which may lead to significant long-term complications.[7,8] Survival rates for patients with intermediate- and high-risk disease, which account for about 40% of the population, are approximately 50% and 15%, respectively.[5,6] The largest prospective study to date is the recent Children's Oncology Group (COG) study ARST0332, whose primary aim is to define a risk-based treatment strategy for pediatric patients with NRSTS using a combination of surgery with or without chemotherapy and radiation therapy. At the conclusion of ARST0332 in February 2012, approximately 600 patients enrolled over a 5-year period, which will be adequate to satisfy the primary aim of the study. The chemotherapy backbone of ifosfamide and doxorubicin (ID) used in ARST0332 is considered to be the most active and among the most commonly used regimens in NRSTS.[9] Although this chemotherapy combination is considered "standard of care", the radiographic response rate to chemotherapy is only 35-40% and outcomes remain poor for those with large, high-grade tumors and those with unresectable or metastatic disease.[2,3]

Given the limited efficacy of chemotherapy for NRSTS and the poor outcomes of a significant fraction of the patient population, novel therapeutic approaches are needed. As knowledge of the tumor biology among the various soft tissue subtypes begins to expand, more biologically-driven, targeted therapy study designs are beginning to emerge.[10,11] In children and young adults with NRSTS the extreme biological heterogeneity across each of the histologic subtypes and involvement of multiple signaling pathways in tumorigenesis suggests that using single targeted agents would be suboptimal. Further, the limited number of patients with each histologic subtype makes single-histology studies impractical in this age group. An alternative approach, particularly for this patient population, is to inhibit more than one oncogenic pathway with a multi-targeted agent. Ideally, the drug targets should be found within the majority, if not all, of the NRSTS subtypes and their disruption should counter the malignant phenotype. Moreover, because single drug approaches have not traditionally had a great impact on outcome, combining the novel agent with traditional cytotoxic chemotherapy may maximize the benefit.

The therapeutic approach for intermediate- and high-risk pediatric patients builds on ARST0332 by adding a multitargeted tyrosine kinase inhibitor (TKI) to standard chemotherapy. This approach takes advantage of the ability of this drug to target multiple signaling pathways that may be disrupted in many NRSTS. This study will determine the

feasibility of adding a TKI to standard chemotherapy and radiotherapy, and will determine if it produces a higher rate of pathologic tumor response in patients with unresected chemotherapy-sensitive tumors compared to those receiving standard chemotherapy alone. Additionally, the study will assess the tumor response in pediatric patients with historically chemotherapy-resistant histologic subtypes given a TKI in combination with radiotherapy.

2.2 Adult NRSTS

In adults, NRSTS comprise < 1% of adult malignancies affecting nearly 10,000 adults in the United States each year (median age of 50). While local control rate is excellent for intermediate-to-high grade STS of extremity or trunk, the risk for metastasis remains significant. Forty percent of patients die of either loco-regional recurrence or distant metastases. Efforts are needed to improve distant control. It has been shown in some studies that complete or near-complete pathologic response (necrosis rate of > 90%) is a significant prognostic factor in patients with STS treated with neoadjuvant radiotherapy or neoadjuvant chemoradiotherapy. The rate of near-complete pathologic response (> 90%) after neoadjuvant radiotherapy alone is reported to be ~ 5-10% and is associated with more favorable disease outcomes.[12] Neoadjuvant chemoradiotherapy has been shown to significantly improve the pathologic response rate compared to historical controls of neoadjuvant radiotherapy alone. Similarly, the rate of significant pathologic necrosis after neoadjuvant chemoradiotherapy has been shown to predict distant control.[13,14] In RTOG 95-14, a Phase II study of doxorubicin and ifosfamide based neoadjuvant chemoradiotherapy for high risk truncal and extremity sarcomas, the rate of complete pathologic response was 27% and rate of > 75% necrosis was 37%.[15,16] However, the chemoradiotherapy regimen was associated with significant toxicities, which continue to make adoption of this neoadjuvant chemoradiotherapy regimen challenging and controversial. Efforts to improve outcomes with dose intensification or other cytotoxic chemotherapy combinations in adult NRSTS have failed or have proven to be too toxic.[17,18] Preoperative radiotherapy is now a widely accepted standard for the treatment of localized NRSTS. The radiation treatment on this protocol builds on RTOG 0630, a Phase II trial evaluating preoperative image guided radiotherapy (IGRT) in STS, which recently completed accrual. Thus far, it appears that IGRT was feasible with centralized review of target volume definition with acceptable toxicities (June 2012 RTOG Semi-Annual Meeting). Results presented at ASTRO 2013 showed that IGRT with smaller margins resulted in reduced lymphedema, fibrosis, and joint stiffness for adult NRSTS.[19] Furthermore, a consensus atlas was built on appropriate CT-based GTV and CTV to improve target volume consistency for preoperative radiotherapy for extremity STS.[20] Therefore, preoperative radiotherapy with IGRT will serve as the backbone for radiotherapy used for all patients on this study.

2.3 Rationale for Inhibition of Angiogenesis in Soft Tissue Sarcomas

Targeted therapy has particular appeal in the treatment of STS. STS require angiogenesis. VEGF expression is upregulated in STS and elevated pre-treatment VEGF levels have been correlated with worse histologic grade survival.[21-23] Anti-VEGF therapy has been shown in preclinical models as well as clinical trials in other solid tumors to normalize permeable and tortuous tumor blood vessels leading to improved delivery of oxygen and potentially augmentation of the effects of radiotherapy.[24] Various studies have demonstrated that the combination of anti-angiogenic agent and radiotherapy can improve tumor response to treatment.[25-27]

A pilot study conducted at Massachusetts General Hospital demonstrated that neoadjuvant bevacizumab enhanced pathologic response to radiotherapy to levels nearly comparable to neoadjuvant doxorubicin based chemoradiotherapy.[28] Forty-five percent of patients treated with bevacizumab had ≥ 80% necrosis, 35% had > 90% necrosis, and 15% had complete pathologic response. The regimen was well tolerated with < 20% Grade 3 toxicities. High microvessel density and gene array profile correlated with high pathological responders.[28]

2.4 Rationale for Tyrosine Kinase Inhibitors in Non-Rhabdomyosarcoma Soft Tissue Sarcomas

Tyrosine kinases (TKs) are critical regulators of cellular growth, proliferation, and survival. TK dysregulation is felt to be a major contributor to tumorigenesis in a variety of cancer types.[29] Certain TKs have been found to be expressed in a range of NRSTS subtypes. Among these, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-Kit, and epidermal growth factor receptor (EGFR) have been the most prevalent and dysregulated across histologic subtypes.[30-33] Tumor growth and metastatic spread are critically dependent on tumor angiogenesis. VEGF and PDGFR are two of the main receptor proteins involved in this process.[31-34] Further, their elevated expression has correlated with higher malignancy grade and worse outcome.[35,36] Preclinical research demonstrates that the effect of simultaneous inhibition of VEGF and PDGFR on tumor angiogenesis and growth is additive suggesting that concurrent targeting of multiple signaling pathways may be more effective than targeting either pathway alone.[37,38] The multi-targeted TKI pazopanib (GW786034) is a potent inhibitor of VEGFR, PDGFR and c-Kit.[39] While VEGFR and PDGFR are critical regulators of tumor angiogenesis, c-Kit is associated with tumor progression.[40]

2.5 Pazopanib in Adults with Soft Tissue Sarcomas

Pazopanib has undergone Phase I and II studies in adults with advanced, refractory sarcomas.[41,42] As a single agent, pazopanib demonstrated antitumor activity in patients with leiomyosarcoma, synovial sarcoma, chondrosarcoma, and "other" sarcomas. A Phase I trial of pazopanib in 63 patients with advanced cancers demonstrated partial responses in 3 patients and stable disease ≥ 6 months in 14 patients.[41] Three of the 6 sarcoma patients enrolled were among those with prolonged stable disease, including a patient with leiomyosarcoma and 2 patients with chondrosarcoma. Pazopanib was evaluated in a Phase II study in patients with refractory advanced soft tissue sarcoma using PFS at 12 weeks as the primary endpoint.[42] One hundred and forty-two patients were enrolled and placed into 4 different strata: adipocytic STS, leiomyosarcoma, synovial sarcoma, and "other" sarcoma. The adipocytic stratum was closed early due to inadequate predetermined statistical response (5 (26%) of 19). In the leiomyosarcoma, synovial sarcoma, and "other" sarcoma cohorts, PFS was 44% (18 of 41), 49% (18 of 37), and 39% (16 of 41), respectively. Four of the 5 patients with synovial sarcoma were still progression free at last follow-up (range, 415 to 812 days after treatment start). Compared to historical controls, PFS and overall survival (OS) were prolonged in the collective group of the 3 active strata in which the primary endpoint was reached.

Van der Graaf *et al*. conducted a multi-center, international, double-blind, placebo-controlled Phase III trial of pazopanib in patients with metastatic soft tissue sarcoma.[43] Three hundred and sixty-nine patients were randomized in a 2:1 fashion (246 pazopanib, 123 placebo). The primary endpoint of PFS was significantly prolonged with pazopanib versus placebo (median: 20 weeks versus 7 weeks; $P<0.0001$). The interim analysis for overall survival demonstrated a non-significant improvement of pazopanib versus placebo

(median: 11.9 months versus 10.4 months). Based upon these results, the FDA approved pazopanib for advanced soft tissue sarcoma in April 2012.

The maximum tolerated dose (MTD) for pazopanib is 800 mg once daily.[41] Pazopanib was generally well-tolerated and produced toxicities that were easily manageable in doses at or below the MTD. Common toxicities for pazopanib have included myelosuppression, hepatic enzyme elevation, proteinuria, hypertension, fatigue, hypopigmentation, hand-foot syndrome, rash, anorexia, diarrhea and nausea.[41-43] The majority of drug-related adverse events have been Grade 1 or 2 and reversible on treatment dose reduction or discontinuation. Much of the severe toxicity with TKI use has been observed within 2 weeks of the start of treatment.[44] Moreover, hypertension has typically occurred early in treatment (within the first 4 weeks) and only a few have developed it beyond this time period.[42]

2.6 Pazopanib use in Children

A COG Phase I study of pazopanib in children with relapsed or refractory solid tumors (ADVL0815) was recently conducted.[45] Twenty-five patients were eligible for the dose escalation phase and 23 of the patients were evaluable for DLT. Observed Cycle 1 DLTs included lipase elevation (n=1, 275 mg/m^2), proteinuria and Grade 3 hypertension (n=1, 450 mg/m^2), amylase elevation (n=1, 600 mg/m^2), and Grade 3 hypertension (n=1, 600 mg/m^2). Cycle 1 non-hematologic toxicities observed in > 10% of patients included Grade 2 hypertension (n=6), left ventricular dysfunction (n=1), fatigue (n=3), rash (n=2), hypothyroidism (n=1), diarrhea (n=1), nausea (n=1), vomiting (n=1) amylase (n=1), lipase (n=2), proteinuria (n=1), abdominal pain (n=2) and headache (n=5), and reversible Grade 3 hypophosphatemia (n=1). DLTs observed in later courses of therapy included diarrhea (n=1, 275 mg/m^2, course 2), neutropenia (n=1, 275 mg/m^2, course 12), hand-foot syndrome (n=1, 350 mg/m^2, course 3), ALT (n=1, 450 mg/m^2, course 7 and 13), myalgia (n=1, 600 mg/m^2, course 2 and 3), and mucositis (n=1, 600 mg/m^2, course 2). The time to achieve maximal concentration was constant across dose levels with a median of 4 hours. Steady state concentrations were achieved by Day 15. The MTD for pazopanib in tablet form was determined to be 450 mg/m^2 on a once daily continuous dosing schedule. This is comparable to the adult dose of 800 mg daily. A suspension dose escalation cohort began once the MTD from the tablet form was determined. The starting dose was 50% of the MTD determined in part 1 (225 mg/m^2) due to preliminary data in adults which suggested a nearly 2-fold increase in mean systemic exposure to pazopanib. Two of the first 4 patients experienced reversible Grade 3 ALT elevation. The dose was lowered to 160 mg/m^2 with only one of 6 patients experiencing a DLT (cerebral hemorrhage) establishing 160 mg/m^2 as the recommended Phase II dose for the suspension. Five NRSTS patients were included on study (3 synovial sarcoma, 2 ASPS). Three patients demonstrated a minor response and 2 patients received ≥ 6 cycles including a synovial sarcoma patient who has received 18 cycles to date (Julia Glade-Bender, personal communication). No pazopanib Phase II studies in children have been completed to date.

Another multi-targeted TKI, sorafenib, has been studied in adults and children with sarcoma.[44,46-48] While the mechanism of action and toxicity profiles for pazopanib and sorafenib are similar, important differences have been noted. The dermatologic adverse events (rash/desquamation, hand-foot syndrome) have been more pronounced and frequent with the use of sorafenib often leading to dose reductions and/or discontinuations.[41,42,44,47,49] Among the more prevalent NRSTS histologic subtypes in children, such as synovial sarcoma and undifferentiated sarcomas, pazopanib has demonstrated greater efficacy.[42,43]

2.7 Combination of TKIs and Cytotoxic Chemotherapy in Soft Tissue Sarcomas

Preclinical studies have demonstrated a potential synergistic interaction between multi-targeted TKIs and conventional cytotoxic chemotherapy, suggesting that these drug combinations may overcome chemoresistance.[50-55] Pazopanib, when used in combination with cytotoxic agents, has demonstrated similar preclinical findings.[56,57]

The potential for a synergistic relationship has been tested clinically in a variety of different tumor types. The majority of these studies have involved the use of the sorafenib, particularly in combination with doxorubicin.[58-66] Most of these are Phase I or II designed, for which efficacy conclusions cannot be reliably drawn. The one randomized study suggested a synergistic efficacy relationship between the agents without overlapping toxicities.[58] However, this study has been criticized because the role of doxorubicin for hepatocellular cancer appears to be modest at best.[67,68]

There is a substantial body of data on the addition of VEGFR2 TKIs to chemotherapy. For example, a number of VEGFR2 TKIs have been evaluated with chemotherapy regimens in patients with advanced non-small-cell lung cancer (NSCLC). Morgensztern and Herbst[69] summarize results from 6 randomized Phase II or III clinical evaluations that included approximately 5000 adults with NSCLC. The overall conclusion from these trials is that the addition of a VEGFR2 TKI to chemotherapy generally resulted in less than 1 month improvement in PFS and OS for patients with NSCLC. Negative results with chemotherapy given with TKIs are not restricted to NSCLC, and have also been reported for cediranib for colorectal cancer[70,71], for vatalanib with colorectal cancer[72,73], for sunitinib for colorectal cancer[74], and for sunitinib for breast cancer[75]. One recent positive study was for cediranib for patients with advanced platinum-sensitive ovarian cancer in which patients receiving chemotherapy with concurrent and maintenance cediranib had significantly longer PFS and OS compared to patients receiving chemotherapy alone.[76] In this study, the effect of cediranib in prolonging PFS may be related to its extended single agent use during maintenance therapy.

The above referenced studies have not included patients with STS. Further, none have involved the use of pazopanib. A limited number of early phase combination studies with the use of pazopanib and cytotoxic chemotherapy have been conducted. An abstract by Hamberg et al. presented at the 2012 ASCO annual meeting[77] reported on a Phase I pharmacokinetic study of pazopanib in combination with 2 schedules of ifosfamide (9 mg/m^2/cycle, continuously or bolus for 3 days) in patients with advanced solid tumors. MTDs and toxicities differed based on the treatment schedule but observed toxicities were generally predictable. Pharmacokinetic analysis demonstrated no effect of pazopanib on ifosfamide exposure. Differences in agent dosing and administration timing preclude direct comparison and toxicity predictions as it relates to this study.

Preliminary results from an open-label, safety pharmacokinetic, and pharmacodynamic dose escalation Phase Ib study of pazopanib in combination with epirubicin or doxorubicin in subjects with advanced solid tumors have been reported (http://download.gsk-clinicalstudyregister.com/files/d8007df9-87bf-4df3-8832-ff75c1cbd173). Three different dose schedules of pazopanib in combination with epirubicin were initially studied. Safety and tolerability assessments were used to determine the optimal pazopanib dose schedule to combine with doxorubicin. Information regarding tumor types was not provided. The combination was overall well tolerated with the 3 most common adverse events

experienced by subjects including neutropenia, nausea and diarrhea. The one arm of the study in which patients received continuous pazopanib (given Days 1-21 of a 21 day cycle) in combination with epirubicin did not progress to the second part of the study secondary to DLTs exceeding the protocol-defined MTD for the optimum tolerated regimen. The majority of DLTs involved neutropenia. The recommended dose and schedule for pazopanib with doxorubicin was established at pazopanib 800 mg oral daily dosing on Days 1-8 with doxorubicin 60 mg/m^2 infusion on Day 3 of a 21 day cycle based on a preliminary analysis of the safety data demonstrating fewer overall Grade 3 or 4 adverse events, fewer serious adverse events, and lower percentage of adverse events leading to treatment discontinuation and withdrawal from the study compared to the other arms. Since a continuous pazopanib dosing schedule is what has demonstrated efficacy in clinical studies for STS, the difficulty in extrapolating pazopanib and epirubicin combination toxicity outcomes onto that of pazopanib and doxorubicin, and the general manageability of neutropenia as an adverse event, we feel our proposed study design remains justified for this specific patient population.

Due to the anticipated tolerable safety profile, single agent activity of pazopanib, and potential synergistic interaction between multi-targeted TKIs and conventional cytotoxic chemotherapy in NRSTS, we aim to add pazopanib to the "standard" ifosfamide and doxorubicin backbone in our study.

2.7.1 Rationale for Pazopanib Dose in Chemotherapy Cohort

The first 10 patients enrolled onto the chemotherapy cohort received pazopanib at dose level 1 (Pediatric: 350 mg/m^2; Adult: 600 mg) during the dose-finding phase of the study. Criteria to determine feasibility were analyzed as outlined in Section 9.2. There were 2 protocol-defined dose-limiting toxicities: one patient experienced a Grade 3 ALT and one patient was removed from protocol therapy as a result of "intolerable toxicity". Eight of 10 patients received greater than 75% of the prescribed full pazopanib dosing. Based on the review outcome, the dose-finding phase for the chemotherapy cohort completed and dose level 1 was the dose of pazopanib established for the efficacy phase for the chemotherapy cohort.

2.7.2 Rationale for Pazopanib Dose in Non-Chemotherapy Cohort

The first 11 patients enrolled onto the non-chemotherapy cohort received pazopanib at dose level 1 (Pediatric: 350 mg/m^2; Adult: 600 mg) during the dose-finding phase of the study. Criteria to determine feasibility were analyzed as outlined in Section 9.2. There were no reported protocol-defined targeted toxicities. Grade 3 fatigue resulted in the pazopanib being held for 1 week. Otherwise, no additional reported Week 1-6 toxicities appeared directly attributable to pazopanib. No patients received less than the 75% of full dose pazopanib. Two patients never received protocol therapy and were not evaluable. Based on these findings and our parameters outlined in Section 9.2, we escalated to pazopanib dose level 2.

The next 10 patients enrolled onto the non-chemotherapy cohort received pazopanib at dose level 2 (Pediatric: 450 mg/m^2; Adult: 800 mg) during the dose-finding phase of the study. Once again, criteria to determine feasibility were analyzed as outlined in Section 9.2. There were 2 protocol-defined dose-limiting toxicities: one patient experienced a Grade 3 dermatitis radiation and one patient was removed from protocol therapy as a result of "intolerable toxicity". Grade 3 diarrhea resulted in the pazopanib being held for 1 week. Otherwise, no additional reported Week 1-6

toxicities appeared directly attributable to pazopanib. Nine of 10 patients received greater than 75% of the prescribed full pazopanib dosing. Based on these findings, the dose-finding phase for the non-chemotherapy cohort completed and dose level 2 was the dose of pazopanib established for the efficacy phase for the non-chemotherapy cohort.

2.8 Combination of TKIs and Radiotherapy in Soft Tissue Sarcomas

Data regarding concomitant radiotherapy with TKIs in adults with solid tumors are limited. Reports of multi-targeted TKI use in combination with radiation in patients with advanced hepatocellular carcinoma have demonstrated clinical and radiologic benefit with manageable toxicities.[78,79] Similar findings have been reported in patients with renal cell carcinoma.[80,81]

Conversely, reports of enhanced toxicities have been noted in renal cell and hepatocellular carcinoma patients receiving TKIs and have included radiation recall dermatitis and bowel perforation.[82-84] A larger, Phase I study of sorafenib and palliative radiation in adult patients with malignancies of the thorax, abdomen, or pelvis was reported at the American Society of Clinical Oncology 2011 meeting.[85] Thirty-four patients were enrolled on study and received sorafenib at dose levels of 200 mg once daily (level 1), 200 mg BID (level 2), and 400 mg BID (level 3) while receiving radiation (30 Gy in 10 daily fractions) in Weeks 2 and 3. Two of the 3 anatomic cohorts reached dose level 3. Significant sorafenib dose modifications occurred in 6 of 10 patients on dose level 3 due to sorafenib systemic toxicities. DLTs were noted in each cohort (thorax dose level 2 – Grade 3 esophagitis; abdominal dose level 3 – Grade 3 ALT elevation; pelvis dose level 1 – Grade 5 bowel perforation). No other high grade, radiation-related toxicities were noted. Grade 2 radiation dermatitis was observed in 7 of 8 patients who completed continuous sorafenib at 200 or 400 mg BID and planned radiation. The trial was terminated early once systemic toxicity of sorafenib resulted in drug dose reductions and discontinuations at 400 mg BID preventing proper evaluation of radiation-related toxicity combined with this dose of sorafenib.

2.9 Response Assessment in NRSTS: Radiologic versus Pathologic

It has not been well established whether a significant change in the size of the tumor mass, as determined by RECIST, is a meaningful surrogate of patient outcome in NRSTS. Previous randomized studies comparing chemotherapy regimens for soft tissue sarcoma have shown significant differences in radiologic response rates but no difference in outcome.[86,87] While some studies have described a significant correlation between tumor response and improved survival[88,89] others have found no such correlation.[90-92] Likewise, after neoadjuvant radiotherapy or chemoradiation, radiographic response is highly variable. In one series, 4 of the 6 patients defined as having progressive disease by standard imaging after neoadjuvant therapy had ≥ 90% necrosis following surgical excision.[91] In another series of 50 patients undergoing neoajduvant RT, radiographic decrease in tumor volume was 0.5% (range -85% to 285%, P=0.15).[93] When pathologic response was plotted versus radiographic response, imaging progression did not predict poor pathological response (range 0-100%, p=0.8).This suggests that the tumor was sensitive to the cytotoxic effects of the therapy and the increase in tumor size did not accurately reflect the actual disease response. Given the heterogeneous composition of soft tissue sarcomas, in which viable tumor is often admixed with areas of pre-existing necrosis, hemorrhage, and fibrosis, tumor size may not accurately reflect chemotherapeutic effect, and ultimately, outcome.[90,94,95] Recent studies involving

multi-targeted TKIs have demonstrated similar discrepancies in response interpretation by noting individuals with cystic changes on imaging not associated with a RECIST response.[42,44]

Treatment-induced tissue necrosis following neoadjuvant therapy has been established as a reliable predictor of outcome in bone sarcomas.[96,97] Similar attempts have been made to study this relationship in soft tissue sarcomas. Although more limited representation in the literature compared to standard imaging assessments, the association of pathologic response and prognosis in soft tissue sarcomas is well-founded. In the largest study evaluating this association, 496 patients with intermediate to high-grade extremity soft tissue sarcomas underwent surgical resection following protocol neoadjuvant chemoradiotherapy.[98] The 5 and 10 year local recurrence rates for patients with ≥ 95% pathologic necrosis were significantly lower (6% and 11%, respectively) compared to those patients with < 95% pathologic necrosis (17% and 23%, respectively, *p=0.002*). The 5- and 10-year survival rates were also significantly higher for patients with ≥ 95% pathologic necrosis (80% and 71%, respectively) than those with < 95% pathologic necrosis (62% and 55%, respectively, *p=0.0001*). When analyzed in a multivariate manner, pathologic necrosis was an independent predictor of survival.

Another study involving 34 patients with locally advanced soft tissue sarcomas of the extremity received neoadjuvant chemoradiotherapy followed by surgical resection.[13] Fifty percent of tumors demonstrated ≥ 90% pathologic necrosis. The 5-year freedom from distant metastasis was superior if treatment-induced tumor necrosis was ≥ 90% (85% vs 20%, p=*0.02*). Further understanding of the relationship between radiographc and pathologic response after neoadjuvant therapy and ultimate patient outcome is necessary.

2.10 ARST0332 Preliminary Data Regarding Pathologic Response in Pediatric NRSTS

The pathologic response rates in advanced soft tissue sarcomas appear to be consistent across multiple studies.[13,14,98,99] Only 40-50% of STS patients achieve a good response (≥ 90% necrosis) with preoperative chemotherapy. With permission from the COG DSMC, we analyzed the distribution of pathologic response by histology in Arm D patients (neo-adjuvant chemoradiotherapy) on ARST0332. Those histologies demonstrating an overall good pathologic response (≥ 90% necrosis) at Week 13 included synovial sarcoma, unclassified sarcoma, and embryonal sarcoma of the liver, which were among the most common histologies seen on ARST0332. Good pathologic response was seen in a smaller number of 'other' histologies, including fibrosarcoma, mesenchymal chondrosarcoma and angiosarcoma. Taken together, these favorable subtypes represent 80% of all Arm D patients enrolled on ARST0332 and the majority of these patients underwent resection at Week 13.

A review of the literature lends further support to the pathologic response findings achieved within these specific histologies on ARST0332. Chemotherapy-sensitive NRSTS tumor types have predominantly included synovial sarcoma,[87,100] angiosarcoma,[101,102] undifferentiated sarcoma,[103] mesenchymal chondrosarcoma,[104] and embryonal sarcoma of the liver.[105] Some subtypes, such as leiomyosarcoma and liposarcoma, demonstrate modest response to single agent chemotherapy but mixed response and outcome when used in combination.[100,106]

Data from ARST0332 demonstrated pathologic necrosis rates at Week 13 similar to literature-based estimates. The consistency of this finding among such a heterogeneous group of diseases, compared to standard imaging, further strengthens its selection as an

appropriate primary response surrogate for our study population. Since pathologic response is associated with outcome and only about 40% of pediatric chemotherapy-sensitive NRSTS patients achieve a good pathologic response with ID + RT (radiotherapy), this study's primary end point will be to determine whether the addition of pazopanib to ID + RT increases the rate of pathologic response.

2.11 Chemotherapy-Resistant Pediatric NRSTS

Although encompassing an extremely heterogeneous population of histologic subtypes, therapeutic trial designs in adults with NRSTS have historically been all inclusive and have delivered uniform chemotherapy to all patients. Counter to this approach, it has been demonstrated that chemotherapy sensitivity is oftentimes histology-dependent. Subtypes generally considered chemotherapy-resistant include alveolar soft part sarcoma,[107] epitheloid sarcoma,[2,108,109] clear cell sarcoma,[110,111] malignant fibrous histiocytoma,[112] hemangiopericytoma,[113] solitary fibrous tumor,[114] and extraskeletal myxoid chondrosarcoma.[115,116] Chemotherapy responsiveness in malignant peripheral nerve sheath tumor is somewhat variable but largely has been reported as resistant.[117]

An analysis of preliminary data from ARST0332 (with permission from the DSMC) was undertaken to examine the distribution of pathologic response by histology in Arm D patients historically considered chemotherapy-resistant. Reassuringly, the most represented histologies with < 90% pathologic response included malignant peripheral nerve sheath tumor (only 10% of MPNST patients had ≥ 90% pathologic response) and alveolar soft part sarcoma (none had pathologic response ≥ 90%). Similar poorer response rates were seen in a few 'other' subtypes such as malignant fibrous histiocytoma. Collectively, these histologies represent nearly 20% of all Arm D patients and demonstrated a good pathologic response rate of only 15%.

The anticipated outcomes of these intermediate- and high-risk patients with chemotherapy-resistant tumors are poor. Those with intermediate-risk features have an approximately 50% survival, and those with high-risk features have an approximately 15% survival. Thus, novel therapies are needed for these rare soft tissue sarcomas. The combination of supportive literature and analysis of data from ARST0332 provide justification for treatment of these patients with pazopanib in a single-arm study. Observing responses in patients on this non-randomized arm, even in exceedingly rare histologies, would generate important information for patients with these rare sarcomas.

2.12 RTOG 95-14 Data Regarding Pathologic Response in Adult NRSTS

Based on data on histology specific response provided by RTOG statisticians from RTOG 95-14 (neoadjuvant chemoradiation trial for high risk adult soft tissue sarcomas ≥ 8 cm and Grade 3), we identified histologies with more than 50% of cases showing significant pathologic response (which in that trial was defined as having 0% viable cells or only 0-25% viable cells) as potentially chemotherapy-sensitive. These included fibrosarcoma (60% of cases had 0% viable cells or 0-25% viable cells), pleomorphic sarcoma (72%), leiomyosarcoma (80%), liposarcoma (100%), and undifferentiated/NOS (100%). Conversely, those histologies in RTOG 95-14 showing poor response included MPNST (0% of cases had 0% viable cells or 0-25% viable cells), epithelioid sarcoma (0%), and myxofibrosarcoma (33%).

2.13 Rationale for Chemotherapy and Non-Chemotherapy Cohorts

The objectives of this trial are to determine the additional benefit (rate of near total pathological necrosis for the Phase II endpoint, and event free survival for the Phase III endpoint) of adding pazopanib to 2 currently accepted approaches to treating intermediate to high risk sarcomas in clinical practice: (1) preoperative chemoradiation and (2) preoperative radiation alone.

The 2 treatment arms have been named "Chemotherapy" and "Non-Chemotherapy" cohorts instead of "Chemosensitive" and "Chemoresistant" cohorts, recognizing that histological subtype and chemosensitivity are 2 important factors but insufficient to determine whether a subject should be receiving chemotherapy as the backbone of the preoperative therapy for the unresected sarcoma. Currently, tumor size and tumor grade are routinely used to assess a patient's risk of distant metastasis to determine whether chemotherapy should be considered. However, because chemotherapy is very toxic and its survival benefits marginal in most NRSTS, the role of chemotherapy is less clear. Because the benefits of chemotherapy are limited and the potential toxicity high, it is considered within the standard of care for patients to choose whether or not to receive chemotherapy. It is also routine for clinicians to avoid chemotherapy in older patients and those with comorbidities that would make chemotherapy more risky, given the marginal benefits that chemotherapy provides.

Neoadjuvant ifosfamide/doxorubicin-based chemotherapy combined with preoperative radiotherapy has been utilized to treat certain "chemosensitive" types of adult NRSTS with large size (> 5 cm) and high-to-intermediate grade in some institutions. However, randomized comparison of preoperative chemoradiation versus preoperative radiation alone is not available. It is also important to note that neoadjuvant chemotherapy alone failed to show survival benefits for large (>8 cm) high-to-intermediate grade NRSTS in adult patients (EORTC STBSG 62871 Phase IIR study).[118] Furthermore, the high toxicity of chemotherapy in adults (RTOG 95-14) makes it difficult to recommend preoperative chemoradiation in all adult NRSTS, even for the chemosensitive histologies.

For the remaining patients, including patients with chemoresistant histologies, chemosensitive histologies but of smaller size (< 5 cm) and low grade, and even high risk patients unwilling or unable to receive chemotherapy, preoperative radiation before resecting the primary sarcoma is a widely accepted standard. Based on the accrual pattern to RTOG 0630 which contained both a Chemotherapy and a Non-Chemotherapy Cohort, more adult NRSTS are treated with preoperative radiation than preoperative chemoradiation.

Based on the literature and data obtained from the recent COG and RTOG studies (ASRT0332 and RTOG 94-15), we have identified 3 histologies that have most consistently and significantly demonstrated sensitivity to chemotherapy. These include: unclassified (including undifferentiated and NOS) soft tissue sarcomas in patients < 30 years of age, synovial sarcoma, and embryonal sarcoma of the liver. As such, patients with these histologies meeting the grade and size criteria (Grade 2 or 3, > 5 cm) associated with high risk of metastatic disease, may ONLY enroll on the Chemotherapy Cohort (see Section 3.2.2.1). For all the other histologies with some evidence of chemosensitivity, we feel that allowing for enrollment on either cohort reflects the current pattern of care. Allowing these patients on the Non-Chemotherapy Cohort can still help answer the

question of whether pazopanib improves near total pathologic necrosis rate and event free survival over preoperative radiation alone.

Lastly, allowing "chemosensitive histologies" in the Non-Chemotherapy cohort will not dilute the primary objective of this study. Patients with "chemosensitive histologies" will be randomized to both treatment arms in each cohort. Therefore, sensitivity to chemotherapy should not influence the study outcomes. In addition, whether chemosensitive or chemoresistant, preoperative radiation alone results in a low rate of near total pathologic necrosis across all NRSTS histologies of only 8-10%. Radiation sensitivity and chemotherapy sensitivity is not the same. Pazopanib sensitivity and chemotherapy is also not the same. Therefore, we will receive important information about pathologic necrosis and patterns of failure of preoperative radiotherapy +/- neoadjuvant pazopanib in patients with both chemo-sensitive histologies and chemo-resistant histologies who do not receive neoadjuvant chemotherapy.

We believe that this study design best reflects the accepted standards for NRSTS treatment in both adult and pediatrics: a risk adapted approach that takes into account tumor size, grade, patient age, chemosensitivity, and ability to tolerate chemotherapy. For the patients with highest risk for metastatic disease from chemotherapy sensitive NRSTS histologies who are able to tolerate and accept chemotherapy, the study seeks to answer the question, what does pazopanib add to preoperative chemoradiation. For other patients, the study will answer the question, what benefits does pazopanib add to preoperative radiation. Both will advance our current approaches to NRSTS. This design will also maximize accrual since many practitioners feel strongly about the decision to offer or not offer chemotherapy to patients with NRSTS.

2.13.1 Rationale for the FNCLCC Grading System and Inclusion of FNCLCC Grade 2 or 3 Tumors in the Chemotherapy Cohort

On the predecessor study, ARST0332, one of the secondary study aims included a comparison of the Pediatric Oncology Group (POG) and Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) pathologic grading systems to determine which better correlates with clinical outcomes. While awaiting the results of this analysis, we chose the FNCLCC grading system for our study largely due its more generalizable acceptance and familiarity among adult sarcoma providers. However, a retrospective study from Khoury et al. found that while that both systems provided adequate prognostic measures of outcome, a fairly significant subset of cases were graded differently by the two systems in patients with NRSTS.[119] This discrepancy appeared to have largely resulted from the value assigned to the mitotic index. Further, the mitotic index demonstrated a highly significant correlation with EFS as a prognostic factor when assessed using univariate analysis ($p<0.001$). While both grading systems incorporate the mitotic index, each utilizes different cutoff points. The POG system has a lower cutoff compared to the FNCLCC system which resulted in upward assignment of FNCLCC Grade 2 cases to POG Grade 3 in this retrospective study. None of the FNCLCC Grade 3 tumors received lower grades with the POG system. Conversely, 44 POG Grade 3 tumors met criteria for FNCLCC Grade 1 (n=3) or 2 (n=41). The study found the 44 patients whose tumors were graded discrepantly (FNCLCC Grade 1 or 2 and POG Grade 3, 48% EFS) had a prognosis that was intermediate between those whose tumors were graded in concordance (FNCLCC Grade 1 or 2 and POG Grade 1 or 2, 68% EFS; FNCLCC Grade 3 and POG Grade

3, 26% EFS; p=0018). Moreover, a mitotic count using a cutoff of 10 mitotic figures per 10 high power fields was found to be a significant EFS outcome discriminator in this subset of patients (p=0.0055). A mitotic count of ≥ 10 contributes a mitotic count score of 2 to the cumulative grade score in the FNCLCC system and a mitotic count of ≥ 5 is designated a Grade 3 in the POG system.

Other recent, large adult studies using chemotherapy in high-risk soft tissue sarcomas (STS) have defined FNCLCC Grade 2 or 3 as high-grade.[120-123] Based upon historical pediatric data and inclusion parameters on more recent, large adult high-risk STS studies, patients with FNCLCC Grade 2 OR 3 tumors are eligible for the chemotherapy cohort assuming size and histologic criteria are met.

2.14 Pazopanib and Radiotherapy

While preclinical data on pazopanib and radiotherapy specifically in NRSTS is not available, there is pre-clinical data showing synergistic effect with the combination of pazopanib and radiation in a number of in vivo tumor models.[124] In addition, other TKIs have been safely combined with RT with beneficial effects in patients with advanced hepatocellular carcinoma and renal cell carcinoma.[125,126]

Currently, NRG Oncology has an active study (RTOG 0912) of combined IMRT, paclitaxel, and pazopanib in the treatment of anaplastic thyroid cancer, with no major adverse events reported thus far. We will continue to assess the safety and tolerability profile of pazopanib given in combination with preoperative radiation in the proposed study. Furthermore, there also is emerging data that the combination of pazopanib and radiation is safe in the Phase I portion of an ongoing investigator-initiated/GlaxoSmithKline-supported Phase 1/2I trial using pazopanib and radiation therapy in sarcomas by Hass and colleagues, the Netherlands Cancer Institute– Antoni van Leeuwenhoek Hospital (personal communications, July 2012).

2.15 Rationale for Concurrent Sequencing of Pazopanib and Preoperative Radiotherapy in the Non-Chemotherapy Cohort

Based on the experience with the MGH bevacizumab and radiotherapy pilot study, this proposed trial is designed without a lead-in period of pazopanib alone prior to radiation therapy. The use of VEGF-inhibitors has been shown to potentially increase the metastatic potential of malignancies in other sites (colon and preclinical) if the tumor is not responsive to the agent. The effect of VEGF inhibition on intra-tumoral hypoxia and HIF-1α activity may vary between different tumors. Tumor blood vessels are immature, dilated, tortuous, and highly permeable with erratic flow[127,128] and many of these abnormalities can be attributed to the overexpression of VEGF-A.[129] These characteristics lead to areas of hypoxia in tumors. Administration of anti-VEGF agents can result in reduced vessel irregularity, diameter, and permeability, and transiently improve the delivery of oxygen.[24] However, sustained anti-VEGF therapy can ultimately lead to loss of tumor vessels and increased hypoxia.[130] Recently, there has been significant controversy regarding the effects of VEGF inhibition on primary tumor invasiveness and metastatic potential.[131] Casanovas and colleagues[132] found that VEGF receptor 2 (VEGFR-2) inhibition of RIP1-Tag2 mouse pancreatic endocrine tumors led to increased intra-tumoral hypoxia along with increased tumor invasiveness and liver metastases.[133] Similarly, Ebos et al.[134] found that sunitinib (which targets VEGF and other pathways) increased liver and lung metastases for both experimental and spontaneous metastases. The effects of VEGF inhibition in primary

sarcomas on hypoxia, HIF-1α activity, and HIF-related phenotypes such as tumor progression, metastasis, and radiation response are currently unknown. Cooke et al.[135] found that PDGF inhibition in mouse models of primary breast cancer lead to loss of pericytes, increased hypoxia, and increased metastasis.

It is important to note that the vast majority of cancer patients treated with VEGF and PDGF inhibitors prior to this proposal have established metastatic disease and relatively few studies have examined the use of these inhibitors in patients with primary tumors and no clinically evident metastases. For anti-angiogenic agents to be more broadly used in the neoadjuvant setting with radiation or chemoradiation, it is vital to determine under what circumstances these inhibitors may increase the invasiveness and metastatic potential of primary tumors. Clinical concern for increased invasiveness or metastasis following anti-VEGF-A therapy has focused on glioblastoma, where the phenomenon of increased invasiveness following anti-angiogenic therapy is commonly observed.[136] Since we do not know the responsiveness of soft tissue sarcomas, we do not feel it prudent to treat with single agent pazopanib at this time, and that is the rationale for starting pazopanib concurrently with radiation in the proposed study.

2.16 Wound Complications

The care of soft tissue sarcomas is complex and multidisciplinary in nature. Even without radiation or chemotherapy wound complications are common after surgical resection of soft tissue sarcomas with a reported incidence of 6-42%.[137] The known 30% incidence of wound complications with the approach of pre-operative radiation ± chemotherapy followed by surgical resection has been well documented and accepted in the literature.[91,137-142] More relevant to this study, Yoon et al conducted a trial evaluating the neoadjuvant use of a VEGF receptor inhibitor (bevacizumab) in combination with radiation followed by resection in patients with soft tissue sarcomas. Major post-operative wound complications occurred in 25% of patients.[28] Our current rate of major wound complications (14%), even with a small sample size, is within what would be expected based upon the above detailed literature review.

The study design of ARST1321 provides us a unique ability to gain a clearer understanding of how pazopanib, and other tyrosine kinase inhibitors, may impact wound complication rates in this clinical setting. Since pazopanib will be the only variable on both the chemotherapy and non-chemotherapy arms, direct toxicity comparisons can be made within each treatment cohort in the randomized portion of the study. In addition to detailed protocol therapy management of wound complications within the dose modification section and the real time review of reported wound complication adverse events, expanded wound complication data collection is planned on the study reporting period and surgery central review case report forms (wound complication grading adapted from Dindo et al. 2004 and characterization of the wound complication adapted from O'Sullivan et al. 2013)[143,144] as well as the required submission of any wound-related institutional procedure or operative reports.

2.17 FDG PET in NRSTS

Tumor response to neoadjuvant therapy in NRSTS has been historically based upon standard anatomical imaging and histopathologic review. More recently, FDG PET has emerged as a surrogate predictor of early response in soft tissue sarcomas.[145,146] Additionally, there is a suggestion of improved accuracy in assessing pathologic response to neoadjuvant therapy using FDG PET compared to standard sized-base criteria in NRSTS

patients.[147] Based on studies demonstrating a positive correlation between histopathologic response to neoadjuvant chemotherapy and outcome in soft tissue sarcoma patients,[13,98] incorporation of FDG PET into early treatment decisions could be beneficial. Studies evaluating FDG PET in children and adults with NRSTS is limited. To determine its predictive significance in these patients and its potential role in therapy-related decisions, as an exploratory aim of the study, we will attempt to correlate Week 10 or 13 response assessed by FDG PET maximum standard uptake value (SUVmax) with pathologic response and EFS.

2.18 Correlative Biology Studies

2.18.1 Analysis of Actionable Mutations and Whole Genome Sequencing in NRSTS

Given the rarity of the various subtypes of NRSTS, it is highly unlikely that development of drugs targeted to these particular tumors will be feasible. Thus, improvements in outcome depend on the optimal use of drugs developed for other diseases. It has already been shown that drugs developed for other indications may target signaling pathways important in specific subtypes of NRSTS. The best example of this is imatinib, which was developed for chronic myeloid leukemia but is effective in gastrointestinal stromal tumors (GIST) and dermatofibrosarcoma protuberans because of targeting of shared pathways. In an effort to better understand the biologic abnormalities in NRSTS that may be targeted by existing drugs, one of the exploratory aims of this clinical trial will be to identify actionable mutations in children, adolescents, and adults with NRSTS.

Genetic abnormalities (eg, single nucleotide polymorphisms (SNPs), single nucleotide variants (SNVs), and small deletions/insertions) that can be targeted, often referred to as "actionable" mutations, are being identified in a growing number of adult cancers including NRSTS.[148-150] MacConaill *et al* found actionable mutations in up to ~75% of carcinoma cases, depending on the specific cancer.[148] Another study revealed actionable mutations in RAS and KIT using MassARRAY in adult sarcomas.[150] Additional smaller mutational analysis reports among individual NRSTS subtypes demonstrate that actionable mutations have been identified.[32,151-153]

We expect the experiments proposed in this component of the exploratory aim to reveal the proportion of NRSTS cases with the tested potentially actionable mutations. Further, we will define the frequency with which individual genes are mutated and whether individual mutations are found across multiple histological subtypes. Finding that some mutations are independent of NRSTS histology will support the notion that functional classification of NRSTS based on molecular defects may more accurately guide the use of personalized anti-cancer therapy.

Comprehensive genomics studies to identify mutations, structural abnormalities and copy number variation across the genome will provide insight into NRSTS disease biology that can be leveraged to achieve better risk stratification and more rational therapeutic approaches. To accomplish this task and as a final component to this exploratory aim, we plan to conduct whole genome sequencing in children and adults with NRSTS.

2.18.2 Microvessel Density and Circulating Tumor DNA as Predictors of Tumor Response and Outcome

Numerous correlative science studies were performed as part of the MGH Phase II clinical trial of neoadjuvant bevacizumab and radiation therapy for resectable sarcomas.[28] Twenty patients with intermediate-or high-grade sarcomas, > 5 cm in size, received bevacizumab for 2 weeks followed by 6 weeks of bevacizumab and radiation therapy (50 Gy). Tumor tissue samples were obtained before treatment and 10 days after the start of bevacizumab. Bevacizumab and radiation resulted in ≥80% pathologic necrosis in 9 of 20 tumors (45%), which is over double the historical rate with radiation alone. High initial microvessel density (MVD) (tau=0.53, p=0.0031) and decrease in MVD after bevacizumab alone (tau=0.43, p=0.0154) significantly correlated with ≥ 80% histologic necrosis. This suggests tumors with bevacizumab-responsive vasculature were more likely to have a good response to combination therapy with bevacizumab plus radiation.

The bevacizumab and preop RT pilot study also included extensive analysis of (1) circulating factors and cells in blood, (2) gene and protein expression in tumors, and (3) tumor vasculature using perfusion CT scans to identify biomarkers for response to therapy. They found that gene expression signatures and tumor microvessel density were the most reliable biomarkers of treatment response. They also found that high expression of HIF-1α and downstream targets of HIF-1α predicted a poor response to therapy. One goal of the correlative studies in the current proposal is to confirm that initial microvessel density is a biomarker of response to treatment.

Another goal of the correlative science studies is to identify a circulating biomarker that may serve as a biomarker for response. In RTOG's previous study, they analyzed 9 circulating angiogenic and growth factors and 3 types of circulating cells during the course of therapy, and a few correlations were made to treatment response. None of these correlations were reliable enough to base clinical decisions upon. In search of a more reliable circulating biomarker, we will attempt in this study to replicate the "personalized analysis of rearranged ends (PARE)" strategy proposed by Leary *et al.* at Johns Hopkins Medical Institutions (JHMI).[154] In this strategy, first a patient's tumor and normal tissue are whole genome sequenced to identify chromosomal translocations. Second, PCR primers are designed and tested that span the breakpoint. Third, circulating DNA is isolated from patient plasma, and sensitive quantitative PCR techniques (eg, digital PCR or BEAMing) are used to determine the amount of circulating tumor DNA. In one JHMI study, 4 colon cancer and 2 breast cancers were tested and found to have between 7 and 21 chromosomal rearrangements, and levels of circulating tumor DNA allowed investigators to monitor response to therapy.[154] In a larger JHMI study of 18 colorectal cancer patients, circulating tumor DNA was detected in all patients prior to surgical resection of the tumor.[155] Following 20 surgical resections, circulating tumor DNA was detected in 16 of 20 patients. Recurrence occurred in 15 of the 16 patients with persistent circulating tumor DNA and 0 of 4 patients without persistent circulating DNA.

The application of the PARE strategy to STS is intuitively reasonable given about one-third of STS subtypes (synovial sarcoma, myxoid/round cell liposarcoma, clear cell sarcoma, extraskeletal myxoid chondrosarcoma) have known

chromosomal translocations that occur at high frequency. For example, over 90% of synovial sarcomas have translocation t(X;18)(p11.2;q11,.2) which fuses the SYT gene to either the SSX1 or SSX1 gene and over 75% of myxoid-round cell liposarcomas have translocation t(12;16)(q13;p111) which fuses the TLS(FUS) gene to the CHOP gene.[156] The first step of the JHMI strategy (eg, whole genome sequencing) is currently quite costly, and thus the PARE strategy will be attempted in patients in our study who have a STS subtype with a high frequency of known translocations such as synovial sarcoma. Translocations will be identified using published PCR primers, and the PARE strategy will only be applied to patients whose tumors have an identified translocation.

As a preliminary proof of principal experiment in a single myxoid liposarcoma patient with a t(12;16)(q13;p111) translocation, DNA was isolated from the tumor as well as the mononuclear cells contained in the buffy coat of the patient. The presence of the t(12;16)(q13;p111) translocation was found in tumor DNA but not in mononuclear cell DNA by PCR.[155] When plasma samples obtained from the patient before and during treatment were examined for ctDNA, we were able to identify ctDNA, and levels of ctDNA decreased with therapy.

2.18.3 Doxorubicin Pharmacokinetics in Combination with Pazopanib

TKIs are known to modulate cellular ATP binding cassette (ABC) membrane transporters which can affect the efflux and intracellular accumulation of anticancer agents.[157,158] The newer, multi-targeted TKIs appear to inhibit the activity of ABC transporters, increasing the bioavailability of co-administered drugs and potentially reversing multi-drug resistance.[159,160] Doxorubicin is a known substrate for drug efflux pumps (ABC transporters);[161] thus, its exposure may be altered by the concomitant use of pazopanib. In addition, pazopanib is a potent inhibitor of the liver uptake transporter organic anion-transporting polypeptide 1B1 (OATP1B1),[162] and this may represent another pathway for a potential drug interaction with doxorubicin.[163] We aim to collect doxorubicin pharmacokinetic data in hopes of gaining an enhanced understanding of the relationship among this novel drug combination. It is anticipated the results will continue to facilitate our ability to design future effective and safe drug combination therapies for children and adults with NRSTS.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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

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

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

3.1.2 IRB Approval

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

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

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

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

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

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory

Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

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

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

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

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

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps above. Reservations may be obtained 24 hours a day through the OPEN system.

3.1.4 Study Enrollment

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

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

crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

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

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

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

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

3.1.5 Timing

Patients must be enrolled before protocol therapy begins. The date protocol therapy is projected to start must be no later than **fourteen (14)** calendar days after the date of study enrollment. **Patients who start protocol therapy prior to study enrollment will be ineligible**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.6 Note for Baseline Imaging

- Primary Tumor
  - If a subtotal resection of the primary tumor was performed prior to enrollment, the baseline study should be done after this operation.

Note: Eligibility for this study depends on the pre-subtotal resection tumor size (see Section 3.2.2.1 and Section 3.2.2.2 for eligibility size criteria).

- Lymph Node Bed
  - It is required that the baseline imaging also include imaging of the regional lymph node bed for clear cell sarcoma and epithelioid sarcoma only. If a subtotal resection of the lymph node bed was done, the baseline study (CT or MRI) should be done after this operation (unless proven to be biopsy negative).

3.1.7 Randomization

Randomization will take place at the time a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit. The investigator is responsible for ensuring that all eligibility criteria are met.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, including those used to determine eligibility, must be obtained within 4 weeks prior to enrollment (repeat imaging if necessary). Cardiac and pulmonary function studies, including those used to determine eligibility, must be obtained within 3 weeks prior to enrollment.

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

3.2.1 Age

Patients must be ≥ 2 years at the time of the biopsy that established the diagnosis of NRSTS will be eligible.

Note: Eligible patients must have a Body Surface Area ≥ 0.5 m^2 AND be able to swallow whole tablets (see Section 3.2.9.17 and Section 3.2.9.18).

3.2.2 Diagnosis

Newly diagnosed and histopathologically confirmed, potentially resectable NRSTS of the **extremity** and **trunk** will be eligible for the chemotherapy or non-chemotherapy cohort based on:

- Evidence of chemotherapy sensitivity of the histologic sarcoma subtype based on existing evidence from prior clinical trials
- Sufficient risk of metastatic disease to warrant chemotherapy based on size and grade and
- Medically deemed able or unable to undergo chemotherapy.

Notes:
An incisional biopsy or core biopsy is preferred. Fine needle aspiration biopsy is not acceptable to establish the diagnosis.

ELIGIBLE SITES: Please refer to Appendix II.

- Extremities: upper (including shoulder) and lower (including hip)
- Trunk: body wall

INELIGIBLE SITES: Head and neck, visceral organs (with the exception of embryonal sarcoma of the liver), retroperitoneum, peritoneum, pelvis within the confines of the bony pelvis.

3.2.2.1 Eligibility for chemotherapy cohort:

- Stage T2a/b (> 5 cm) and Grade 2 or 3 (see Appendix III)
  AND
- One of the following chemosensitive histologies as defined in the WHO Classification of Soft Tissue Tumours (with some evidence of good response to chemoradiation and of sufficient high risk of metastases, or clear evidence of metastases) (Appendix IV):
  - Unclassified soft tissue sarcomas that are too undifferentiated to be placed in a specific pathologic category in the WHO classification (often called "undifferentiated soft tissue sarcoma" or "soft tissue sarcoma NOS")
  - Synovial sarcoma
  - Angiosarcoma of soft tissue
  - Adult fibrosarcoma
  - Mesenchymal (extraskeletal) chondrosarcoma
  - Leiomyosarcoma
  - Liposarcoma (**excluding** myxoid liposarcoma)
  - Undifferentiated pleomorphic sarcoma
  - Embryonal sarcoma of the liver

3.2.2.1.1 Patients meeting the above criteria (histology, size, and grade) with the EXCEPTION of histologies noted in 3.2.2.1.2 may enroll on the chemotherapy cohort or the non-chemotherapy cohort at the discretion of the enrolling investigator. Patients meeting these criteria with the EXCEPTION of histologies noted in 3.2.2.1.2 but medically deemed unable to receive chemotherapy or who elect not to receive chemotherapy are eligible for the non-chemotherapy cohort.

3.2.2.1.2 Patients with the following histologies are only eligible for the chemotherapy cohort and cannot enroll on the non-chemotherapy cohort:

- Unclassified soft tissue sarcomas that are too undifferentiated to be placed in a specific pathologic category in the WHO classification (often called "undifferentiated soft tissue sarcoma" or "soft tissue sarcoma NOS") in patients < 30 years of age
- Synovial sarcoma
- Embryonal sarcoma of the liver

3.2.2.2 Eligibility for non-chemotherapy cohort:
Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

- Patients with any size of Grade 2 or 3 of the following "Intermediate (rarely metastasizing)" or "malignant" tumors, as defined in the WHO Classification of Soft Tissue Tumours (see Appendices II and III) for

which we have consensus data of chemotherapy-resistance are eligible only for the non-chemotherapy cohort:

- So-called fibrohistiocytic tumors – plexiform fibrohistiocytic tumor, giant cell tumor of soft tissues
- Fibroblastic/myofibroblastic tumors – solitary fibrous tumor, malignant solitary fibrous tumor, inflammatory myofibroblastic tumor, low grade myofibroblastic sarcoma, myxoinflammatory fibroblastic sarcoma, atypical myxoinflammatory fibroblastic tumor, myxofibrosarcoma, low grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma
- Tumors of uncertain differentiation – epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma of soft tissue, angiomatoid fibrous histiocytoma, ossifying fibromyxoid tumour, myoepithelioma, myoepithelial carcinoma, extraskeletal myxoid chondrosarcoma, neoplasms with perivascular epithelioid cell differentiation (PEComa), intimal sarcoma, atypical fibroxanthoma, mixed tumor NOS, phosphaturic mesenchymal tumor, malignant ossifying fibromyxoid tumor, malignant mixed tumor, malignant phosphaturic mesenchymal tumor
- Chondro-osseous tumors – extraskeletal osteosarcoma
- Pericytic (perivascular) tumors – malignant glomus tumor
- Nerve sheath tumors - malignant peripheral nerve sheath tumor, malignant granular cell tumor, epithelioid malignant peripheral nerve sheath tumor, malignant Triton tumor
- Undifferentiated sarcomas (with a specific pathologic category in the WHO classification) - undifferentiated round cell sarcoma, undifferentiated epithelioid sarcoma, undifferentiated spindle cell sarcoma

3.2.2.2.1 Patients meeting the criteria (histology, size, and grade) in Section 3.2.2.1 with the EXCEPTION of histologies noted in 3.2.2.1.2 may enroll on the non-chemotherapy cohort at the discretion of the enrolling investigator. Patients meeting these criteria with the EXCEPTION of histologies noted in 3.2.2.1.2 but medically deemed unable to receive chemotherapy or who elect not to receive chemotherapy are eligible for the non-chemotherapy cohort.

Note that tumors arising in bone are NOT eligible for this study.

3.2.3 Extent of Disease

a) Patients with non-metastatic and metastatic disease are eligible.

b) Initially unresectable patients, with or without metastatic disease, are eligible as long as there is a commitment at enrollment to resect the primary tumor.

3.2.4 Specimen Submission

Sufficient tissue and blood must be available to submit for required biology studies (see Section 15.1.1).

3.2.5 Performance Level

Lansky performance status score ≥ 70 for patients ≤ 16 years of age.
Karnofsky performance status score ≥ 70 for patients >16 years of age.

3.2.6 Organ Function Requirements

3.2.6.1 Adequate bone marrow function defined as:

- Absolute neutrophil count ≥ 1500/µL
- Platelet count ≥ 100,000/µL
- Hemoglobin:
  - ≥ 8 g/dL for patients ≤ 16 years of age
  - ≥ 9 g/dL for patients > 16 years of age

Note: No transfusions are permitted 7 days prior to laboratory studies to determine eligibility.

3.2.6.2 Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A normal serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.5	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[164] utilizing child length and stature data published by the CDC.

3.2.6.3 Adequate liver function defined as:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age

3.2.6.4 Adequate cardiac function defined as:

- Shortening fraction of ≥ 27% by echocardiogram OR
  Ejection fraction of ≥ 50% by radionuclide angiogram.
- QTc < 480 msec

3.2.6.5 Adequate pulmonary function defined as:

- No evidence of dyspnea at rest, no exercise intolerance, and a resting pulse oximetry reading > 94% on room air if there is clinical indication for determination.

3.2.7 Anticoagulation

Patients on low molecular weight heparin or coumadin (with a stable INR) are eligible.

3.2.8 Life Expectancy

Patient must have a life expectancy of at least 3 months with appropriate therapy.

3.2.9 Exclusion Criteria

3.2.9.1 Patients with Grade 1 NRSTS tumors of any size are not eligible.

3.2.9.2 Patients with known CNS metastases are not eligible.
Note: Brain imaging is not an eligibility requirement.

3.2.9.3 Bleeding Diathesis
Patients with evidence of active bleeding or bleeding diathesis will be excluded (Note: Patients aged > 17 years with excess of 2.5 mL of hemoptysis are not eligible).

3.2.9.4 Tumor Resection
Patients with gross total resection of the primary tumor prior to enrollment on ARST1321 are NOT eligible. Patients who have experienced tumor recurrence after a gross total tumor resection are NOT eligible.

3.2.9.5 Uncontrolled hypertension
Patients with uncontrolled hypertension are ineligible. Uncontrolled hypertension is defined as follows:

- Patients aged ≤ 17 years: greater than 95th percentile systolic and diastolic blood pressure based on age and height (see Appendix V) which is not controlled by one anti-hypertensive medication.
- Patients aged > 17 years: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg that is not controlled by one anti-hypertensive medication.

3.2.9.6 Prior Therapy

3.2.9.6.1 Patients must have had no prior anthracycline (eg, doxorubicin, daunorubicin) or ifosfamide chemotherapy.

3.2.9.6.2 Patients must have had no prior use of pazopanib or similar multi-targeted TKI.

3.2.9.6.3 Patients must have had no prior radiotherapy to tumor-involved sites.

Note: Patients previously treated for a non-NRSTS cancer are eligible provided they meet the prior therapy requirements and the criterion in Section 3.2.9.7 is not applicable. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C)

prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier are excluded.

3.2.9.7 Other types of invasive malignancy that are not disease free within 3 years except for non-melanoma skin cancer, lentigo maligna, any carcinoma-in-situ or prostate cancer with low risk factors.

3.2.9.8 CYP3A4 Substrates WITH Narrow Therapeutic Indices: Patients chronically receiving medications known to be metabolized by CYP3A4 and with narrow therapeutic indices within 7 days prior to study enrollment, including but not limited to pimozide, aripiprazole, triazolam, ergotamine and halofantrine are not eligible. Note: the use of fentanyl is permitted.

3.2.9.9 CYP3A4 Inhibitors: Patients chronically receiving drugs that are known potent CYP3A4 inhibitors within 7 days prior to study enrollment, including but not limited to itraconazole, clarithromycin, erythromycin, many NNRTIs, diltiazem, verapamil, and grapefruit juice are not eligible. See Appendix VI.

3.2.9.10 CYP3A4 Inducers: Patients chronically receiving drugs that are known potent CYP3A4 inducers within 14 days prior to study enrollment, including but not limited to carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort are not eligible (with the exception of Glucocorticoids). See Appendix VI.

3.2.9.11 Certain medications that are associated with a risk for QTc prolongation and/or Torsades de Pointes, although not prohibited, should be avoided or replaced with medications that do not carry these risks, if possible. Comprehensive lists of agents that that are associated with a risk for QTc prolongation and/or Torsades de Pointes can be found in Appendix VII.

3.2.9.12 Subjects with any condition that may impair the ability to swallow or absorb oral medications/investigational product including:

- any lesion, whether induced by tumor, radiation or other conditions, which makes it difficult to swallow capsules or pills
- prior surgical procedures affecting absorption including, but not limited to major resection of stomach or small bowel
- active peptic ulcer disease
- malabsorption syndrome

3.2.9.13 Subjects with any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, including

- active peptic ulcer disease
- known intraluminal metastatic lesions
- inflammatory bowel disease (eg, ulcerative colitis, Crohn's disease) or other gastrointestinal conditions which increase the risk of perforation
- history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days prior to beginning study treatment

3.2.9.14 Subjects with any of the following cardiovascular conditions within the past 6 months

- cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- cardiac arrhythmia
- admission for unstable angina
- cardiac angioplasty or stenting
- coronary artery bypass graft surgery
- pulmonary embolism, untreated deep venous thrombosis (DVT) or DVT which has been treated with therapeutic anticoagulation for less than 6 weeks
- arterial thrombosis
- symptomatic peripheral vascular disease.
- Class III or IV heart failure as defined by the NYHA functional classification system. A subject who has a history of Class II heart failure and is asymptomatic on treatment may be considered eligible.

3.2.9.15 History of serious or non-healing wound, ulcer, or bone fracture.

3.2.9.16 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9.17 Patients who are unable to swallow whole tablets are not eligible.

3.2.9.18 Patients with a Body Surface Area < 0.5 m^2 are not eligible.

3.2.9.19 HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with pazopanib. In addition, these subjects are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.9.20 Patients who are receiving any other investigational agent(s).

3.2.9.21 Pregnancy and Breast Feeding

3.2.9.21.1 Female patients who are pregnant are ineligible due to risks of fetal and teratogenic adverse events as seen in animal/human studies.

3.2.9.21.2 Lactating females are not eligible unless they have agreed not to breastfeed their infants during treatment and for a period of 1 month following completion of treatment.

3.2.9.21.3 Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

3.2.9.22 Unwillingness to use an effective contraceptive method for the duration of their study participation and for at least 1 month after treatment is completed if sexually active with reproductive potential.

3.2.10 Regulatory

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

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

4.0 TREATMENT PROGRAM

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

4.1 Overview of Treatment Plan

This study is designed with 2 independent clinical trials for patients with unresected NRSTS of extremities or trunk. Separate trials will be conducted for patients eligible for the chemotherapy cohort (randomized Phase II study of chemotherapy/RT with or without pazopanib) and non-chemotherapy cohort (randomized Phase II/III study of RT with or without pazopanib).

The study includes a dose-finding and an efficacy phase for therapy with pazopanib. The dose finding phase of the study will assess for dose-limiting toxicities (DLTs) and define the MTD of pazopanib when used in combination with ifosfamide and doxorubicin (ID). The second phase will determine efficacy. Upon successful completion of the dose-finding phase, the protocol will be amended and during the efficacy phase patients will receive the dose of pazopanib defined as the MTD. Patients who received the MTD in the dose-finding phase will not be included in the efficacy phase. The **dose-finding phase for the Chemotherapy Cohort** has been completed and dose level 1 has been identified as the MTD, effective May 2015. The **dose-finding phase for the Non-Chemotherapy Cohort** has been completed and dose level 2 has been identified as the MTD, effective with Amendment #3A. **The Non-Chemotherapy Cohort has been closed to further accrual, effective October 12, 2017.**

4.1.1 Regimens

Patients on this study will be eligible for enrollment either in the chemotherapy cohort or non-chemotherapy cohort based on the criteria as described in Section 3.2. All tumors must be potentially resectable.

Chemotherapy Cohort

Patients eligible for the chemotherapy cohort will be randomized to neoadjuvant combined modality therapy with ID + 45 Gy RT with or without pazopanib:

Regimen A: ID + 45 Gy RT + pazopanib; or

Regimen B: ID + 45 Gy RT

All patients in this cohort will receive radiotherapy (total dose 45 Gy) at Week 4 and will have definitive surgery at Week 13. Week 4 radiotherapy should be started at least 24 hours after completion of the Week 4 doxorubicin. For patients randomized to Regimen A, pazopanib will be held pre- and post-surgery. Post-operatively, patients will proceed with completion of their assigned treatment regimens.

**For gross residual disease, postoperative boost radiotherapy with a dose of 21.6 Gy at 1.8 Gy per fraction is required. For positive microscopic margins, postoperative boost with a dose of 16.2 Gy in 1.8 Gy per fraction is highly recommended but optional based on the discretion of the treating physician. No boost is to be given for negative margins. Negative margin is defined as the microscopic absence of tumor on the inked margins following resection regardless of the proximity of tumor cells to the margin. Week 16 radiotherapy, if required, should start at least 24 hours after completion of the Week 16 doxorubicin. Delay of the postoperative radiotherapy boost should be documented. Omission of the optional postoperative radiotherapy boost (positive microscopic margins) should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10).

Patients with metastatic disease will undergo surgical resection of metastases at the completion of the assigned regimen therapy, with additional radiotherapy for incompletely resectable lesions.

Non-Chemotherapy Cohort
Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

Patients enrolled in the non-chemotherapy cohort will be randomized to neoadjuvant 50 Gy RT with or without pazopanib:

Regimen C: 50 Gy RT + pazopanib; or
Regimen D: 50 Gy RT

All patients in this cohort will begin RT at Week 1 and will have definitive surgery at Week 10. Patients randomized to Regimen C will begin pazopanib concurrently with RT at Week 1 and will resume pazopanib post-operatively. Pazopanib will be held pre- and post-surgery.

**For gross residual disease, postoperative boost radiotherapy with a dose of 20 Gy at 2 Gy per fraction is required. For positive microscopic margins, postoperative boost with a dose of 16 Gy in 2 Gy per fraction is highly recommended but optional based on the discretion of the treating physician. Delay of the postoperative radiotherapy boost should be documented. Omission of the optional postoperative radiotherapy boost (positive microscopic margins) should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10). No boost is to be given for negative margins. Negative margin is defined as the microscopic absence of tumor on the inked

margins following resection regardless of the proximity of tumor cells to the margin.

Patients with metastatic disease will undergo surgical resection of metastases at the completion of the assigned regimen therapy, with additional radiotherapy for incompletely resectable lesions.

4.1.2 Dose-Finding Phase

The dose-finding phase for the Chemotherapy Cohort has been completed and dose level 1 has been identified as the MTD, effective May 2015. The dose-finding phase for the Non-Chemotherapy Cohort has been completed and dose level 2 has been identified as the MTD, effective with Amendment #3A.

The feasibility of combining pazopanib with ID and radiotherapy will be assessed during a carefully designed dose-finding phase. The dose-finding phase will be similar for both treatment cohorts. Initially, 10 patients (minimum of 3 patients < 18 years of age and 3 patients ≥ 18 years of age; eligible for the chemotherapy cohort) will non-randomly be assigned to Regimen A and 10 patients (minimum of 3 patients < 18 years of age and 3 patients ≥ 18 years of age; eligible for the non-chemotherapy cohort) will non-randomly receive Regimen C to assess feasibility (pazopanib pediatric starting dose 350 mg/m^2; adult starting dose 600 mg). The following measures of feasibility will be used: dose-limiting toxicity frequency, total doses of pazopanib delivered, and overall adverse event profile when historically comparing ID to ID + pazopanib or RT alone to RT + pazopanib. Feasibility will be assessed in the first 6 weeks of therapy, during which time patients will have received 2 cycles of ID and/or started RT, to determine pazopanib dose escalations and de-escalations (see table below and Statistical Section).

Pazopanib (Tablet formulation, PO once daily)		
Dose Level	Pediatric Dose	Adult Dose
0	275 mg/m^2	400 mg
1	350 mg/m^2	600 mg
2	450 mg/m^2	800 mg

* Pediatric dosing is for subjects <18 years old and the total daily dose should not exceed the adult dose at the assigned dose level.

4.1.3 Radiation

Radiation is built on the backbone of RTOG 0630 using image guidance. All conformal CT-based techniques including 3D-CRT or IMRT will be permitted. If a 5 mm planning target volume (PTV) is to be used for set-up uncertainty, then daily imaged guided radiotherapy (IGRT) will be required, as in RTOG 0630. For gross residual disease, postoperative boost radiotherapy is required. For positive microscopic margins, postoperative boost radiotherapy is highly recommended but optional based on the discretion of the treating physician. Delay of the postoperative radiotherapy boost should be documented. Omission of the optional postoperative radiotherapy boost (positive microscopic margins) should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10). No boost is to be given for negative margins. Negative margin is defined as the microscopic absence of tumor on the inked

margins following resection regardless of the proximity of tumor cells to the margin.

Clinical target volume will be based on the RTOG Consensus Sarcoma Target Volume Definition[20] using MRI image fusion to encompass areas of T2 edema beyond the T1 post-gadolinium gross tumor or at the minimum using an age specific margin definition (for patients > 18 years, Grade 2 or 3 > 5 cm tumors will be covered using 3 cm CTV margin in the longitudinal directions including suspicious MRI T2 edema and a radial CTV margin of 1.5 cm around portions of the tumor not confined by an intact fascial barrier or bone or skin surface; all other tumors will be covered using a 2 cm CTV margin encompassing suspicious MRI T2 edema and a 1 cm radial CTV margin around portions of the tumor not confined by an intact fascial barrier or bone or skin surface). For skeletally immature patients age ≤ 18, the CTV is based upon ARST0332 and is defined as GTV + 1.5 cm (but not extending outside of the patient).
See Section 17 for complete details of radiation therapy.

4.1.4 Treatment Plan

The chemotherapy regimen to be utilized for the **Chemotherapy Cohort** (Regimen A) will be similar to that used on ARST0332 as described in the table below:

Drug	Dose	Route	Schedule
I: Ifosfamide	2500 mg/m^2/dose (7500 mg/m^2/cycle)	IV	Days 1, 2 and 3 with mesna starting on Day 1 Hour 0 (see Section 4.2)
D: DOXOrubicin	37.5 mg/m^2/dose (75 mg/m^2/cycle) If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days.	IV	Days 1 and 2 with dexrazoxane for all doses
P: Pazopanib **(Only in Regimen A)**	350 mg/m^2 (pediatric) 600 mg (adult)	Oral	Daily in Weeks 1 - 25 except around the time of surgery (see Section 4.2)

For those patients in the Non-Chemotherapy Cohort randomized to receive pazopanib (Regimen C), the drug will be administered orally, daily in Weeks 1-25 except around the time of surgery (see Section 4.4). The dose is 450 mg/m^2 (pediatric) and 800 mg (adult).

Note: Patients with progressive disease by imaging at Week 10 or 13 who do not have surgery and those with recurrent disease will go off protocol therapy (see Section 10.2.4 for the definition of progressive disease).

4.1.4.1 Treatment Schema for Chemotherapy Cohort

Regimen A: Neoadjuvant Chemotherapy and Radiotherapy with Pazopanib

Regimen A								
Induction Phase				**Surgery**	**Continuation Phase**			
Week 1	Week 4	Week 7	Week 10	Week 13	Week 16	Week 19	Week 22	Weeks 23-25
I	I	I	I	Surgery	I	I		
D	D				D*^	D*@	D	
Pazopanib# Weeks 1-12					Pazopanib# Weeks 16-25			
	Radiotherapy†				Radiotherapy†			

* For patients with liver primary tumors who do not receive neoadjuvant radiotherapy, Weeks 16 and 19 DOXOrubicin doses may be administered at Weeks 7 and 10.

^ Week 16 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving intraoperative RT or brachytherapy following Week 13 surgery.

@ Week 19 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving external beam radiotherapy following Week 13 surgery.

Pazopanib is administered daily but will be held at least 7 days prior to surgery. **For pediatric patients (< 18 years of age) please use dosing tables for pazopanib provided in Appendix XVII.** Week 16 pazopanib therapy (and radiotherapy, if required) may be started up to 7 days early if wound healing is adequate, but should not begin fewer than 14 days after Week 13 surgery.

† See Section 17 for complete radiotherapy guidelines.

- Omit radiotherapy at Week 4 for patients with hepatic primary tumors. Radiotherapy may be given at Week 16 for patients with hepatic primary tumors.
- Postoperative boost radiotherapy dose at Week 16 depends on the extent of Week 13 surgery and the microscopic margin status (see Section 17.6.1).
- Radiotherapy to metastatic sites occurs at the completion of and recovery from all chemotherapy and pazopanib therapy, and after maximal resection of metastases.

Regimen B: Neoadjuvant Chemotherapy and Radiotherapy

Regimen B							
Induction Phase				**Surgery**	**Continuation Phase**		
Week 1	Week 4	Week 7	Week 10	Week 13	Week 16	Week 19	Week 22
I	I	I	I	Surgery	I	I	
D	D				D*^	D*@	D
	Radiotherapy†				Radiotherapy†		

* For patients with liver primary tumors who do not receive neoadjuvant radiotherapy, Weeks 16 and 19 DOXOrubicin doses may be administered at Weeks 7 and 10.

^ Week 16 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving intraoperative RT or brachytherapy following Week 13 surgery.

@ Week 19 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving external beam radiotherapy following Week 13 surgery.

† See Section 17 for complete radiotherapy guidelines.

- Omit radiotherapy at Week 4 for patients with hepatic primary tumors. Radiotherapy may be given at Week 16 for patients with hepatic primary tumors.
- Postoperative boost radiotherapy dose at Week 16 depends on the extent of Week 13 surgery and the microscopic margin status (see Section 17.6.1).
- Radiotherapy to metastatic sites occurs at the completion of and recovery from all chemotherapy and after maximal resection of metastases.

4.1.4.2 Treatment Schema for Non-Chemotherapy Cohort

Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

Regimen C: Neoadjuvant Radiotherapy and Pazopanib

<table>
<tr><th colspan="8">Regimen C</th></tr>
<tr><th colspan="3">Induction Phase</th><th>Surgery</th><th colspan="4">Continuation Phase</th></tr>
<tr><td>Week 1</td><td>Week 4</td><td>Week 7</td><td rowspan="3">Week 10
Surgery</td><td>Week 13</td><td>Week 16</td><td>Week 19</td><td>Weeks 22- 25</td></tr>
<tr><td colspan="3">Pazopanib # Weeks 1-9</td><td colspan="4">Pazopanib # 13-25</td></tr>
<tr><td colspan="3">Radiotherapy†</td><td colspan="2">Radiotherapy†</td><td colspan="2"></td></tr>
</table>

Pazopanib is administered daily but will be held at least 7 days prior to surgery. **For pediatric patients (< 18 years of age), please use dosing tables for pazopanib provided in Appendix XVII.** Week 13 pazopanib therapy (and radiotherapy, if required) may be started up to 7 days early if wound healing is adequate, but should not begin fewer than 14 days after Week 10 surgery.

† See Section 17 for complete radiotherapy guidelines.

- Omit radiotherapy at Week 1 for patients with hepatic primary tumors. Radiotherapy may be given at Week 13 for patients with hepatic primary tumors.
- Postoperative boost radiotherapy dose at Week 13 depends on the extent of Week 10 surgery and the microscopic margin status (see Section 17.6.1).
- Radiotherapy to metastatic sites occurs at the completion of and recovery from all pazopanib therapy and after maximal resection of metastases.

Regimen D: Neoadjuvant Radiotherapy

<table>
<tr><th colspan="6">Regimen D</th></tr>
<tr><th colspan="3">Induction Phase</th><th>Surgery</th><th colspan="2">Continuation Phase</th></tr>
<tr><td>Week 1</td><td>Week 4</td><td>Week 7</td><td rowspan="2">Week 10
Surgery</td><td>Week 13</td><td>Week 16</td><td>Weeks 19-25</td></tr>
<tr><td colspan="3">Radiotherapy†</td><td colspan="2">Radiotherapy†</td><td></td></tr>
</table>

† See Section 17 for complete radiotherapy guidelines.

- Omit radiotherapy at Week 1 for patients with hepatic primary tumors. Radiotherapy may be given at Week 13 for patients with hepatic primary tumors.
- Postoperative boost radiotherapy dose at Week 13 depends on the extent of Week 10 surgery and the microscopic margin status (see Section 17.6.1).
- Radiotherapy to metastatic sites occurs at the completion of and recovery from all other protocol-specified radiotherapy and after maximal resection of metastases.

4.1.5 Response Assessment

During the efficacy phase, response to therapy will be assessed at Week 10 or 13 by histopathologic review (pathologic response), standard imaging (CT or MRI, as appropriate), and FDG PET imaging. Patients with progressive disease by imaging at Week 10 or 13 will go off protocol therapy (see Section 10.2.4 for the definition of progressive disease).

4.1.6 Concomitant Therapy

Pazopanib *in vitro* studies showed that pazopanib is a potent inhibitor of UGT1A1 and OAT1B1 with IC_{50} of 1.2 and 0.79 µM respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGTA1A1 and OATP1B1. The active metabolite of irinotecan, SN-38, is a substrate for OATB1 and several UGT enzymes, including UGT1A1. Co-administration of pazopanib and

irinotecan increase the systemic exposure to both the parent drug and the active metabolite SN-38. Avoid, as much as possible, drugs primarily eliminated through UGTA1A1 and OATP1B1.

Concomitant use of pazopanib and simvastin increases the incidence of ALT elevations. If a patient receiving concomitant simvastin develops ALT elevations, discontinue simvastin.

Co-administration of pazopanib with medicines that increase gastric pH should be avoided. If concomitant administration of an H2 receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist. Pazopanib should be administered at least 1 hour before and 2 hours after administration of short-acting antacids.

Concomitant medications that have narrow therapeutic windows and are substrates of CYP3A4, CYP2D6 or CYP2C8 should be used with caution.

The table below provides examples of agents which should be avoided; note that this is not an exhaustive list.

Class	Drug examples	Rationale	Action
Strong CYP3A4 inhibitors	See Appendix VI Ketaconazole Itraconazole Voriconazole Clarithomycin	May increase pazopanib concentrations	Avoid concomitant administration with pazopanib
Neurokinin Antagonist	Aprepritant	Aprepitant can inhibit and induce CYP3A4 depending on the duration of therapy and may alter concentrations of medications metabolized by CYP3A4	Do NOT give with ifosfamide or doxorubicin; avoid use with pazopanib
CYP3A4 inducers	Rifampin	May decrease pazopanib concentrations	Select an alternative concomitant medication
Simvastatin		Concomitant use with pazopanib increases the risk of ALT elevation	Avoid use if possible. Monitor closely if given concomitantly
Medications eliminated through UGT1A1 and OATP1B1	A list of medications may be found at: http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm	Pazopanib may increase concentrations of drugs primarily eliminated by UGT1A1 and OATP1B1	Avoid concomitant use with these medications. See Section 5.7.2 for recommendations for adjustments for isolated ALT elevations

Proton pump inhibitors	Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	Pazopanib concentrations may be reduced by agents that increase gastric pH	Pazopanib should be taken without food once daily in the evening with the PPI.
H_2-receptor antagonists	Cimetidine Famotidine Nizatidine Ranitidine	Pazopanib concentrations may be reduced by agents that increase gastric pH	Take pazopanib in the a.m. and the H_2-receptor antagonist in p.m.; if bid H_2-receptor antagonist then take pazopanib without food 2 hours before or 10 hours after the H_2-receptor antagonist dose
Short-acting antacids	Aluminum hydroxide Calcium carbonate Magnesium hydroxide	Pazopanib concentrations may be reduced by agents that increase gastric pH	Administer pazopanib 1 hour before or 2 hours after the antacid
Agents with potential to increase QTc	See Appendix VII Chlorpromazine Clarithromycin Erythromycin Haloperidol Methadone Pentamidine	Risk of QTc prolongation &/or Torsades de pointes	Agents "generally accepted" to cause risk of Torsades de pointes are prohibited. Agents "associated" with a risk of Torsades de pointes should be discontinued or replaced with agents that don't carry these risks, if possible. Ondansetron or granisetreon may be used if QTc prolongation is not seen on an EKG during the first week of co-administration. For other agents with an "associated" risk, close monitoring and additional EKGs should be performed at investigator discretion if medications continued. Avoid the use of pentamidine

4.1.7 Supportive Care Guidelines

Please see Appendix VIII for protocol–specific supportive care guidelines. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

4.2 Treatment Administration Schedule for Patients on Regimen A

Note: See the Parenteral Chemotherapy Administration Guidelines (CAG) for children on the COG website at: https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As

applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

4.2.1 Induction Phase for Regimen A (Weeks 1-12)

Induction therapy consists of 12 weeks of chemotherapy plus pazopanib along with radiation therapy (see Section 17 for RT details). Week 4 radiotherapy should be started at least 24 hours after completion of the Week 4 doxorubicin.
Note: omit radiotherapy at Week 4 for patients with hepatic primary tumors. For patients with liver primary tumors who do not receive neoadjuvant radiotherapy, Weeks 16 and 19 DOXOrubicin doses may be administered at Weeks 7 and 10 (scheduling of ifosfamide should remain the same).

Therapy is presented as four 21-day cycles in the therapy delivery map.

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

Dexrazoxane: Slow IV push/infusion over 5-15 minutes given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 1 and 4
Dose: 375 mg/m^2/dose (eg, 10 mg of dexrazoxane for every mg of DOXOrubicin).

Note: Administer DOXOrubicin after completing the infusion of dexrazoxane. The administration of dexrazoxane plus doxorubicin should be completed within a total of 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes.
Days: 1 and 2 of Weeks 1 and 4
Dose: 37.5 mg/m^2/dose (**75 mg/m^2/cycle**). If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days.

Administer at a concentration not to exceed 2 mg/mL. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Ifosfamide: IV, infuse the diluted solution over 2-4 hours
Days: 1, 2 and 3 of Weeks 1, 4, 7 and 10
Dose: 2500 mg/m^2/dose (**7500 mg/m^2/cycle)**

Mesna must be administered in conjunction with ifosfamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for ifosfamide: Administer 3,000 mL/m^2/day (125 mL/m^2/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl.

Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with Ifosfamide

Administer MESNA by IV infusion or IV/PO on Days 1-3 of Weeks 1, 4, 7 and 10

Total IV Dose: 2500 mg/m^2/day.

Mesna IV short or continuous infusion:

For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily ifosfamide dose. Mesna can be administered in 5 divided doses by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the ifosfamide dose; subsequent doses are given 3, 6, 9, and 12 hours after the start of ifosfamide.

For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; 200 mg of mesna will be given 15 minutes before or with the ifosfamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide and finished no sooner than 12 hours after the end of the ifosfamide infusion.

For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; the 1,000 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide and be completed no sooner than 12 hours after **the end** of the ifosfamide infusion. If ifosfamide is administered over 2 hour and mesna is started 30 minutes before the ifosfamide infusion, the total mesna infusion will last at least 14 hours and 30 minutes.

Use of oral mesna:

The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **FOUR** bolus doses (originally at Hours 3, 6, 9, and 12) orally at 40% of the ifosfamide dose. The oral doses will be administered at Hours 1, 4, 7, and 10.

For example: if the ifosfamide dose is 1,000 mg, then the first 200 mg dose of mesna will be given IV 15 minutes before or with the ifosfamide dose (Hour 0) and **FOUR** oral doses of 400 mg each will be given at Hours 1, 4, 7, and 10.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parenteral solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Pazopanib: PO
Days: Daily from Weeks 1-12. **To be held at least 7 days PRIOR to surgery.** This may mean stopping pazopanib before the end of Week 12 and will depend upon the timing of surgery.
Dose: Dose level 1: 350 mg/m^2 (pediatric), 600 mg (adult). **For pediatric patients (< 18 years of age), please use dosing tables for pazopanib provided in Appendix XVII.** Pediatric dosing is for subjects < 18 years old and the total daily dose should not exceed the adult dose at the assigned dose level.

Subjects should be instructed to swallow tablets once a day (preferably in the morning) on an empty stomach, either 1 hour before or 2 hours after food with about 1 cup (240 mL.) water. **Tablets should be swallowed whole; they must not be chewed, broken, or crushed.**

NOTE: If a dose is missed, do not take or "make up" the dose unless there is at least 12 hours until the next scheduled dose. If the patient vomits within 30 minutes of taking the dose, the dose may be repeated. If more than 30 minutes have elapsed, do not repeat the dose.

Growth Factor Support
Administration of growth factor is required after all chemotherapy cycles *except* when doxorubicin is administered alone. Use of growth factor after doxorubicin alone is optional. Begin myeloid growth factor support (filgrastim or pegfilgrastim according to institutional standards) at least 24-36 hours after the last dose of myelosuppressive chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/μL post nadir (continue without regard to pazopanib administration) and discontinue at least 24 hours prior to next cycle of chemotherapy.

Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Induction are provided in Appendix IX.

Following the Induction phase, surgery (see Section 13 for details) will be done at Week 13. See Section 7.1.1 for observations prior to Local Control. The Continuation phase of therapy (detailed below) will follow Local Control.

4.2.2 Continuation Phase for Regimen A (Weeks 16-25)

Continuation therapy consists of 10 weeks of chemotherapy plus pazopanib along with radiation therapy. Therapy is presented as three 21-day cycles plus one extra week of pazopanib in the therapy delivery map.

Criteria to start each cycle: ANC ≥ 750/μL and platelet count ≥ 75,000/μL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/μL after the nadir but then falls the next cycle should be given despite ANC < 750/μL.

Week 16 chemotherapy (and radiotherapy, if required) may be started up to 7 days early if wound healing is adequate, but should not begin fewer than 14 days after Week 13 surgery. Also, Week 16 radiotherapy, if required, should start at least 24 hours after administration of DOXOrubicin.

Initiation of postoperative chemotherapy (and radiotherapy, if required or indicated by residual disease or positive margin) should begin within 6 weeks of the date of Week 13 surgery. If wound complications preclude initiating postoperative chemotherapy within 6 weeks of the date of surgery, this should be documented on the appropriate case report form (CRF). Documentation of the delay to postoperative boost radiotherapy should be submitted with the RT QA materials (see Section 17.10).

PLEASE NOTE:

- Week 16 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving intraoperative RT or brachytherapy following Week 13 surgery.
- Week 19 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving external beam radiotherapy following Week 13 surgery.
- See Section 17 for complete radiotherapy guidelines, these include:
  - Postoperative boost radiotherapy dose at Week 16 depends on the extent of Week 13 surgery and the microscopic margin status.
  - Week 16 radiotherapy is optional for patients with hepatic primary tumors.
  - Radiotherapy to metastatic sites occurs at the completion of and recovery from all chemotherapy and pazopanib therapy, and after maximal resection of metastases.

Dexrazoxane: Slow IV push/infusion over 5-15 minutes given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 16, 19 and 22
Dose: 375 mg/m^2/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin).

Note: Administer DOXOrubicin after completing the infusion of dexrazoxane. The administration of dexrazoxane plus doxorubicin should be completed within a total of 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes.
Days: 1 and 2 of Weeks 16, 19 and 22
Dose: 37.5 mg/m^2/dose (**75 mg/m^2/cycle**). If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days.

Administer at a concentration not to exceed 2 mg/mL. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Ifosfamide: IV, infuse the diluted solution over 2-4 hours
Days: 1-3 of Weeks 16 and 19
Dose: 2500 mg/m^2/dose **(7500 mg/m^2/cycle)**

Mesna must be administered in conjunction with ifosfamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for ifosfamide: Administer 3,000 mL/m^2/day (125 mL/m^2/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with Ifosfamide
Administer MESNA by IV infusion or IV/PO on Days 1-3 of Weeks 16 and 19
Total IV Dose: 2,500 mg/m^2/day.

Mesna IV short or continuous infusion:
For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily ifosfamide dose. Mesna can be administered in 5 divided doses by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the ifosfamide dose; subsequent doses are given 3, 6, 9, and 12 hours after the start of ifosfamide.
For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; 200 mg of mesna will be given 15 minutes before or with the ifosfamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide and finished no sooner than 12 hours after the end of the ifosfamide infusion.
For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; the 1,000 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide and be completed no sooner than 12 hours after **the end** of the ifosfamide infusion. If ifosfamide is administered over 2 hour and mesna is started 30 minutes before the ifosfamide infusion, the total mesna infusion will last at least 14 hours and 30 minutes.

Use of oral mesna:
The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **FOUR** bolus doses (originally at Hours 3, 6, 9, and 12) orally at 40% of the ifosfamide dose. The oral doses will be administered at Hours 1, 4, 7, and 10.
For example: if the ifosfamide dose is 1,000 mg, then the first 200 mg dose of mesna will be given IV 15 minutes before or with the ifosfamide dose (Hour 0) and **FOUR** oral doses of 400 mg each will be given at Hours 1, 4, 7, and 10.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parenteral solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and

orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of cyclophosphamide/ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Pazopanib: PO
Days: Daily from Weeks 16-25 **(resume no sooner than 14 days FOLLOWING primary surgery; discontinue at least 7 days PRIOR to any surgery planned at the completion of Continuation therapy).**
Dose: Dose level 1: 350 mg/m^2 (pediatric), 600 mg (adult). **For pediatric patients (< 18 years of age), please use dosing tables for pazopanib provided in Appendix XVII.** Pediatric dosing is for subjects < 18 years old and the total daily dose should not exceed the adult dose at the assigned dose level.

Subjects should be instructed to swallow tablets once a day (preferably in the morning) on an empty stomach, either 1 hour before or 2 hours after food with about 1 cup (240 mL.) water. **Tablets should be swallowed whole; they must not be chewed, broken, or crushed.**

NOTE: If a dose is missed, do not take or "make up" the dose unless there is at least 12 hours until the next scheduled dose. If the patient vomits within 30 minutes of taking the dose, the dose may be repeated. If more than 30 minutes have elapsed, do not repeat the dose.

Growth Factor Support
Administration of growth factor is required after all chemotherapy cycles *except* when doxorubicin is administered alone. Use of growth factor after doxorubicin alone is optional. Begin myeloid growth factor support (filgrastim or pegfilgrastim according to institutional standards) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/μL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy.

Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Regimen A Continuation therapy are provided in Appendix IX.

4.3 Treatment Administration Schedule for Patients on Regimen B

4.3.1 Induction Phase for Regimen B (Weeks 1-12)

Induction therapy consists of 12 weeks of chemotherapy along with radiation therapy (see Section 17 for RT details). **Note: omit radiotherapy at Week 4 for patients with hepatic primary tumors. For patients with liver primary tumors who do not receive neoadjuvant radiotherapy, Weeks 16 and 19**

DOXOrubicin doses may be administered at Weeks 7 and 10. (scheduling of ifosfamide should remain the same).

Therapy is presented as four 21-day cycles in the therapy delivery map.

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

Dexrazoxane: Slow IV push/infusion over 5-15 minutes given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 1 and 4
Dose: 375 mg/m^2/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin).

Note: Administer DOXOrubicin after completing the infusion of dexrazoxane. The administration of dexrazoxane plus doxorubicin should be completed within a total of 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes.
Days: 1 and 2 of Weeks 1 and 4
Dose: 37.5 mg/m^2/dose (**75 mg/m^2/cycle**). If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days.

Administer at a concentration not to exceed 2 mg/mL. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Ifosfamide: IV, infuse the diluted solution over 2-4 hours
Days: 1-3 of Weeks 1, 4, 7, and 10
Dose: 2500 mg/m^2/dose (**7500 mg/m^2/cycle)**

Mesna must be administered in conjunction with ifosfamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for ifosfamide: Administer 3,000 mL/m^2/day (125 mL/m^2/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with Ifosfamide
Administer MESNA by IV infusion or IV/PO on Days 1-3 of Weeks 1, 4, 7, and 10.
Total IV Dose: 2500 mg/m^2/day.

Mesna IV short or continuous infusion:
For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily ifosfamide dose. Mesna can be administered in 5 divided doses by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the ifosfamide dose; subsequent doses are given 3, 6, 9, and 12 hours after the start of ifosfamide.
For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; 200 mg of mesna will be given 15 minutes before or with the ifosfamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide and finished no sooner than 12 hours after the end of the ifosfamide infusion.
For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; the 1,000 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide and be completed no sooner than 12 hours after **the end** of the ifosfamide infusion. If ifosfamide is administered over 2 hour and mesna is started 30 minutes before the ifosfamide infusion, the total mesna infusion will last at least 14 hours and 30 minutes.

Use of oral mesna:
The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **FOUR** bolus doses (originally at Hours 3, 6, 9, and 12) orally at 40% of the ifosfamide dose. The oral doses will be administered at Hours 1, 4, 7, and 10.
For example: if the ifosfamide dose is 1,000 mg, then the first 200 mg dose of mesna will be given IV 15 minutes before or with the ifosfamide dose (Hour 0) and **FOUR** oral doses of 400 mg each will be given at Hours 1, 4, 7, and 10.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parenteral solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of cyclophosphamide/ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

<u>Growth Factor Support</u>
Administration of growth factor is required after all chemotherapy cycles *except* when doxorubicin is administered alone. Use of growth factor after doxorubicin alone is optional. Begin myeloid growth factor support (filgrastim or pegfilgrastim according to institutional standards) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/μL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy.

Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Regimen B Induction are provided in Appendix X.

Following the Induction phase, surgery (see Section 13 for details) will be done at Week 13. See Section 7.1.2 for observations prior to surgery. The Continuation phase of therapy (detailed below) will follow Local Control.

4.3.2 Continuation Phase for Regimen B (Weeks 16-24)

Continuation consists of 9 weeks of chemotherapy along with radiation therapy. Therapy is presented as three 21-day cycles in the therapy delivery map.

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

Week 16 chemotherapy (and radiotherapy, if required) may be started up to 7 days early if wound healing is adequate, but should not begin fewer than 14 days after Week 13 surgery. Also, Week 16 radiotherapy, if required, should start at least 24 hours after administration of DOXOrubicin.

Initiation of postoperative chemotherapy (and radiotherapy, if required or indicated by residual disease or positive margin) should begin within 6 weeks of the date of Week 13 surgery. If wound complications preclude initiating postoperative chemotherapy within 6 weeks of the date of surgery, this should be documented on the appropriate case report form (CRF). Documentation of the delay to postoperative boost radiotherapy should be submitted with the RT QA materials (see Section 17.10).

PLEASE NOTE:

- Week 16 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving intraoperative RT or brachytherapy following Week 13 surgery.
- Week 19 DOXOrubicin may be omitted and administered instead at Week 25 if necessary in patients receiving external beam radiotherapy following Week 13 surgery.
- See Section 17 for complete radiotherapy guidelines, these include:
  - Postoperative boost radiotherapy dose at Week 16 depends on the extent of Week 13 surgery and the microscopic margin status.
  - Week 16 radiotherapy is optional for patients with hepatic primary tumors.
  - Radiotherapy to metastatic sites occurs at the completion of and recovery from all chemotherapy, and after maximal resection of metastases.

Dexrazoxane: Slow IV push/infusion over 5-15 minutes given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 16, 19 and 22
Dose: 375 mg/m^2/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin).

Note: Administer DOXOrubicin after completing the infusion of dexrazoxane. The administration of dexrazoxane plus doxorubicin should be completed within a total of 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes.
Days: 1 and 2 of Weeks 16, 19 and 22
Dose: 37.5 mg/m^2/dose (**75 mg/m^2/cycle**). If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days.

Administer at a concentration not to exceed 2 mg/mL. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Ifosfamide: IV, infuse the diluted solution over 2-4 hours
Days: 1-3 of Weeks 16 and 19
Dose: 2500 mg/m^2/dose (**7.5 grams/m^2/cycle)**

Mesna must be administered in conjunction with ifosfamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for ifosfamide: Administer 3,000 mL/m^2/day (125 mL/m^2/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with Ifosfamide
Administer MESNA by IV infusion or IV/PO on Days 1-3 of Weeks 16 and 19
Total IV Dose: 2500 mg/m^2/day.

Mesna IV short or continuous infusion:
For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily ifosfamide dose. Mesna can be administered in 5 divided doses by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the ifosfamide dose; subsequent doses are given 3, 6, 9, and 12 hours after the start of ifosfamide.
For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; 200 mg of mesna will be given 15 minutes before or with the ifosfamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide and finished no sooner than 12 hours after the end of the ifosfamide infusion.

For example: if the ifosfamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; the 1,000 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide and be completed no sooner than 12 hours after **the end** of the ifosfamide infusion. If ifosfamide is administered over 2 hour and mesna is started 30 minutes before the ifosfamide infusion, the total mesna infusion will last at least 14 hours and 30 minutes.

Use of oral mesna:
The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **FOUR** bolus doses (originally at Hours 3, 6, 9, and 12) orally at 40% of the ifosfamide dose. The oral doses will be administered at Hours 1, 4, 7, and 10.
For example: if the ifosfamide dose is 1,000 mg, then the first 200 mg dose of mesna will be given IV 15 minutes before or with the ifosfamide dose (Hour 0) and **FOUR** oral doses of 400 mg each will be given at Hours 1, 4, 7, and 10.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parenteral solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of cyclophosphamide/ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Growth Factor Support
Administration of growth factor is required after all chemotherapy cycles *except* when doxorubicin is administered alone. Use of growth factor after doxorubicin alone is optional. Begin myeloid growth factor support (filgrastim or pegfilgrastim according to institutional standards) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/μL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy.

Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Regimen B Continuation are provided in Appendix X.

4.4 Treatment Administration Schedule for Patients on Regimen C

Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

4.4.1 Induction Phase for Regimen C (Weeks 1-9)

Induction therapy consists of 9 weeks of pazopanib therapy along with radiation therapy (see Section 17 for RT details). **Note: omit radiotherapy at Week 1 for patients with hepatic primary tumors.**

Therapy is presented as three 21-day cycles in the therapy delivery map.

Pazopanib: PO
Days: Daily from Weeks 1-9. **To be held at least 7 days PRIOR to surgery.** This may mean stopping pazopanib before the end of Week 9 and will depend upon the timing of surgery.
Dose: Dose level 2: 450 mg/m^2 (pediatric), 800 mg (adult). **For pediatric patients (< 18 years of age), please use dosing tables for pazopanib provided in Appendix XVII.** Pediatric dosing is for subjects < 18 years old and the total daily dose should not exceed the adult dose at the assigned dose level.

Subjects should be instructed to swallow tablets once a day (preferably in the morning) on an empty stomach, either 1 hour before or 2 hours after food with about 1 cup (240 mL.) water. **Tablets should be swallowed whole; they must not be chewed, broken, or crushed.**

NOTE: If a dose is missed, do not take or "make up" the dose unless there is at least 12 hours until the next scheduled dose. If the patient vomits within 30 minutes of taking the dose, the dose may be repeated. If more than 30 minutes have elapsed, do not repeat the dose.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Induction are provided in Appendix XI. Following Induction phase, surgery (see Section 13 for details) and will be done at Week 10. See Section 7.1.3 for observations prior to Surgery. The Continuation phase of therapy (detailed below) will follow Local Control.

4.4.2 Continuation Phase for Regimen C (Weeks 13-25)

Continuation therapy consists of 13 weeks of pazopanib therapy along with radiation therapy. Therapy is presented as four 21-day cycles plus one extra week of pazopanib in the therapy delivery map.

Initiation of postoperative therapy (and radiotherapy, if required or indicated by residual disease or positive margin) should begin within 6 weeks of the date of Week 10 surgery. If wound complications preclude initiating postoperative pazopanib within 6 weeks of the date of surgery, this should be documented on the appropriate case report form (CRF). Documentation of the delay to postoperative boost radiotherapy should be submitted with the RT QA materials (see Section 17.10).

PLEASE NOTE:

- See Section 17 for complete radiotherapy guidelines, these include:
  - Postoperative boost radiotherapy dose at Week 13 depends on the extent of Week 10 surgery and the microscopic margin status.
  - Week 13 radiotherapy is optional for patients with hepatic primary tumors.
  - Radiotherapy to metastatic sites occurs at the completion of and recovery from all pazopanib therapy, and after maximal resection of metastases.

Pazopanib: PO
Days: Daily from Weeks 13-25
Dose: Dose level 2: 450 mg/m^2 (pediatric), 800 mg (adult). **For pediatric patients (<18 years old), please use dosing tables for pazopanib provided in Appendix XVII.** Pediatric dosing is for subjects < 18 years old and the total daily dose should not exceed the adult dose at the assigned dose level.

Subjects should be instructed to swallow tablets once a day (preferably in the morning) on an empty stomach, either 1 hour before or 2 hours after food with about 1 cup (240 mL.) water. **Tablets should be swallowed whole; they must not be chewed, broken, or crushed.**

NOTE: If a dose is missed, do not take or "make up" the dose unless there is at least 12 hours until the next scheduled dose. If the patient vomits within 30 minutes of taking the dose, the dose may be repeated. If more than 30 minutes have elapsed, do not repeat the dose.

Week 13 pazopanib therapy (and radiotherapy, if required) may be started up to 7 days early if wound healing is adequate, but should not begin fewer than 14 days after Week 10 surgery.
Discontinue pazopanib at least 7 days PRIOR to any surgery planned at the completion of Continuation therapy.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Continuation phase are provided in Appendix XI.
See Section 7.1.3 for observations required at the end of therapy.

4.5 Treatment Administration Schedule for Patients on Regimen D

Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

Patients on Regimen D will receive radiotherapy as described in Section 17 and surgery as described in Section 13.

PLEASE NOTE:

- See Section 17 for complete radiotherapy guidelines, these include:
  - Omit radiotherapy at Week 1 for patients with hepatic primary tumors.
  - Postoperative boost radiotherapy dose at Week 13 depends on the extent of Week 10 surgery and the microscopic margin status.
  - Initiation of postoperative radiotherapy, if required or indicated by residual disease or positive margin should begin within 6 weeks of the date

of Week 10 surgery. If wound complications preclude initiating postoperative boost radiotherapy within 6 weeks of the date of surgery, documentation of the delay to postoperative boost radiotherapy should be submitted with the RT QA materials (see Section 17.10).
- Week 13 radiotherapy is optional for patients with hepatic primary tumors.
- Radiotherapy to metastatic sites occurs at the completion of and recovery from all other protocol-specified radiotherapy, and after maximal resection of metastases.

Therapy delivery maps for radiotherapy administration are not provided in this protocol.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose-Limiting Toxicity

The following TKI-associated adverse events will be defined as dose-limiting toxicities (DLTs):

Dose-limiting hypertension:
- Grade 3 hypertension not controlled after a week on 2 anti-hypertensive medications
- Grade 4 hypertension

Dose-limiting cardiotoxicity
- Grade 3+ left ventricular systolic dysfunction

Dose-limiting dermatitis
- Grade 3+ hand-foot skin reaction (palmar-plantar erythrodysesthesia syndrome)
- Grade 3+ dermatitis radiation

Dose-limiting gastrointestinal toxicity:
- Grade 3+ ALT
- Grade 3+ bilirubin
- Grade 4 amylase
- Grade 4 lipase
- Grade 4 mucositis

Dose-limiting nephrotoxicity:
- Grade 3+ proteinuria

In addition, any death as a first event not attributable to disease will be counted as a dose-limiting toxicity event, as will any withdrawal from protocol treatment as a result of "intolerable toxicity".

5.2 Pazopanib Dose Reductions Table

	Chemotherapy Cohort		Non-Chemotherapy Cohort	
Starting Dose	Pediatric Dose* 350 mg/m^2	Adult Dose 600 mg	Pediatric Dose* 450 mg/m^2	Adult Dose 800 mg
Dose Reduction Level 1	Decrease weekly dosing by 25% from the starting dose	400 mg	Decrease weekly dosing by 25% from the starting dose	600 mg
Dose Reduction Level 2	Decrease weekly dosing by 50% from the starting dose	200 mg	Decrease weekly dosing by 50% from the starting dose	400 mg
Dose Reduction Level 3	Decrease weekly dosing by 75% from the starting dose	off protocol	Decrease weekly dosing by 75% from the starting dose	200 mg

* Refer to Appendix XVII. Pediatric dosing for patients < 18 years of age.

5.3 Hematologic Toxicity

5.3.1 Prolonged Neutropenia and Thrombocytopenia

If a chemotherapy cycle is delayed for > 7 days (ie, beyond Day 28 of the prior cycle), reduce the dose of doxorubicin/ifosfamide (and pazopanib for Regimen A) as outlined below. Consider holding trimethoprim-sulfamethoxazole prophylaxis in the event of prolonged neutropenia (Grade 4 for > 7 days), and utilizing a different type of Pneumocystis (carinii) jirovecii prophylaxis (see Appendix VIII).

5.3.1.1 Patients randomized to Ifosfamide/Doxorubicin **WITHOUT** Pazopanib

Delay prior to Ifosfamide AND Doxorubicin **WITHOUT** Pazopanib Cycle		
Hematologic Parameters	**Delay Occurrence with this Combination**	**Dose Modifications***
ANC < 750/µL OR Platelets < 75,000/µL	First	• **Ifosfamide:** Reduce dose to **2000** mg/m2/day x 3 days (6000 mg/m^2/cycle) • **Doxorubicin:** No change
	Second	• **Ifosfamide**: Reduce dose to **1500** mg/m^2/day x 3 days (4500 mg/m^2/cycle) • **Doxorubicin**: No change
	Third	• **Ifosfamide**: Continue dose of **1500** mg/m^2/day x 3 days • **Doxorubicin**: Reduce dose to **30** mg/m^2/day x 2 days (60 mg/m^2/cycle)

* Delay therapy until counts are met. Any cycle delay >3 weeks (ie, beyond Day 42 of the prior cycle) due to neutropenia or thrombocytopenia will result in the patient being removed from protocol therapy.
If counts are met (ANC ≥750/µL and Platelets ≥75,000/µL) by the time of the next scheduled chemotherapy cycle following the dose reduction(s), subsequent cycles of therapy should be at the same reduced dose unless the apparent cause of delayed recovery is no longer present.
Dose reductions will be made for neutropenia only during chemotherapy cycles that include both ifosfamide and doxorubicin. If single-agent therapy with either ifosfamide or doxorubicin is due, there will be no dose reduction.

5.3.1.2 Patients randomized to Ifosfamide/Doxorubicin **WITH** Pazopanib

Delay prior to Ifosfamide AND Doxorubicin **WITH** Pazopanib Cycle		
Hematologic Parameters	**Delay Occurrence with this Combination**	**Dose Modifications***
ANC < 750/µL OR Platelets < 75,000/µL	First	• **Ifosfamide:** Reduce dose to **2000** mg/m2/day x 3 days (6000 mg/m^2/cycle) • **Doxorubicin:** No change • **Pazopanib:** No change
	Second	• **Ifosfamide**: Reduce dose to **1500** mg/m^2/day x 3 days (4500 mg/m^2/cycle) • **Doxorubicin**: No change • **Pazopanib:** No change
	Third	• **Ifosfamide**: Continue dose of **1500** mg/m^2/day x 3 days • **Doxorubicin**: Reduce dose to **30** mg/m^2/day x 2 days (60 mg/m^2/cycle) • **Pazopanib:** No change
	Fourth	• **Ifosfamide**: Continue dose of **1500** mg/m^2/day x 3 days • **Doxorubicin**: Continue dose of **30** mg/m^2/day x 2 days (60 mg/m^2/cycle) • **Pazopanib:** Reduce to Dose Reduction Level 1 (see the table in Section 5.2)

* Delay therapy until counts are met. Any cycle delay >3 weeks (ie, beyond Day 42 of the prior cycle) due to neutropenia or thrombocytopenia will result in the patient being removed from protocol therapy.
If counts are met (ANC ≥750/µL and Platelets ≥75,000/µL) by the time of the next scheduled chemotherapy cycle following the dose reduction(s), subsequent cycles of therapy should be at the same reduced dose unless the apparent cause of delayed recovery is no longer present.
If hematologic parameters (ANC ≥ 750/µL or platelet ≥ 75,000/µL) are not met within 7 days of a scheduled subsequent cycle, the dose of pazopanib should be held until count recovery. The patient may resume pazopanib at the same dose level for the subsequent cycle unless criteria for the above dose modification toxicities are met.

5.3.1.2.1 Delay prior to Pazopanib and Ifosfamide Cycle

Delay prior to Pazopanib AND Ifosfamide Cycle		
Hematologic Parameters	**Delay Occurrence with this Combination**	**Dose Modifications***
ANC < 750/µL OR Platelets < 75,000/µL	First	• **Ifosfamide:** No change • **Pazopanib:** No change
	Second	• **Ifosfamide**: Reduce dose to **2000** mg/m^2/day x 3 days (6000 mg/m^2/cycle) • **Pazopanib:** No change
	Third	• **Ifosfamide**: Reduce dose to **1500** mg/m^2/day x 3 days (4500 mg/m^2/cycle) • **Pazopanib:** No change

* Delay therapy until counts are met. Any cycle delay >3 weeks (ie, beyond Day 42 of the prior cycle) due to neutropenia or thrombocytopenia will result in the patient being removed from protocol therapy.
If counts are met (ANC ≥750/µL and Platelets ≥75,000/µL) by the time of the next scheduled chemotherapy cycle following the dose reduction, subsequent cycles of therapy should be at the same reduced dose unless the apparent cause of delayed recovery is no longer present.
If hematologic parameters (ANC ≥ 750/µL or platelet ≥ 75,000/µL) are not met within 7 days of a scheduled subsequent cycle, the dose of pazopanib should be held until count recovery. The patient may resume pazopanib at the same dose level for the subsequent cycle unless criteria for the above dose modification toxicities are met.

5.3.1.2.2 Delay prior to Pazopanib and Doxorubicin Cycle

Delay prior to Pazopanib AND Doxorubicin Cycle		
Hematologic Parameters	**Delay Occurrence with this Combination**	**Dose Modifications***
ANC < 750/µL OR Platelets < 75,000/µL	First	• **Doxorubicin:** No change • **Pazopanib:** No change
	Second	• **Doxorubicin:** Reduce dose to **30** mg/m^2/day x 2 days (60 mg/m^2/cycle) • **Pazopanib:** No change
	Third	• **Doxorubicin**: Reduce dose to **30** mg/m^2/day x 2 days (60 mg/m^2/cycle) • **Pazopanib:** Reduce to Dose Reduction Level 1 (see the table in Section 5.2)

* Delay therapy until counts are met. Any cycle delay >3 weeks (ie, beyond Day 42 of the prior cycle) due to neutropenia or thrombocytopenia will result in the patient being removed from protocol therapy.
If counts are met (ANC ≥750/µL and Platelets ≥75,000/µL) by the time of the next scheduled chemotherapy cycle following the dose reduction, subsequent cycles of therapy should be at the same reduced dose unless the apparent cause of delayed recovery is no longer present.
If hematologic parameters (ANC ≥ 750/µL or platelet ≥ 75,000/µL) are not met within 7 days of a scheduled subsequent cycle, the dose of pazopanib should be held until count recovery. The patient may resume pazopanib at the same dose level for the subsequent cycle unless criteria for the above dose modification toxicities are met.

5.4 Mucositis

If Grade 3 mucositis develops for the first time following a doxorubicin-containing chemotherapy cycle, the same dose of doxorubicin should be given in the next cycle. If a second episode of Grade 3 mucositis develops, the dose of doxorubicin in the next doxorubicin-containing cycle should be decreased to 60 mg/m^2 (30 mg/m^2/dose) and continued at the reduced dose for all subsequent doxorubicin-containing cycles. If Grade 3 mucositis develops following the dose-reduction of doxorubicin, the pazopanib dose should be reduced to Dose Reduction Level 1 (see the table in Section 5.2 for dosage) when administered in any subsequent doxorubicin-containing cycles.

If Grade 4 mucositis develops following a doxorubicin-containing chemotherapy cycle, the dose of doxorubicin in the next doxorubicin-containing cycle should be decreased to 60 mg/m^2 (30 mg/m^2/dose) and the dose of pazopanib should be reduced to Dose Reduction Level 1 (see the table in Section 5.2 for dosage). The reduced doxorubicin and pazopanib doses should be administered in any subsequent doxorubicin-containing cycles.

See Appendix VIII and also see https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines for supportive care recommendations for mucositis.

5.5 Nephrotoxicity

Renal impairment is the primary, long-term dose-limiting side effect of ifosfamide. Available information indicates that the renal injury produced by ifosfamide is permanent, and in some cases progressive. Renal irradiation, young age (< 3 years of age), and absence of one kidney are risk factors for severe renal toxicity. All patients must be carefully monitored for declining renal function and Fanconi syndrome.

If the estimated or measured creatinine clearance/GFR (see Section 3.2.6.2) drops below the abnormal range for age and the patient is well-hydrated, defer ifosfamide-containing chemotherapy for 1 week. The ifosfamide should then be dose reduced from

7500 mg/m^2/cycle to 6000 mg/m^2/cycle. A timed, 24-hour urine collection for creatinine clearance or radionuclide GFR measurement should be considered to confirm renal dysfunction. If an abnormal creatinine clearance/GFR for age is still present after a 1-week delay in ifosfamide-containing chemotherapy (in a well-hydrated patient), replace ifosfamide in all subsequent cycles with cyclophosphamide 700 mg/m^2/dose IV over 1 hour on Days 1, 2, and 3 and decrease the mesna dose to 140 mg/m^2/dose IV over 15 minutes prior to and at 3, 6, and 9 hours after the start of the cyclophosphamide dose.

Cyclophosphamide also should be substituted for ifosfamide in an identical manner if Fanconi syndrome develops (see definition below).

For patients receiving cyclophosphamide, the dose of cyclophosphamide should be reduced to 525 mg/m^2/dose and the mesna dose should be reduced to 105 mg/m^2/dose if the estimated creatinine clearance is < 10 mL/min/1.73 m^2. A 24-hour urine collection for creatinine clearance or a radionuclide GFR should be obtained prior to cyclophosphamide dose reduction, making certain that the patient is well-hydrated before this evaluation.

Fanconi Syndrome
Elements of Fanconi syndrome include:

- Renal phosphorus wasting with hypophosphatemia
- Renal bicarbonate wasting with acidosis
- Renal potassium wasting with hypokalemia (< 3.0 mEq/L)
- 1+ or greater glycosuria with serum glucose < 150 mg/dL
- Proteinuria: A ratio of urine protein:urine creatinine > 0.2 occurring in the absence of significant malnutrition and acidosis due to sepsis/infection
- Decreased GFR

Incomplete Fanconi syndrome, with only one or a few of these elements, is common. Over time, these abnormalities may resolve, remain static, or progress. Any patient who has any 2 of the metabolic abnormalities listed above other than (or in addition to) glycosuria should have the following studies done within 2 weeks after the onset of the abnormalities:

- Measurement of GFR by Tc^{100} DTPA clearance or 24 hour urine collection
- Measurement of non-fasting serum phosphorus (off supplementation, in the absence of malnutrition) on 2 consecutive days.
- Measurement of serum bicarbonate (off supplementation), on 2 consecutive days.

For the purposes of this study, Fanconi syndrome is defined as either:

- GFR < 50 mL/min/1.73 m^2 in a well-hydrated patient, that is associated with mineral/electrolyte wasting and is not due to other causes such as aminoglycoside toxicity, amphotericin B, etc.

OR

- Any GFR, with evidence of persistent renal tubular acidosis AND phosphorous wasting defined as:
  - Serum bicarbonate < 14 mmol/L

  AND
  - Serum phosphorous < 2 mg/dL (pre-pubertal) or < 1.5 mg/dL (post-pubertal)

IF FANCONI SYNDROME OCCURS, REPORT IMMEDIATELY AS AN ADVERSE DRUG REACTION AND NOTIFY THE STUDY CHAIR. Future cycles of chemotherapy should include cyclophosphamide rather than ifosfamide.

5.6 Proteinuria

Proteinuria is a pazopanib-targeted toxicity. Management of pazopanib-induced proteinuria will proceed as follows:

- If urinalysis shows ≥ 2+ protein then obtain a urine protein:creatinine ratio (UPC).
- If UPC is > 2, then obtain a 24-hour urine collection for protein estimation.
- If the urine protein is < 3.5 grams/24 hours continue pazopanib at current dosing. If the urine protein is ≥ 3.5 grams/24 hours then hold pazopanib treatment and re-assess weekly.
- If pazopanib is held for > 21 days then remove from protocol therapy. If the urine protein decreases to < 3.5 grams/24 hours in ≤ 21 days then resume pazopanib at Dose Reduction Level 1 (see the table in Section 5.2 for dosage).
- Monitor the 24 hour urine protein weekly for 2 consecutive weeks once pazopanib resumes.
    - If the urine protein again exceeds 3.5 grams/24 hours and occurs within the first 12 weeks of therapy, then remove from protocol therapy.
    - If the urine protein again exceeds 3.5 grams/24 hours and occurs beyond the first 12 weeks of therapy, then hold pazopanib treatment and re-assess weekly.
        - If pazopanib is held for > 21 days then remove from protocol therapy. If the urine protein decreases to < 3.5 grams/24 hours in ≤ 21 days then resume pazopanib at Dose Reduction Level 1 (see the table in Section 5.2).

Urinary Tract Obstruction by Tumor

Unobstructed urine flow (via a catheter or percutaneous, endoscopic, or open decompression) should be established prior to administering either ifosfamide or cyclophosphamide to prevent nephrotoxicity (ifosfamide) and hemorrhagic cystitis (both ifosfamide and cyclophosphamide).

5.7 Cardiotoxicity

5.7.1 Left Ventricular Systolic Dysfunction

Dexrazoxane will be given for all doxorubicin containing cycles.

If left ventricular systolic dysfunction (ejection fraction < 50% or shortening fraction < 27%) develops:

- Hold pazopanib
- Postpone the doxorubicin-containing chemotherapy cycle
- Correct any malnutrition present
- Repeat the echocardiogram/MUGA in 7 days
    - If the abnormalities persist, patient will be taken off protocol therapy and should be referred to a cardiologist.
    - If repeat echocardiogram/MUGA shows resolution of the abnormalities, patient may start next cycle of therapy on schedule with repeat echocardiogram/MUGA 14 days after start of next cycle. The pazopanib should be resumed at Dose Reduction Level 1 (see the table in Section 5.2).

No changes in therapy are recommended for an asymptomatic decrease in cardiac ejection or shortening fraction provided they remain at or above 50% and 27% respectively.

If patient develops Grade ≥ 3 left ventricular systolic dysfunction, patient will be taken off protocol therapy.

5.7.2 QTc Prolongation

Guidelines for the management of prolonged QTc interval are as follows:

- Measure the QT interval (from the start of the Q wave to the end of the T wave) and the preceding RR interval. The QTc interval will be calculated as the QT interval (msec) divided by the square root of the RR interval (msec).
- QTc interval < 500 msec: No specific therapy needed. Continue pazopanib. Serum K+, Ca++, Mg++ and Phos should be monitored and repleted only if low.
- QTc interval ≥ 500 msec or an increase in the QTc by at least 60 msec from baseline: Hold pazopanib, review concomitant medications, and replete serum K+, Ca++, Mg++ and Phos as needed. The EKG should be repeated within 7 days and, if the QTc interval remains ≥ 500 msec or an increase in the QTc by at least 60 msec from baseline persists, the patient should be removed from protocol therapy.

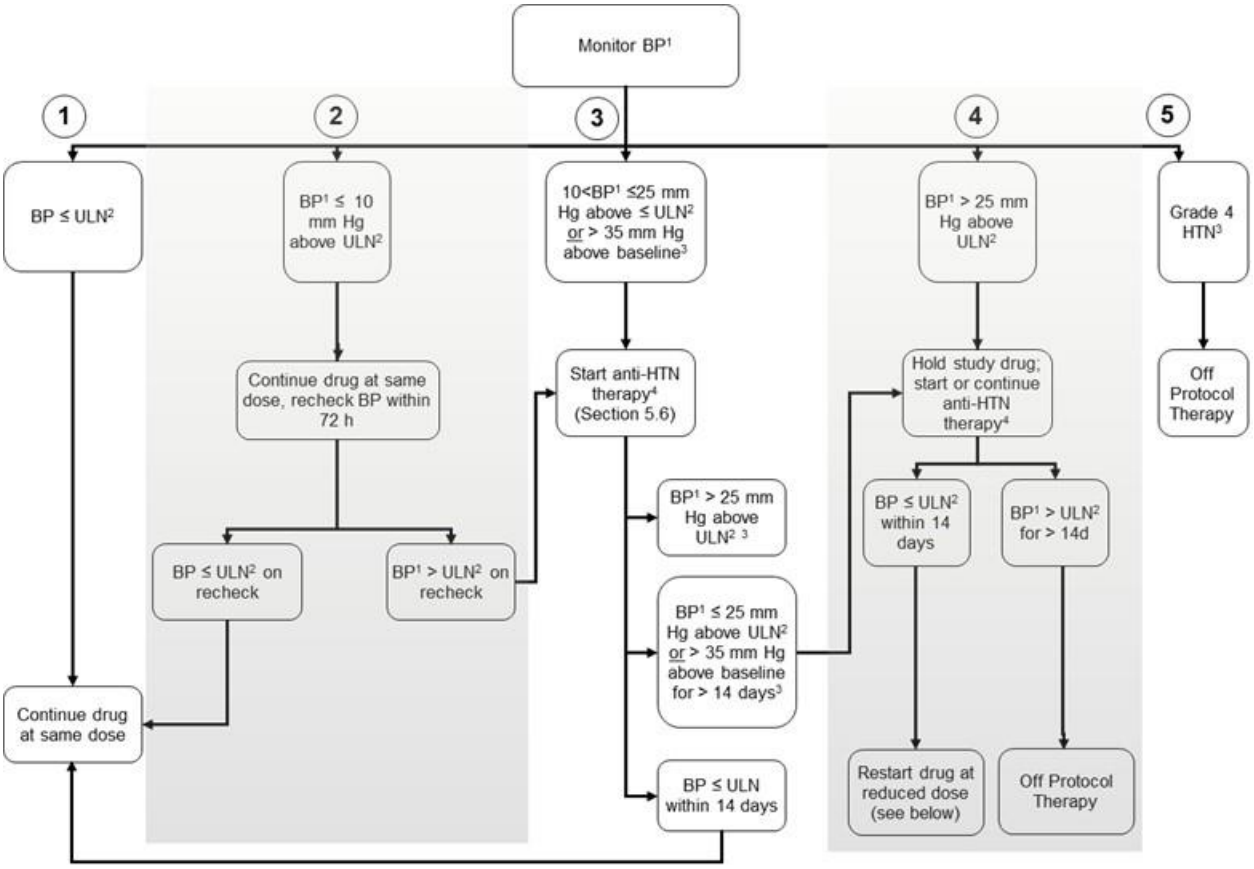
Please see Section 4.1.6 for guidance on concomitant medications that are associated with a risk of QTc prolongation and/or Torsades de pointes

5.8 Hypertension

Hypertension is a pazopanib-targeted toxicity. Hypertension typically occurs early in the course of pazopanib treatment (approximately 40% of cases occur by Day 9 and 90% occur in the first 18 weeks).

5.8.1 Dose Modification for Hypertension in Patients < 18 Years

Age- and gender-adjusted norms will be used to determine whether the blood pressure is elevated.[165] The upper limit of normal (ULN) is defined as a BP equal to the 95th percentile for age, height, and gender for patients < 18 years (see Appendix VA and VB). A previously described algorithm (adapted from Fox et al.[166] and used within ADVL0815: A Phase I Study of Pazopanib as a Single Agent for Children with Refractory Solid Tumors) will be used to manage TKI-related hypertension for pediatric patients < 18 years of age. Management of pazopanib-induced hypertension will proceed as follows:



Elevations in BP are based on systolic or diastolic pressures.

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

Arm 1 of algorithm:

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

Arm 2 of algorithm:

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

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the 95% for age, height, and gender on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy, continue pazopanib at the same dose, and monitor BP at least twice weekly.
- If the BP returns to ≤ ULN within 14 days, continue pazopanib at the same dose and continue anti-hypertensive therapy.
- If the BP remains elevated ≤ 25 mm Hg above the 95% for more than 14 days or > 35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy, **hold** pazopanib, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that pazopanib is held. The antihypertensive therapy should be continued until the BP is less than the ULN.
    - If the BP returns to ≤ ULN within 14 days, restart pazopanib at Dose Reduction Level 1 (see the table in Section 5.2).
    - If the BP remains > ULN for more than 14 days, patient should be removed from protocol therapy.
- If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, **hold** pazopanib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that pazopanib is held.
    - If the BP is ≤ ULN within 14 days, pazopanib may be restarted at Dose Reduction Level 1 (See the table in Section 5.2).
    - If the BP is > ULN for > 14 days, the patient should be removed from protocol therapy.

Arm 4 of algorithm:

- If BP is >25 mm Hg above the 95% for age, height, and gender, **hold** pazopanib, monitor BP and administer anti-hypertensive therapy as clinically indicated. If the BP returns to ≤ ULN within 14 days, pazopanib may be restarted at Dose Reduction Level 1 (see the table in Section 5.2).
- If the BP is > ULN for >14 days, the patient should be removed from protocol therapy.

Arm 5 of algorithm:

- If the participant develops Grade 4 hypertension (CTCAE v.5), **discontinue** pazopanib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient should be removed from protocol therapy.

5.8.2 Dose Modification for Hypertension in Patients ≥ 18 Years

Please refer to Appendix VC for a list of suggested oral antihypertensive medications.

Recommended Hypertension Monitoring and Management
(BP in mmHg)

Grade (CTCAE v5)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-89		Standard	No Change

Persistent Grade 2-Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v5	Step 1) Initiate BB treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another anti-hypertensive Rx, a LA DHP CCB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of pazopanib or stopping pazopanib *NOTE: Stopping or reducing the dose of pazopanib is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician	No change except as described in step 4
Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v5	HOLD pazopanib until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions:** **1) If systolic BP >180 or diastolic BP >110 and the subject is symptomatic: optimal management with intensive IV support in ICU; STOP pazopanib and notify hospital staff that stopping pazopanib may result in a decrease in BP** **and** **2) If systolic BP >180 or diastolic BP >110 and the subject is asymptomatic, 2 new antihypertensives must be given together in step 1**	BP should be monitored as recommended by the treating physician **unless the subject is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD pazopanib until systolic BP ≤159 and diastolic BP ≤99. After this, pazopanib may be re-administered. If BP is still grade 2, manage as described above for Grade 2 hypertenison. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of pazopanib when systolic BP ≤159 and diastolic BP ≤99 or stopping pazopanib. **HOWEVER, If the subject requires hospitalization for**

	(and dose escalated appropriately as in step 1). *NOTE: Stopping or reducing the dose of pazopanib is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*		**management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue pazopanib or if BP is controlled to systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib at 1 lower dose level after consultation with the study Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP pazopanib and notify hospital staff that stopping pazopanib may result in a decrease in BP**	Intensive	Permanently discontinue pazopanib or if systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib at 1 lower dose level after consultation with the study Principal Investigator

Abbreviations: Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB), alpha beta blocker (ABB)

- *See table below for suggested antihypertensive medications by class
- If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If subjects require >2 dose reductions, discontinue protocol therapy
- Subjects may have up to 2 drugs for management of hypertension prior to any dose reduction in pazopanib
- 24-48 hours should elapse between modifications of antihypertensive therapy
- Hypertension should be graded using CTCAE v5

5.9 Gastrointestinal Toxicity

5.9.1 Hyperbilirubinemia

Patients with an elevated total bilirubin without elevation of direct (conjugated) bilirubin do not require chemotherapy dose modifications. However, patients with direct (conjugated) hyperbilirubinemia (direct bilirubin > 35% of total bilirubin) do require modification of pazopanib and doxorubicin as follows:

Total bilirubin < 1.2 mg/dL	Full doses of pazopanib and doxorubicin
Total bilirubin 1.2 – 3.0 mg/dL	Reduce dose of pazopanib to Dose Reduction Level 2* Reduce dose of doxorubicin by 25%
Total bilirubin 3.1 – 5.0 mg/dL	Reduce dose of pazopanib to Dose Reduction Level 3* Reduce dose of doxorubicin by 50%
Total bilirubin > 5.0 mg/dL	Withhold pazopanib and doxorubicin

*See table in Section 5.2.

If the bilirubin falls prior to subsequent chemotherapy cycles, increase the dose of doxorubicin as indicated above. Pazopanib can be resumed as soon as toxicity resolves at a dose indicated above. Do not make up missed doses.

Ifosfamide doses are not adjusted for hepatic dysfunction.

5.9.2 Hypertransaminasemia

Elevations in alanine transaminase (ALT) can be seen with the use of pazopanib. Dose modifications should be made as follows:

ALT < 3 x Upper Limit of Normal (ULN)	Full dose of pazopanib
Isolated ALT 3-8 x ULN	Continue full dose pazopanib, but monitor weekly until ALT returns to ≤ 2.5 X ULN or baseline
ALT 3-8 x ULN **and** total bilirubin < 2 mg/dL (with elevation in direct bilirubin as defined in Hyperbilirubinemia section)	Reduce dose of pazopanib to Dose Reduction Level 2* Reduce doxorubicin as outlined above (see Hyperbilirubinemia section)
ALT > 3 x ULN **and** total bilirubin ≥ 2 mg/dL (with elevation in direct bilirubin as defined in Hyperbilirubinemia section)	Withhold pazopanib Reduce doxorubicin as outlined above (see Hyperbilirubinemia section)
ALT > 8 x ULN	Withhold pazopanib and doxorubicin Monitor weekly until ALT returns to baseline then reduce dose of pazopanib to Dose Reduction Level 2* and reduce doxorubicin as outlined above (see Hyperbilirubinemia section)

*See table in Section 5.2.

If the ALT falls prior to subsequent chemotherapy cycles, increase the doses of pazopanib and doxorubicin as indicated above. Note exception: for ALT > 8 x ULN, maintain pazopanib at Dose Reduction Level 2 (see table in Section 5.2) without further escalation when ALT returns to baseline.

Ifosfamide doses are not adjusted for hepatic dysfunction.

5.9.3 Hyperamylasemia and/or Hyperlipasemia:

Elevations in amylase and lipase can be seen with the use of pazopanib. Dose modifications should be made as follows:

Grade 1	Full dose of pazopanib
Grade 2	Full dose of pazopanib
Grade 3 (Asymptomatic)	Decrease pazopanib to Dose Reduction Level 2* until improvement to Grade ≤ 1 then resume pazopanib at full dose
Grade 3 (Symptomatic)	Withhold pazopanib until improvement to Grade ≤ 1 then resume pazopanib at full dose
Grade 4 (Asymptomatic)	Withhold pazopanib until improvement to Grade ≤ 1 then resume pazopanib at full dose
Grade 4 (Symptomatic)	Withhold pazopanib until improvement to Grade ≤ 1 then resume pazopanib Dose Reduction Level 2*

*See table in Section 5.2.

Discontinue pazopanib and remove patient from protocol therapy for any recurrence of symptomatic Grade 3 or Grade 4 toxicity.

Doxorubicin and ifosfamide doses are not adjusted for elevations in amylase or lipase.

5.10 Radiation Toxicity

Radiation toxicity can be seen with the concomitant administration of radiotherapy and doxorubicin. Similar toxicities have been reported with the use of TKIs.[82-85,167] The most common adverse effect is acute radiation dermatitis and post radiation recall dermatitis.

5.10.1 Radiation Dermatitis

If radiation dermatitis develops, dose modifications to pazopanib during radiation will be made as follows:

Toxicity	**Dose modification**
Grade 1	Full dose of pazopanib
Grade 2	Full dose of pazopanib
Grade 3	Discontinue pazopanib until improvement to Grade ≤ 2 then resume pazopanib at Dose Reduction Level 2*
Grade 4	Discontinue pazopanib and remove patient from protocol therapy

*See table in Section 5.2.

Pazopanib can be increased to full dose at the completion of radiation once Grade ≤ 2 toxicity is achieved.

Ifosfamide doses are not adjusted for radiation dermatitis.

5.10.2 Radiation Recall Reaction

If a radiation recall reaction develops, dose modifications to pazopanib will be

made as follows:

Toxicity	Appearance	Dose modification
Grade 1	Any	Full dose of pazopanib
Grade 2	First Appearance	Discontinue pazopanib until improvement to Grade ≤ 1 then resume pazopanib at full dose
	Second Appearance	Discontinue pazopanib until improvement to Grade ≤ 1 then resume pazopanib at Dose Reduction Level 2*
	Third Appearance	Discontinue pazopanib until improvement to Grade ≤ 1 then resume pazopanib at Dose Reduction Level 2*
	Fourth Appearance	Discontinue pazopanib and remove patient from protocol therapy
Grade 3	First Appearance	Discontinue pazopanib until improvement to Grade ≤ 1 then resume pazopanib at Dose Reduction Level 2*
	Second Appearance	Discontinue pazopanib until improvement to Grade ≤ 1 then resume pazopanib at Dose Reduction Level 2*
	Third Appearance	Discontinue pazopanib and remove patient from protocol therapy
Grade 4	Any	Discontinue pazopanib and remove patient from protocol therapy

*See table in Section 5.2.

Doxorubicin and ifosfamide doses are not adjusted for a radiation recall reaction.

5.11 Impaired Wound Healing and Wound Complications

5.11.1 Impaired Wound Healing

Delays in wound healing have been reported with the use of TKIs.[168,169] The most significant complications have been associated with the use of anti-VEGF monoclonal antibody bevacizumab which has a half-life of 20 days.[170,171] Based upon the half-life of pazopanib (31-35 hours) significant peri-surgical complications are not expected. To minimize the risk of complications in patients undergoing surgery, pazopanib will be held for 7 days prior to and 14 days following surgery. Central venous catheter placement is considered a minor surgery that does not require a delay in therapy start. Pazopanib should be held for delayed wound healing and resumed once appropriate healing has occurred.

For patients on the chemotherapy cohort (Regimen A or B), initiation of postoperative chemotherapy with or without pazopanib (and radiotherapy, if indicated by positive margin or residual disease) should begin within 6 weeks of the date of Week 13 surgery. If impaired wound healing precludes initiating postoperative therapy within 6 weeks of the date of surgery, this should be documented on the appropriate case report form (CRF). Week 16 chemotherapy should be postponed until radiotherapy (if needed) begins. If impaired wound healing precludes initiating postoperative therapy within 8 weeks of the date of surgery, the patient should be removed from protocol therapy effective the date 8 weeks after Week 13 surgery.

For patients on the non-chemotherapy cohort (Regimen C or D), initiation of postoperative pazopanib (and radiotherapy, if indicated by positive margin or residual disease) should begin within 6 weeks of the date of Week 10 surgery. If impaired wound healing precludes initiating postoperative therapy within 6 weeks of the date of surgery, this should be documented on the appropriate case report form (CRF). If impaired wound healing precludes initiating postoperative therapy within 8 weeks of the date of surgery, the patient should be removed from protocol therapy effective the date 8 weeks after Week 10 surgery.

If the criteria for a CTCAE v5.0 wound complication is met at any time during the wound healing process, refer to Section 5.11.2 below.

5.11.2 Wound Complications

Please refer to the table below for pazopanib therapy modifications for wound complications that occur anytime during therapy:

CTCAE v5.0 Toxicity	Grade	Therapy Modifications
Wound Infection	1-3	• Hold pazopanib and resume at full dose when toxicity is brought to a satisfactory resolution • During Induction or Continuation Phases of therapy: if therapy delayed > 8 weeks, patient should be removed from protocol therapy • During Surgery Phase of therapy: if the start of the Continuation Phase is delayed > 8 weeks from date of surgery, patient should be removed from protocol therapy
	4	• Patient should be removed from protocol therapy
Wound Dehiscence	1-3	• Hold pazopanib and resume at full dose when toxicity is brought to a satisfactory resolution • During Induction or Continuation Phases of therapy: if therapy delayed > 8 weeks, patient should be removed from protocol therapy • During Surgery Phase of therapy: if the start of the Continuation Phase is delayed > 8 weeks from date of surgery, patient should be removed from protocol therapy • If recurrence of Grade 3 toxicity, patient should be removed from protocol therapy
	4	• Patient should be removed from protocol therapy
Wound Complication	1-3	• Hold pazopanib and resume at full dose when toxicity is brought to a satisfactory resolution • During Induction or Continuation Phases of therapy: if therapy delayed > 8 weeks, patient should be removed from protocol therapy • During Surgery Phase of therapy: if the start of the Continuation Phase is delayed > 8 weeks from date of surgery, patient should be removed from protocol therapy • If recurrence of Grade 3 toxicity, patient should be removed from protocol therapy
	4	• Patient should be removed from protocol therapy

For patients on the chemotherapy cohort (Regimen A or B), initiation of postoperative chemotherapy (and radiotherapy, if indicated by positive margin or residual disease) should begin within 6 weeks of the date of Week 13 surgery. If a wound complication precludes initiating postoperative chemotherapy ± radiotherapy within 6 weeks of the date of surgery, this should be documented on the appropriate case report form (CRF). Week 16 chemotherapy should be postponed until radiotherapy (if needed) begins. If a wound complication precludes initiating postoperative chemotherapy ± radiotherapy within 8 weeks of the date of surgery, the patient should be removed from protocol therapy effective the date 8 weeks after Week 13 surgery.

For patients on the non-chemotherapy cohort (Regimen C or D), initiation of radiotherapy, if indicated by positive margin or residual disease, should begin within 6 weeks of the date of Week 10 surgery. If a wound complication precludes initiating postoperative radiotherapy within 6 weeks of the date of surgery, this should be documented on the appropriate CRF. If a wound complication precludes initiating postoperative radiotherapy within 8 weeks of the date of surgery, the patient should be removed from protocol therapy effective the date 8 weeks after Week 10 surgery.

Any wound complication, regardless of attribution, should be recorded on the CRF for the reporting period in which the complication occurred. Additionally, any wound-related institutional procedure or operative reports (procedure reports would include radiologically-guided procedures such as drainage of collections) should be submitted.

5.12 Rash

A variety of rashes have been demonstrated with the use of TKIs including hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome), erythema, pruritis, follicular rash, xerosis and skin dryness. Hand-foot syndrome is the most prevalent.

5.12.1 Hand-Foot (Palmar-Plantar Erythrodysesthesia) Syndrome

Initiate vitamin B6 (pyridoxine) as outlined in the supportive care guidelines (Appendix VIII).

- Grade 1 toxicity: Start immediately with prevention/supporting measures and continue treatment.
- Grade 2 toxicity:
    - First appearance:
        - Immediately start with prevention/supporting measures and dose reduce pazopanib to Dose Reduction Level 2 (see the table in Section 5.2 for dosage) for 21 days.
        - If after pazopanib dose reduction toxicity decreases to Grade ≤ 1, return to full dose.
        - If after pazopanib dose reduction toxicity does not revert to Grade ≤ 1, discontinue treatment for a minimum of 7 days until toxicity decreases to Grade ≤ 1.
            - If after discontinuation toxicity reverts to Grade ≤ 1, start treatment again at Dose Reduction Level 2 (see the table in Section 5.2 for dosage) for 21 days.
                - If at the reduced dose Grade ≤ 1 toxicity continues, return to full dose after 21 days.
            - If after discontinuation toxicity does not revert to

Grade ≤ 1 within 21 days, patient is to be taken off protocol therapy.

- Second/Third appearance:
  - As for the first appearance, but start treatment again permanently at Dose Reduction Level 2 (see the table in Section 5.2 for dosage).
- Fourth appearance:
  - Discontinue pazopanib and the patient is to be taken off protocol therapy.

- Grade 3 toxicity:
  - First appearance:
    - Start immediately with prevention/supporting measures and discontinue treatment for at least 7 days.
    - If after pazopanib dose discontinuation toxicity decreases to Grade ≤ 1, start treatment again at Dose Reduction Level 2 (see the table in Section 5.2 for dosage) for 21 days.
      - If at the reduced dose Grade ≤ 1 toxicity continues, return to full dose after 21 days.
    - If after discontinuation toxicity does not revert to Grade ≤ 1 within 21 days, patient is to be taken off protocol therapy.
  - Second appearance:
    - As for the 1st appearance, but start treatment again permanently at Dose Reduction Level 2 (see the table in Section 5.2 for dosage).
  - Third appearance:
    - Discontinue pazopanib and the patient is to be taken off protocol therapy.
- Grade 4 toxicity:
    - Discontinue pazopanib and the patient is to be taken off protocol therapy.

Dose modifications for radiation recall reaction and dermatitis radiation are provided in Section 5.8.

Refer to Appendix VIII for additional supportive care measures.

5.13 Neurotoxicity

Ifosfamide-induced neurotoxicity is a syndrome characterized by altered mentation ranging from mild confusion and disorientation to ataxia, myoclonus, seizures, and coma. The precise cause of this syndrome is unknown, but the metabolite chloroacetaldehyde appears to be a principal neurotoxin. Impaired renal function and low serum albumin may enhance the neurotoxicity of ifosfamide. Symptoms are usually but not always reversible, and may or may not recur with subsequent doses.

After ruling out other causes of the neurologic abnormalities, acute neurotoxicity following ifosfamide administration should be treated with 1 mg/kg (max dose 50 mg) IV methylene blue.[172] The dose may be repeated every 6 hours until symptoms resolve. Patients who experience acute ifosfamide-induced neurotoxicity should receive methylene blue 1 mg/kg (max dose 50 mg) IV daily prior to each subsequent dose of ifosfamide to prevent recurrence of the neurotoxicity. Note: methylene blue should not be used in patients who are G6PD deficient.

5.14 Hematuria

5.14.1 Microscopic Hematuria

No modification of ifosfamide, cyclophosphamide, or mesna administration will be made for microscopic hematuria (defined as > 50 RBC/hpf) that is transient (occurring on no more than two separate days during a 21-day cycle of chemotherapy). For persistent microscopic hematuria (3 or more abnormal urinalyses on different days), increase IV hydration to 3500-4000 mL/m^2/day and administer mesna equal to 100% of the daily ifosfamide or cyclophosphamide dose by IV continuous infusion over 24 hours during the next chemotherapy cycle. The continuous infusion should be started 15-30 minutes before or at the same time as the ifosfamide/cyclophosphamide infusion.

5.14.2 Gross Hematuria

All episodes of gross hematuria should be evaluated by urine culture and cystoscopy should be considered. If cystoscopy reveals a cause other than hemorrhagic cystitis for the gross hematuria, therapy may proceed without modification. If the gross hematuria is due (or possibly due) to hemorrhagic cystitis, management depends on the timing and duration of the episode:

- Single < 24 hour long episode of gross hematuria that clears to microscopic hematuria during or following a cycle of therapy:
  - Increase IV hydration to 3500-4000 mL/m^2/day and administer mesna equal to 100% of the daily ifosfamide/cyclophosphamide dose by IV continuous infusion over 24 hours for all subsequent ifosfamide doses, as described in Section 4. The continuous infusion should be started 15-30 minutes before or at the same time as the ifosfamide/cyclophosphamide infusion.
- Gross hematuria that persists for > 24 hours during or after an ifosfamide-containing chemotherapy cycle:
  - Withhold further ifosfamide until the next cycle of therapy and use hydration and continuous infusion mesna as described in Section 4 for all subsequent ifosfamide doses.
- Gross hematuria present at the time of scheduled ifosfamide-containing chemotherapy:
  - Withhold chemotherapy for up to 7 days to allow the gross hematuria to clear to microscopic levels.
  - Use hydration and continuous infusion mesna as described in Section 4 for all subsequent ifosfamide doses.
- Recurrent gross hematuria *or* persistent microscopic hematuria following use of continuous infusion mesna:
  - Omit all further ifosfamide doses. Doxorubicin should be continued according to protocol guidelines.

5.15 Electrolyte Abnormalities

Management of Grade 2 or higher hypokalemia and hyperkalemia, management of Grade 3 or higher hypomagnesemia and hypermagnesemia, Grade 3 or higher hypophosphatemia, and Grade 3 or higher hypocalcemia and hypercalcemia.

Management of Abnormal Laboratory Assessments	
Hypokalemia or hyperkalemia ≥ Grade 2, Hypocalcemia or hypercalcemia ≥ Grade 3, Hypophosphatemia ≥ Grade 3, or Hypomagnesemia or hypermagnesemia ≥ Grade 3	• EKG must be performed. • Laboratory values should be corrected as soon as possible in a manner consistent with good medical judgment. • Hold pazopanib until: – hypokalemia or hyperkalemia is Grade 1 or within institutional limits – hypocalcemia or hypercalcemia is ≤ Grade 2 – hypophosphatemia is ≤ Grade 2 – hypomagnesemia or hypermagnesemia is ≤ Grade 2

6.0 DRUG INFORMATION

6.1 PAZOPANIB

(Votrient™, GW786034, Pazopanib HCl, GW786034B (monohydrochloride salt)) NSC#737754, IND#118613 **(04/05/19)**

Source and Pharmacology:

The chemical name for pazopanib is 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl) methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. The molecular formula is $C_{21}H_{23}N_7O_2S$-HCl. The molecular weight is 474.0 (monohydrochloride salt) and 437.5 (free base). The monohydrochloride salt is very slightly soluble in 0.1 M HCl (0.65 mg/mL), practically insoluble in pH 7.0 phosphate buffer (0.00005 mg/mL), and practically insoluble in pH 11 piperidine buffer (0.0002 mg/mL).

Pazopanib is a multi-targeted inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3), platelet-derived growth factor receptor kinases (PDGFR-α and –β), fibroblast growth factor receptor-1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In vitro, pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit and PDGFR-β receptors. In vivo, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice.

In adults, pazopanib is orally absorbed with median time to peak concentration of 2 to 4 hours after the dose. Also in adults, the administration of a single, crushed pazopanib 400 mg tablet increased $AUC_{(0\text{-}72)}$ by 46%, increased Cmax by approximately 2 fold, and decreased Tmax by approximately 2 hours compared to administration of the whole tablet. Due to this potential for increased exposure (increased bioavailability, increased rate of absorption), tablets of pazopanib should not be crushed. Systemic exposure is increased when pazopanib is administered with food. Administration with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and Cmax. Therefore, pazopanib

should be administered at least 1 hour before or 2 hours after a meal. Pazopanib is more than 99% bound to human plasma protein in vivo.

In adults, pazopanib has a mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via feces with renal elimination accounting for <4% of the administered dose. To date there are no data on patients with mild or severe hepatic impairment. However, data in adult patients with cancer indicate that moderate hepatic impairment decreased the clearance of pazopanib is by 50%.

Pazopanib may cause prolongation of the QT interval and torsades de pointes. Refer to Appendix VII for agents to avoid during administration of pazopanib.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pazopanib (GW786034, NSC 737754)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2383 patients.* Below is the CAEPR for Pazopanib (GW786034).

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

Version 2.8, January 31, 2019[1]

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome[2]	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (Torsades de Pointes)	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
	Hypothyroidism		

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS			
		Eye disorders - Other (eye hemorrhage, retinal hemorrhage)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
		Gastrointestinal fistula[3]	***Gastrointestinal fistula[3] (Gr 2)***
		Gastrointestinal hemorrhage[4]	
		Gastrointestinal perforation[5]	***Gastrointestinal perforation[5] (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
		Infection[6]	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 4)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Ejection fraction decreased	
		Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypermagnesemia		
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Hematuria	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	***Urinary fistula (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Reproductive system and breast disorders - Other (female genital tract fistula)	***Reproductive system and breast disorders - Other (female genital tract fistula) (Gr 2)***
		Uterine fistula	***Uterine fistula (Gr 2)***
		Vaginal fistula	***Vaginal fistula (Gr 2)***
		Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[7]		***Respiratory hemorrhage[7] (Gr 2)***

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[8]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
Hair color changes			***Hair color changes (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[9]	
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event[9]	

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

[2]Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.

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

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

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

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

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

[8]Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis),

Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).

[9]These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications.

Adverse events reported on pazopanib (GW786034) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pazopanib (GW786034) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Chest pain - cardiac; Pericardial effusion; Supraventricular tachycardia
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood lactate dehydrogenase increased; Cardiac troponin T increased; Cholesterol high; GGT increased; INR increased; Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

Note: Pazopanib (GW786034) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Pregnancy and lactation:
Pazopanib can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, pazopanib is expected to result in adverse reproductive effects. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic,

and abortifacient. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of ≥ 3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was reduced fetal body weight, and pre- and post-implantation embryolethality in rats administered pazopanib at doses ≥3 mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses ≥ 30 mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses ≥ 100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses ≥ 3 mg/kg/day (AUC not calculated).

There are no adequate and well-controlled studies of pazopanib in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking pazopanib.

Excretion in breast milk unknown and breast-feeding while on pazopanib is not recommended.

Formulation and Stability:
Novartis supplies and the PMB, DCTD, NCI distributes commercially-labeled 200 mg pazopanib tablets (as free base). Gray, film-coated tablets are debossed with "GS JT" on one side and packaged in bottles of 120 tablets.
Tablet excipients include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, iron oxide black, macrogol/polyethylene glycol 400 and polysorbate 80.

Store tablets at room temperature (20° C to 25° C or 68° F to 77° F); excursions permitted to 15° C to 30° C (59 F° to 86° F) [USP controlled room temperature].

If a storage temperature excursion is identified, promptly return pazopanib to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to package label for expiration date of commercially-labeled supplies.

Repackaging is not allowed and tablets must be dispensed in the original container. If exact quantity must be dispensed, then extra tablets should be removed, documented as waste and destroyed immediately.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Pazopanib should be taken on an empty stomach at least 1 hour before or 2 hours after a meal. The tablets should be swallowed whole and cannot be crushed or broken.

If a dose is missed, do not take or "make up" the dose unless there is at least 12 hours until the next scheduled dose. If the patient vomits within 30 minutes of taking the dose, the dose may be repeated. If more than 30 minutes have elapsed, do not repeat the dose.

Potential Drug Interactions: In vitro data indicate that pazopanib is primarily metabolized by CYP3A4 isoenzyme with minor contributions from CYP 1A2 and 2C8. Potent CYP3A4 inducers and inhibitors are prohibited on pazopanib trials. Refer to Appendix VI for agents that should be avoided. Pazopanib is also a substrate for p-glycoprotein and breast cancer resistance protein (BCRP) transporters and concomitant administration of inhibitors such as lapatinib will result in increased plasma pazopanib concentrations.

Clinical studies indicate that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Use caution when combining pazopanib with CYP3A4, CYP2C8, and CYP2D6 substrates known to have a narrow therapeutic window.

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1. Pazopanib may increase concentrations of drugs primarily eliminated through these systems.

Avoid co-administration of pazopanib with medicines that increase gastric pH. If the concomitant use of a proton pump inhibitor (PPI) is medically necessary, pazopanib should be taken without food once daily in the evening with the PPI. If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist. Administer pazopanib at least 1 hour before or 2 hours after administration of short-acting antacids.

Avoid co-administration of pazopanib with simvastatin. Concomitant use of pazopanib and simvastatin increases the risk of ALT elevation. Data are not sufficient to assess the risk of concomitant administration of other statins and pazopanib.

Precautions: Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Monitor EKGs and serum electrolytes (e.g., calcium, magnesium, potassium) at baseline and periodically and maintain within the normal range.

Refer to Appendix VII for agents to avoid during administration of pazopanib.

For patients who develop hepatic impairment, refer to Section 5 for appropriate dose modification or dose delay.

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

Obtaining the Agent
Agent Ordering:
NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through

an annual submission of FDA form 1572 (Statement of Investigator), NIH Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

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

Agent Accountability

Agent Inventory Records:

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

Investigator Brochure Availability:

The current version(s) of the IB(s) for the PMB-supplied agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email IBcoordinator@mail.nih.gov

Useful Links and Contacts

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

6.2 DEXRAZOXANE

(ICRF-187, ADR-529, ZINECARD®, Totect®) NSC #169780 **(11/17/17)**

Source and Pharmacology:

Dexrazoxane is a synthetic chemical, a cyclic derivative of EDTA that readily penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring opened chelating agent that interferes with iron mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy. The disposition kinetics of dexrazoxane are dose-dependent with administered doses from 60 to 900 mg/m^2. The plasma half-life is 2 to 2.5 hours. Qualitative metabolism studies have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. Metabolite levels were not measured in the pharmacokinetics studies. Urinary excretion plays an important role in the elimination of dexrazoxane: 42% of the drug (500 mg/m^2) was excreted in the urine. *In vitro* studies have shown that dexrazoxane is not bound to plasma proteins. The pharmacokinetics of dexrazoxane have not been evaluated in patients with hepatic or renal insufficiency. There was no significant effect of dexrazoxane on the pharmacokinetics of doxorubicin (50 mg/m^2) or its predominant metabolite, doxorubicinol, in a crossover study in cancer patients.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Pain on injection, phlebitis, transient increases in triglycerides and amylase, increase in SGPT (ALT)/ SGOT (AST) and bilirubin, mild nausea, vomiting, diarrhea, increase in serum iron, decrease in serum zinc and calcium	Anorexia, malaise, extravasation (rare) but if occurs may = ulceration
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression		Prolongation of PT/PTT
Late: Any time after completion of treatment			Secondary malignancies (have been reported with oral razoxane; the racemic mixture, of which dexrazoxane is the S(+)-enantiomer)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects have been noted in animals. Dexrazoxane was maternotoxic, embryotoxic, and teratogenic when given to pregnant rats and rabbits during the period of organogenesis. It is not known whether dexrazoxane is excreted in human milk.		

Formulation and Stability:

Three products are available:

1. **Dexrazoxane for Injection (generic)**
   a. Available as a sterile, pyrogen-free lyophilized powder in the following strengths: 250 mg single dose vial packaged with a 25 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, *USP,* and 500 mg single dose vial packaged with a 50 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, *USP*.

b. Store protected from light at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

2. Dexrazoxane (Zinecard®, Pfizer brand)

a. Available in as a sterile, pyrogen-free lyophilized powder in 250 mg and 500 mg single use vials. Hydrochloric Acid, NF is added to the vials for pH adjustment.
b. Intact vials should be stored at 25°C (77°F); excursions are permitted to 15° to 30°C (59° to 86°F).

3. Totect® (dexrazoxane for anthracycline extravasation only)

a. Totect is packaged as an emergency treatment carton for single patient use. Each carton contains 10 vials of Totect (dexrazoxane for injection) 500 mg and 10 vials of 50 mL diluent, which provides a complete three day treatment.

Reconstitution and dilution requirements and expiration dating vary based on the product used. Refer to package insert for additional details.

1. Dexrazoxane (generic)

a. Dexrazoxane (250 mg or 500 mg vials) must be reconstituted with a sufficient quantity of 0.167 Molar (M/6) Sodium Lactate Injection, *USP*, to a concentration of 10 mg dexrazoxane for each mL of sodium lactate.
b. Further dilute solution in either D_5W or NS to a final concentration of 1.3 to 5 mg/mL.
c. The final solution is stable for up to 6 hours at room temperature, 15°C to 30°C (59°F to 86°F), or under refrigeration, 2°C to 8°C (36°F to 46°F).

2. Dexrazoxane (Zinecard®, Pfizer brand)

a. Reconstitute with Sterile Water for Injection, USP as follows:
   - For 250 mg vials, reconstitute with 25 mL.
   - For 500 mg vials, reconstitute with 50 mL.
   - The resultant reconstituted solutions will have a concentration of 10 mg/mL.
b. Following initial reconstitution, ZINECARD is stable for 30 minutes at room temperature or up to 3 hours when stored under refrigeration, 2° to 8°C (36° to 46°F).
c. The pH of the resultant solution is 1.0 to 3.0. Further dilution with Lactated Ringer's Injection, USP is required to achieve a final concentration range of 1.3 to 3 mg/mL in intravenous infusion bags. The infusion solution has a pH of 3.5 to 5.5.
d. The infusion solution is stable for one (1) hour at room temperature or if storage is necessary, up to 4 hours when stored under refrigeration, 2° to 8°C (36° to 46°F).

3. Totect® (dexrazoxane for anthracycline extravasation only)

a. Totect® must be reconstituted with supplied diluent to provide a final concentration of 10 mg/mL. The patient's dose of Totect® (based on body surface area) should be injected into a 1000 mL bag of NS for infusion.
b. This solution is stable for 4 hours (begin infusion within 2 hours of preparation) when stored at temperatures <25°C (<77°F).
c. Stability studies indicate that Totect® is chemically and physically stable after reconstitution with sterile water for injection and dilution in Lactated Ringer's Injection when stored in refrigerated conditions (2-8°C) for no more than 8 hours (email communication Cumberland Pharma).

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

For the prevention of anthracycline-induced cardiomyopathy, administer IV immediately prior to anthracycline dose. Administer the anthracycline after completing the infusion of dexrazoxane but within 30 minutes of beginning of the dexrazoxane infusion.

The first infusion of Totect® should be administered as soon as possible and within the first 6 hours following the extravasation.

Supplier: Commercially available. See package insert for further information.

CANADIAN SITES
In Canada, Pfizer brand of Zinecard® is the only product commercially available and now has the same reconstitution, dilution, and expiration dating as the USA Pfizer Zinecard® above.

6.3 DOXORUBICIN
(Adriamycin®) NSC #123127 **(05/09/11)**

Source and Pharmacology:
An anthracycline antibiotic isolated from cultures of Streptomyces peucetius. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) (L)	Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans		

[1] *Risk increases with cardiac irradiation, exposure at a young or advanced age.*
(L) Toxicity may also occur later.

Formulation and Stability:
Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1]vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.

[1]: *Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of doxorubicin, to enhance dissolution.*

[2] *Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.*

Aqueous Solution: Store refrigerated 2°-8°C, (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection: Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration, 2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50 – 1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Administer IV through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

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

6.4 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio®) NSC#614629 **(11/15/16)**

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

Toxicity:

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

Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.

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

Neupogen®, Granix®, and Zarxio® are also available as single use prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim for subcutaneous administration. Store refrigerated at 2º-8ºC (36º-46ºF). Protect from light. Do not shake. Prior to injection, filgrastim and filgrastim-sndz may be allowed to reach room temperature for a maximum of 24 hours (infusion must be completed within 24 hours of preparation). TBO-filgrastim may be removed from 2°C-8°C (36°F-46°F) storage for a single period of up to 5 days between 23°C to 27°C (73°F to 81°F). Avoid freezing and temperatures > 30ºC.

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

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

Guidelines for Administration:
See Treatment, Dose Modification and Supportive Care sections of the protocol.

Filgrastim biosimilar products should not be administered within 24 hours of (before AND after) chemotherapy.

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

6.5 IFOSFAMIDE

(Isophosphamide, Iphosphamide, Z4942, Ifex®) NSC #109724 **(05/09/11)**

Source and Pharmacology:
Ifosfamide is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation (P450 3A isoenzymes) for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of acrolein and phosphoramide mustard which is an active bifunctional alkylating species. Acrolein is thought to be the cause of the hemorrhagic cystitis as seen with cyclophosphamide. Ifosfamide demonstrates dose-dependent pharmacokinetics whereby the terminal half-life ranges from 7 to 16 hours at doses of 1.6-2.4 g/m² to 3.8-5 g/m², respectively. At 1.6-2.4 g/m²/d, 12 to 18% of the dose was excreted as unchanged drug

in the urine, whereas at a 5 g/m² single-dose, 61% was excreted in the urine as the parent drug. Evidence also exists to suggest that ifosfamide metabolism is inducible, with more rapid clearance occurring in the second and later doses when a course of therapy is given as fractionated doses over 3 to 5 days. There is more chloroethyl side chain oxidation of ifosfamide (up to 50%) than of cyclophosphamide (< 10%), and the degree of such metabolism is more variable than with cyclophosphamide. Oxidation of the chloroethyl groups produces chloroacetaldehyde, which is thought to be responsible for the neurotoxicity and renal toxicity that have been seen with ifosfamide therapy.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea & vomiting (acute and delayed)	CNS toxicity (somnolence, depressive psychosis and confusion)	Anorexia, diarrhea, constipation, encephalopathy which may progress to coma (L), seizure, SIADH, phlebitis, hypokalemia
Prompt: Within 2-3 weeks, prior to next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, cardiac toxicities (arrhythmia, asymptomatic ECG changes), microscopic hematuria, metabolic acidosis	↑ liver enzymes, ↑ bilirubin, hemorrhagic cystitis with macroscopic hematuria, dysuria, cystitis and urinary frequency (< 5% with mesna and vigorous hydration) (L), bladder fibrosis
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)		Renal failure acute or chronic, renal tubular acidosis, Fanconi-like syndrome gonadal dysfunction, ovarian failure[1] (L), CHF
Late: Any time after completion of treatment	Moderate nephrotoxicity (↓ in glomerular filtration rate, renal tubular threshold for phosphate, and serum bicarbonate)		Secondary malignancy, hypophosphatemic rickets
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of ifosfamide have been noted in animals. Ifosfamide is excreted into breast milk.		

[1] *Dependent on dose, age, gender and degree of pubertal development at time of treatment*
(L) Toxicity may also occur later.

Formulation and Stability:
Ifosfamide is available in 1 g and 3 g single dose vials of lyophilized white powder without preservatives and as a 50 mg/mL solution in 20 mL and 60 mL vials.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Reconstitute ifosfamide lyophilized powder with sterile water for injection or bacteriostatic water for injection(use 20 mL for the 1 g vial and 60 mL for the 3 g vial) to produce a final concentration of 50 mg/mL. **Use sterile water for injection without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.** Although the reconstituted product is stable for 7 days at room temperature and up to 6 weeks

under refrigeration, the manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. Store unreconstituted vials at room temperature 20°-25°C (68°-77°F). Protect from temperatures above 30°C (86° F). Ifosfamide may liquefy at temperatures > 35°C.

Reconstituted solutions of ifosfamide or ifosfamide solution should be diluted further to concentrations of 0.6 to 20 mg/mL in dextrose or saline containing solutions. Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags or PAB bags, are physically and chemically stable for 1 week at 30°C (86°F) or 6 weeks at 5°C (41°F). The manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination.

Mesna must always be administered in conjunction with ifosfamide. Adequate hydration is required. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Refer to the Chemotherapy Administration Guidelines for additional information.

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

6.6 MESNA – ORAL and IV

(sodium 2-mercaptoethane sulfonate, UCB 3983, Mesnex®) NSC #113891 **(05/11/18)**

Source and Pharmacology:
Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

After an 800 mg dose the half lives for mesna and dimesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna tablets have an oral bioavailability of 45-79% and a urinary bioavailability which ranged from 45-79% of intravenously administered mesna. The oral bioavailability is unaffected by food. When compared to intravenously administered mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of mesna in the urine over a 24-hour period.

Toxicity[1]:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Bad taste with oral use	Nausea, vomiting, stomach pain, fatigue, headache	Facial flushing, fever, pain in arms, legs, and joints, rash, transient hypotension, tachycardia, dizziness, anxiety, confusion, periorbital swelling, anaphylaxis, coughing
Prompt: Within 2-3 weeks, prior to the next course		Diarrhea	
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mesna have not been noted in animals fed 10 times the recommended human doses. There are however no adequate and well-controlled studies in pregnant women. It is not known if mesna or dimesna is excreted into human milk		

[1]All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 g and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. In pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually preceding death. [For comparison in the ICE regimen of 3000 mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800mg/m²/day; a child would be expected to receive 18 mL/m²/day of mesna (concentration of 100 mg/mL and 10.4 mg/mL of benzyl alcohol) 187.2 mg/m²/day of benzyl alcohol or 6.24 mg/kg/day.]

Formulation and Stability:
Mesna is available as scored 400 mg oral tablets. Excipients include lactose, microcrystalline cellulose, calcium phosphate, cornstarch, povidone, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and simethicone.

Mesna for injection is available as 100 mg/mL in 10 mL multidose vials which contain 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. Store product at controlled room temperature, 15°-25°C (68-77ºF). Mesna is not light-sensitive, but is oxidized to dimesna when exposed to oxygen. Mesna as benzyl alcohol-preserved vials may be stored and used for 8 days.

Guidelines for Administration: See Treatment, Dose Modifications and Supportive Care sections of the protocol.

The oral dose of mesna is **twice** the IV dose.

For IV administration, dilute mesna to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide or cyclophosphamide. After dilution for administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Carefully expel air in syringes prepacked for use to avoid oxidation to dimesna.

For oral administration, administer as tablets or diluted parenteral solution.

Oral tablets:
Mesna tablets are scored and doses can be rounded to half a tablet (200 mg).

Injection for oral use:
Dilute the mesna parenteral solution before oral administration to decrease the sulfur odor associated with the product. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice.

Mesna may cause false positive test for urinary ketones.

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

6.7 PEGFILGRASTIM

(pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®) NSC #725961 **(02/10/16)**

Source and Pharmacology:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

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

Toxicity:

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

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

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

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

Supplier: Commercially available. See package insert for further information.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

7.1 Required Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. **Obtain other studies prior to start of phase unless otherwise indicated.**

These tables only include evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.1.1 Required and Optional Clinical, Laboratory and Disease Evaluations for Patients Randomized to Regimen A

Regimen A: CHEMORADIOTHERAPY + Pazopanib					
Observation	**Baseline Prior to Treatment Initiation**	**During Induction Therapy**	**Prior to Week 13 Surgery**	**During Continuation Therapy**	**End of Therapy[A]**
History, Physical Exam, Ht, Wt, BSA, Vital Signs	X	X[B]	X	X[B]	X
Blood Pressure[C]	X	Weekly[B]	X	X[B]	X
CBC with differential and platelets	X	Weekly[B]	X	Weekly[B]	X
Electrolytes including Ca, Mg, PO_4	X	Weekly[B]	X	X[B]	X
Creatinine, ALT, Total bilirubin	X[D]	Weekly[B,D]	X [D]	X [B,D]	X[D]
Amylase and lipase[T]	X	X[B]		X[B]	
Urinalysis +/- UPC[E]	X	X[B]	X	X[B]	X
Pregnancy test (females of childbearing potential)	X				
Sperm banking (optional)	X				
EKG and Echocardiogram or MUGA	X	X[F]		X[F]	X
Pulmonary function tests	X[G]				X[G]
MRI or CT scan of primary site	X[H]		X[H]		X[H]
CT chest	X		X		X
Growth plate evaluation[S]	X				X
^{18}FDG PET scan (optional, see Sec 16.4)	X		X		
Metastatic site imaging[I]	X		X		X
Central imaging review[J]	X[J]		X[J]		
Operative notes & pathology reports	X[K]	X[L]	X[L]	X[L]	X[L]
Central pathology review	X[M]		X[M]		
Central radiotherapy review	X[N]	X[O]		X[O]	
Medication Reconciliation		X[P]		X[P]	
Required biology studies[Q]	X				
Optional biology studies[R]	X	X	X		
Patient diary			X		X

A = End of therapy is defined as 21 days after the first day of the last cycle of chemotherapy. The end of therapy date in patients who undergo surgery or radiotherapy for metastases after the completion of chemotherapy should be the date of the last

operation or the date of the last dose of radiotherapy, whichever is later. The specified evaluations can occur ± 7 days from these end of therapy dates.

B = Within 4 days prior to the start of each chemotherapy cycle. Laboratory studies can be obtained off-site but norms for off site lab must be available at time of audit.

C = Blood pressure will be measured with an appropriate sized cuff at rest. Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (see Appendix V and Section 5.6). If both BP measurements are elevated, follow the guidelines in Section 5.6. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within an acceptable range.

D = Obtain direct bilirubin if total bilirubin is abnormally elevated.

E = If urinalysis shows ≥ 2+ protein then obtain urine protein:creatinine ratio (UPC) (see Appendix XII). If UPC is > 2, then obtain a 24-hour urine collection for protein estimation (see Section 5.4).

F = Obtain prior to Cycle 3 (Week 7) then prior to every doxorubicin-containing chemotherapy cycle once cumulative doxorubicin dose > 225 mg/m^2 (Weeks 19 and 22). EKGs are to be obtained pre-dose prior to chemotherapy on Weeks 7, 19 and 22.

G = Required only for patients whose radiotherapy field encompasses a portion of the lungs and who are of adequate age to successfully complete the tests.

H = Baseline MRI of the primary site is preferred, or CT if the patient has a contraindication to MRI. It is recommended that the baseline study should also include imaging of regional lymph node bed for clear cell sarcoma and epithelioid sarcoma only. If a subtotal resection was done, the baseline study of the lymph node bed should be done after this operation. Use the same imaging modality for all disease evaluations (see Section 10.2.1 and Section 16).

I = Metastases should be imaged by the most appropriate modality.

J = Submit imaging of the primary and metastatic sites for central review as the scans are acquired (see Section 16 for guidelines). Imaging also must be submitted for central review for patients with either progressive/recurrent disease while on study and within 4 weeks of completing therapy. Note: imaging for suspected tumor progression/recurrence more than 4 weeks after completing therapy or a second malignant neoplasm should be submitted for future review.

K = Operative notes & pathology reports for EVERY surgical procedure (including biopsies) performed on the primary tumor and metastatic sites prior to study enrollment must be submitted. For pathology reports, include baseline or original reports (if the diagnosis was obtained on pathology from elsewhere) and any referral/consultation reports or reports containing ancillary information about the patient's tumor, including but not limited to additional tumor testing such as molecular studies, conventional cytogenetic studies or electron microscopy.

L = Submit operative notes & pathology reports for all procedures performed on primary and metastatic sites during treatment as well as any wound-related institutional procedure or operative reports (procedure reports would include radiologically-guided procedures such as drainage of collections).

M = The pathologic specimen obtained at the time of diagnosis and definitive surgery at Week 13 will be centrally reviewed to assess response to treatment (see Section 14.2). Material is also to be submitted for central review at the time of tumor progression/recurrence and at the development of a second malignant neoplasm.

N = Consultation with a Radiation Oncologist should occur at the time of study entry to facilitate timely initiation of RT at Week 4.

O = Materials must be submitted for central radiotherapy quality assurance review and approval 1 week prior to the start of radiation therapy for the primary site and additional data at the completion of treatment per Section 17.10.

P = Record total number doses of pazopanib omitted on case report form for each reporting period.

Q = Collect required peripheral blood in a PAXgene RNA tube (2.5 mL) and in an EDTA tube (5 mL). See Section 15.1 for details.

R = Slides, snap frozen tissue and blood are requested at diagnosis/pre-treatment. Blood is requested on Days 1-3 of Cycle 2. Snap frozen tissue and blood are requested at the time of surgery. Full details are provided in Sections 15.1, 15.2 and 15.3. A summary is provided in Appendix XIII.

S = Only required for patients aged < 18 years. If patient is found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained at the end of therapy (see Section 16.8).

T = Amylase and lipase should both be performed at centers where both tests are available. For sites where either amylase or lipase are not available (certain Canadian provences), at least 1 of the tests must be performed and will meet the protocol requirement for testing.

7.1.2 Required and Optional Clinical, Laboratory and Disease Evaluations for Patients Randomized to Regimen B

Regimen B: CHEMORADIOTHERAPY					
Observation	**Baseline Prior to Treatment Initiation**	**During Induction Therapy**	**Prior to Week 13 Surgery**	**During Continuation Therapy**	**End of Therapy[A]**
History, Physical Exam, Ht, Wt, BSA, Vital Signs including Blood Pressure	X	X[B]	X	X[B]	X
CBC with differential and platelets	X	X[B]	X	X[B]	X
Electrolytes including Ca, Mg, PO_4	X	X[B]	X	X[B]	X
Creatinine, ALT, Total bilirubin	X[C]	X[B,C]	X[C]	X[B,C]	X[C]
Urinalysis	X	X[B]	X	X[B]	X
Pregnancy test (females of childbearing potential)	X				
Sperm banking (optional)	X				
Echocardiogram or MUGA	X	X[D]		X[D]	X
Pulmonary function tests	X[E]				X[E]
MRI or CT scan of primary site	X[F]		X[F]		X[F]
CT chest	X		X		X
^{18}FDG PET scan (optional, see Sec 16.4)	X		X		
Metastatic site imaging[G]	X		X		X
Central imaging review[H]	X[H]		X[H]		
Operative notes & pathology reports	X[I]	X[J]	X[J]	X[J]	X[J]
Central pathology review	X[K]		X[K]		
Central radiotherapy review	X[L]	X[M]		X[M]	
Required biology studies[N]	X				
Optional biology studies[O]	X		X		

A = End of therapy is defined as 21 days after the first day of the last cycle of chemotherapy. The end of therapy date in patients who undergo surgery or radiotherapy for metastases after the completion of chemotherapy should be the date of the last operation or the date of the last dose of radiotherapy, whichever is later. The specified evaluations can occur ± 7 days from these end of therapy dates.

B = Within 4 days prior to the start of each chemotherapy cycle. Laboratory studies can be obtained off-site but norms for off site lab must be available at time of audit.

C = Obtain direct bilirubin if total bilirubin is abnormally elevated.

D = For patients < 21 years of age obtain prior to cycle 3 (Week 7) then prior to every doxorubicin-containing chemotherapy cycle once cumulative doxorubicin dose > 225 mg/m^2 (Weeks 19 and 22). For patients ≥ 21 years of age only obtain on therapy if clinically indicated.

E = Required only for patients whose radiotherapy field encompasses a portion of the lungs and who are of adequate age to successfully complete the tests.

F = Baseline MRI of the primary site is preferred, or CT if the patient has a contraindication to MRI. It is recommended that the baseline study should also include imaging of regional lymph node bed for clear cell sarcoma and epithelioid sarcoma only. If a subtotal resection was done, the baseline study of the lymph node bed should be done after this operation. Use the same imaging modality for all disease evaluations (see Section 10.2.1 and Section 16).

G = Metastases should be imaged by the most appropriate modality.

H = Submit imaging of the primary and metastatic sites for central review as the scans are acquired (see Section 16 for guidelines). Imaging also must be submitted for central review for patients with either progressive/recurrent disease while on study and within 4 weeks of completing therapy. Note: imaging for suspected tumor progression/recurrence more than 4 weeks after completing therapy or a second malignant neoplasm should be submitted for future review.

I = Operative notes & pathology reports for EVERY surgical procedure (including biopsies) performed on the primary tumor and metastatic sites prior to study enrollment must be submitted. For pathology reports, include baseline or original reports (if the diagnosis was obtained on pathology from elsewhere) and any referral/consultation reports or reports containing ancillary information about the patient's tumor, including but not limited to additional tumor testing such as molecular studies, conventional cytogenetic studies or electron microscopy.

J = Submit operative notes & pathology reports for all procedures performed on primary and metastatic sites during treatment as well as any wound-related institutional procedure or operative reports (procedure reports would include radiologically-guided procedures such as drainage of collections).

K = The pathologic specimen obtained at the time of diagnosis and definitive surgery at Week 13 will be centrally reviewed to assess response to treatment (see Section 14.2). Material is also to be submitted for central review at the time of tumor progression/recurrence and at the development of a second malignant neoplasm.
L = Consultation with a Radiation Oncologist should occur at the time of study entry to facilitate timely initiation of RT at Week 4.
M = Materials must be submitted for central radiotherapy quality assurance review and approval 1 week prior to the start of radiation therapy for the primary site and additional data at the completion of treatment per Section 17.10.
N = Collect required peripheral blood in a PAXgene RNA tube (2.5 mL) and in an EDTA tube (5 mL). See Section 15.1 for details.
O = Slides, snap frozen tissue and blood are requested at diagnosis/pre-treatment. Snap frozen tissue and blood are requested at the time of surgery. Full details are provided in Sections 15.1 and 15.2. A summary is provided in Appendix XIII.

7.1.3 Required and Optional Clinical, Laboratory and Disease Evaluations for Patients Randomized to Regimen C

Regimen C: RADIOTHERAPY + Pazopanib					
Observation	**Baseline Prior to Treatment Initiation**	**During Induction Therapy**	**Prior to Week 10 Surgery**	**During Continuation Therapy**	**End of Therapy[A]**
History, Physical Exam, Ht, Wt, BSA, Vital Signs	X	X[B]	X	X[B]	X
Blood Pressure[C]	X	Weekly[B]	X	X[B]	X
CBC with differential and platelets	X	Weekly[B]	X	X[B]	X
Electrolytes including Ca, Mg, PO_4	X	Weekly[B]	X	X[B]	X
Creatinine, ALT, Total bilirubin	X[D]	Weekly [B,D]	X[C]	X [B,D]	X[D]
Amylase and lipase[T]	X	X[B]		X[B]	
Urinalysis +/- UPC[E]	X	X[B]	X	X[B]	X
Pregnancy test (females of childbearing potential)	X				
Sperm banking (optional)	X				
EKG and Echocardiogram or MUGA	X		X[S]	X[S]	X
Pulmonary function tests	X[F]				X[F]
MRI or CT scan of primary site	X[G]		X[G]		X[G]
CT chest	X		X		X
Growth plate evaluation[R]	X				X
^{18}FDG PET scan (optional, see Section 16.4)	X		X		
Metastatic site imaging[H]	X		X		X
Central imaging review[I]	X[I]		X[I]		
Operative notes & pathology reports	X[J]	X[K]	X[K]	X[K]	X[K]
Central pathology review	X[L]		X[L]		
Central radiotherapy review	X[M,N]				
Medication Reconciliation		X[O]		X[O]	
Required biology studies[P]	X				
Optional biology studies[Q]	X		X		
Patient diary			X		X

A = End of therapy is defined as the completion of Week 25. The end of therapy date in patients who undergo surgery or radiotherapy for metastases after the completion of chemotherapy should be the date of the last operation or the date of the last dose of radiotherapy, whichever is later. The specified evaluations can occur ± 7 days from these end of therapy dates.
B = Within 4 days prior to the start of each chemotherapy cycle. Laboratory studies can be obtained off-site but norms for off site lab must be available at time of audit.
C = Blood pressure will be measured with an appropriate sized cuff at rest. Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (see Appendix V and Section 5.6). If both BP measurements are elevated, follow the guidelines in Section 5.6. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within an acceptable range.
D = Obtain direct bilirubin if total bilirubin is abnormally elevated.
E = If urinalysis shows ≥ 2+ protein then obtain urine protein:creatinine ratio (UPC) (see Appendix XII). If UPC is > 2, then obtain a 24-hour urine collection for protein estimation (see Section 5.4).
F = Required only for patients whose radiotherapy field encompasses a portion of the lungs and who are of adequate age to successfully complete the tests.
G = Baseline MRI of the primary site is preferred, or CT if the patient has a contraindication to MRI. It is recommended that the baseline study should also include imaging of regional lymph node bed for clear cell sarcoma and epithelioid sarcoma only. If a subtotal

resection was done, the baseline study of the lymph node bed should be done after this operation. Use the same imaging modality for all disease evaluations (see Section 10.2.1 and Section 16).

H = Metastases should be imaged by the most appropriate modality.

I = Submit imaging of the primary and metastatic sites for central review as the scans are acquired (see Section 16 for guidelines). Imaging also must be submitted for central review for patients with either progressive/recurrent disease while on study and within 4 weeks of completing therapy. Note: imaging for suspected tumor progression/recurrence more than 4 weeks after completing therapy or a second malignant neoplasm should be submitted for future review.

J = Operative notes & pathology reports for EVERY surgical procedure (including biopsies) performed on the primary tumor and metastatic sites prior to study enrollment must be submitted. For pathology reports, include baseline or original reports (if the diagnosis was obtained on pathology from elsewhere) and any referral/consultation reports or reports containing ancillary information about the patient's tumor, including but not limited to additional tumor testing such as molecular studies, conventional cytogenetic studies or electron microscopy.

K = Submit operative notes & pathology reports for all procedures performed on primary and metastatic sites during treatment as well as any wound-related institutional procedure or operative reports (procedure reports would include radiologically-guided procedures such as drainage of collections).

L = The pathologic specimen obtained at the time of diagnosis and definitive surgery at Week 10 will be centrally reviewed to assess response to treatment (see Section 14.2). Material is also to be submitted for central review at the time of tumor progression/recurrence and at the development of a second malignant neoplasm.

M = Consultation with a Radiation Oncologist should occur at the time of study entry to facilitate timely initiation of RT at Week 1.

N = Materials must be submitted for central radiotherapy quality assurance review and approval 1 week prior to the start of radiation therapy for the primary site and additional data at the completion of treatment per Section 17.10.

O = Record total number doses of pazopanib omitted on case report form for each reporting period.

P = Collect required peripheral blood in a PAXgene RNA tube (2.5 mL) and in an EDTA tube (5 mL). See Section 15.1 for details.

Q = Slides, snap frozen tissue and blood are requested at diagnosis/pre-treatment. Snap frozen tissue and blood are requested at the time of surgery. Full details are provided in Sections 15.1 and 15.2. A summary is provided in Appendix XIII.

R = Only required for patients aged < 18 years. If patient is found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained at the end of therapy (see Section 16.8).

S= Prior to Week 10 Surgery obtain EKG before stopping pazopanib prior to surgery (ECHO or MUGA can be obtained before or after stopping pazopanib but prior to surgery). During continuation therapy obtain EKG only (no ECHO or MUGA), 2-4 weeks after the start of the continuation phase.

T = Amylase and lipase should both be performed at centers where both tests are available. For sites where either amylase or lipase are not available (certain Canadian provences), at least 1 of the tests must be performed and will meet the protocol requirement for testing.

7.1.4 Required and Optional Clinical, Laboratory and Disease Evaluations for Patients Randomized to Regimen D

Regimen D: RADIOTHERAPY			
Observation	**Baseline Prior to Treatment Initiation**	**Prior to Week 10 Surgery**	**End of Therapy[A]**
History and Physical Exam	X		X
CBC with differential and platelets	X	X	X
Electrolytes including Ca, Mg, PO_4	X	X	X
Creatinine, ALT, Total bilirubin	X[B]	X[B]	X[B]
Urinalysis	X[C]	X[C]	X[C]
Pregnancy test (females of childbearing potential)	X		
Sperm banking (optional)	X[D]		
Echocardiogram or MUGA	X[E]		X[E]
Pulmonary function tests	X[F]		X[F]
MRI or CT scan of primary site	X[G]	X[G]	X[G]
CT chest	X	X	X
^{18}FDG PET scan (optional, see Section 16.4)	X	X	
Metastatic site imaging[H]	X	X	X
Central imaging review[I]	X[I]	X[I]	
Operative notes & pathology reports	X[J]	X[K]	X[K]
Central pathology review	X[L]	X[L]	
Central radiotherapy review	X[M,N]		
Required biology studies[O]	X		
Optional biology studies[P]	X	X	

A = End of treatment is defined as 30 days following the last dose of radiotherapy. The specified evaluations can occur ± 7 days from these end of therapy dates.

B = Obtain direct bilirubin if total bilirubin is abnormally elevated.

C = Only for patients whose kidneys, ureters, or bladder will be within the radiotherapy field.

D = Recommended only if the testes are within the radiotherapy field. Surgical repositioning of the testes to the groin may be warranted to protect fertility if the testes will be in the radiotherapy field.

E = Required only for patients whose radiotherapy field encompasses a portion of the heart.

F = Required only for patients whose radiotherapy field encompasses a portion of the lungs and who are of adequate age to successfully complete the tests.

G = Baseline MRI of the primary site is preferred, or CT if the patient has a contraindication to MRI. It is recommended that the baseline study should also include imaging of regional lymph node bed for clear cell sarcoma and epithelioid sarcoma only. If a subtotal resection was done, the baseline study of the lymph node bed should be done after this operation. Use the same imaging modality for all disease evaluations (see Section 10.2.1 and Section 16).

H = Metastases should be imaged by the most appropriate modality.

I = Submit imaging of the primary and metastatic sites for central review as the scans are acquired (see Section 16 for guidelines). Imaging also must be submitted for central review for patients with either progressive/recurrent disease while on study and within 4 weeks of completing therapy. Note: imaging for suspected tumor progression/recurrence more than 4 weeks after completing therapy or a second malignant neoplasm should be submitted for future review.

J = Operative notes & pathology reports for EVERY surgical procedure (including biopsies) performed on the primary tumor and metastatic sites prior to study enrollment must be submitted. For pathology reports, include baseline or original reports (if the diagnosis was obtained on pathology from elsewhere) and any referral/consultation reports or reports containing ancillary information about the patient's tumor, including but not limited to additional tumor testing such as molecular studies, conventional cytogenetic studies or electron microscopy.

K = Submit operative notes & pathology reports for all procedures performed on primary and metastatic sites during treatment as well as any wound-related institutional procedure or operative reports (procedure reports would include radiologically-guided procedures such as drainage of collections).

L = The pathologic specimen obtained at the time of diagnosis and definitive surgery at Week 10 will be centrally reviewed to assess response to treatment (see Section 14.2). Material is also to be submitted for central review at the time of tumor progression/recurrence and at the development of a second malignant neoplasm.

M = Consultation with a Radiation Oncologist should occur at the time of study entry to facilitate timely initiation of RT at Week 1.

N = Materials must be submitted for central radiotherapy quality assurance review and approval 1 week prior to the start of radiation therapy for the primary site and additional data at the completion of treatment per Section 17.10.

O = Collect required peripheral blood in a PAXgene RNA tube (2.5 mL) and in an EDTA tube (5 mL). See Section 15.1 for details.

P = Slides, snap frozen tissue and blood are requested at diagnosis/pre-treatment. Snap frozen tissue and blood are requested at the time of surgery. Full details are provided in Sections 15.1 and 15.2. A summary is provided in Appendix XIII.

7.2 Optional Studies

The correlative biology studies include both required and strongly recommended samples for all patients. These studies are very important to increase our understanding of pediatric and adult NRSTS. If a patient has consented to optional specimen collection on this study, tumor tissue and blood should be submitted to support correlative biology studies.

See Section 15.0 for detailed specimen requirements and Appendix XIII for a summary.

Use of specimens

The tumor and blood samples collected in this study will be used for studies specified in the ARST1321 protocol and for studies to be conducted in the future related to the purposes of the ARST1321 study and not currently described in the protocol document. Detailed protocols for the genomics and proteomics work described in Section 15.0 of the protocol will be developed as separate protocols to include analytical and statistical methodologies and will be submitted for review and approval of these methodologies in accordance with the National Cancer Institute Clinical Trials Network. Studies conducted in the future related to the purposes of the ARST1321 study and not currently described in the protocol document will be submitted for review and approval in accordance with the National Cancer Institute Clinical Trials Network.

The procured specimens, including DNA samples derived from them, will not be used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or parent or guardian or an anonymization process is used. Results of the correlative science studies will not be reported to the patient or their physician and will not have any bearing on their treatment.

The results of the study will be communicated through publications, in peer reviewed scientific literature, and/or through presentations at scientific meetings. However, de-identified or anonymized research data, including genome sequencing data, will be submitted to public research databases such as dbGaP for data sharing with scientific researchers outside of the COG/NRG Oncology.

7.3 Follow-up

See Section 16.2.2 for recommended imaging post-treatment.

Due to concerns of growth disturbances for patients with open growth plates at study entry, plain AP radiographs of the same tibial growth plate are required in follow-up for any patient aged < 18 years assigned to receive pazopanib (see Section 16.8).

In addition, see COG Late Effects Guidelines for recommended post treatment follow-up for children: http://www.survivorshipguidelines.org/

Note: Follow-up data must be submitted per the Case Report Forms (CRFs) schedule.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.

b) Unacceptable toxicity due to protocol therapy (see Section 5.0).

c) Refusal of further protocol therapy by patient/parent/guardian.

d) Completion of planned therapy.

e) Physician determines it is in patient's best interest.

f) Development of a second malignancy.

g) Repeat eligibility studies (if required) are outside the parameters required for eligibility.

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

8.2 Off Study Criteria

a) Death.

b) Lost to follow-up.

c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).

d) Withdrawal of consent for any further data submission.

e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

This study is designed with 2 independent clinical trials for patients with unresected NRSTS of extremities or trunk. Separate trials will be conducted for patients eligible for the chemotherapy cohort (randomized Phase II study of chemo/RT with or without pazopanib) and non-chemotherapy cohort (randomized Phase II/III study of RT with or without pazopanib).

9.1 Sample Size and Study Duration

Enrollment expected from COG: COG recently completed enrollment to enrollment to ARST0332 (Risk-Based Treatment for Pediatric NRSTS). Steady-state enrollment was about 125 patients annually.

Only patients with unresected (ARST0332 Arm D) primary tumors of extremities or trunk will be eligible for this study. Enrollment of such patients was about 29 per year on ARST0332.

Among these patients, 72% have tumors classified as "chemo-sensitive".

Thus, COG yearly enrollment is expected to be about 21 patients with chemo-sensitive tumors and 8 with chemo-resistant tumors. Of these, 15/21 and 5/8 are expected to have localized disease.

Enrollment expected from NRG Oncology: RTOG 0630, a recent study for the treatment of NRSTS accrued 98 patients in 2.5 years (12 to chemotherapy cohort; 86 to no chemotherapy cohort, all with localized disease). Thus, NRG Oncology would be expected to contribute 5 patients to the chemotherapy sensitive cohort and 35 patients to the chemotherapy resistant cohort annually. Additional patients with metastatic tumors are expected, but it is hard to estimate how many will be available.

The table following provides the best estimate of the number of patients available for study annually.

Patient subset	COG annual enrollment	NRG Oncology annual enrollment	Total annual enrollment
Chemo-sensitive, localized disease	15	5	20
Chemo-sensitive, metastatic disease	6	Unknown	6+
Chemo-resistant, localized disease	5	35	40
Chemo-resistant, metastatic disease	3	Unknown	3+

Enrollment is proposed to continue for about 4.5 years, with a total enrollment of up to 340 patients (140 with chemo-sensitive disease and 200 with chemo-resistant disease).

9.2 Dose-Finding Phase for Pazopanib in Both Patient Cohorts

Two of three dose levels of pazopanib (Pediatric patients: 275, 350, 450 mg/m^2 PO once daily; Adult patients: 400, 600, 800 mg PO once daily) may be studied. Initially, up to 10 patients (minimum of 3 patients ≥ 2 and < 18 years of age and 3 patients ≥ 18 years of age) eligible for each of the two study cohorts will be non-randomly assigned (to generate 8 patients evaluable for toxicity) to receive treatment with pazopanib at dose level 1. The following TKI-associated adverse events will be defined as dose-limiting toxicities (DLTs):

Dose-limiting hypertension:
- Grade 3 hypertension not controlled after a week on 2 anti-hypertensive medications
- Grade 4 hypertension

Dose-limiting cardiotoxicity:
- Grade 3+ left ventricular systolic dysfunction

Dose-limiting dermatitis:
- Grade 3+ hand-foot skin reaction (palmar-plantar erythrodysesthesia syndrome)
- Grade 3+ dermatitis radiation

Dose-limiting gastrointestinal toxicity:
- Grade 3+ ALT
- Grade 3+ bilirubin
- Grade 4 amylase
- Grade 4 lipase
- Grade 4 mucositis

Dose-limiting nephrotoxicity:

- Grade 3+ proteinuria

In addition, any death as a first event not attributable to disease will be counted as a dose-limiting toxicity event, as will any withdrawal from protocol treatment as a result of "intolerable toxicity".

The pazopanib dose to be used in each treatment cohort will be determined using the following heuristic (with the DLT evaluation period defined as the first 6 protocol weeks of therapy):

> If 0-1 DLTs at dose level 1, escalate to dose level 2 and treat up to 10 more patients.
> If 2-3 DLTs at dose level 1, dose level 1 is the dose to be used in the study.
> If 4 or more DLTs at dose level 1, reduce to dose level 0 and treat up to 10 more patients.

If 4 or more DLTs are observed at any dose level prior to enrollment of 8 pazopanib-treated patients, further enrollment will be stopped and further dose modification will be made as if 8 pazopanib-treated patients were enrolled.

The DLTs defined above are rare when treatment does not include a TKI.

The table below defines the probability of various actions following the treatment of the first 8 patients, for various true rates of DLT in the first 6 protocol weeks of therapy:

True DLT rate for treatment in the first 6 protocol weeks of therapy	Prob (0-1 DLTs), escalate to dose level 2	Prob (2-3 DLTs), proceed with dose level 1 for randomized phase	Prob (4+ DLTs), de-escalate to dose level 0
0.10	0.81	0.18	0.005
0.25	0.37	0.52	0.11
0.30	0.26	0.55	0.19
0.45	0.06	0.41	0.52

When the rate of DLT is near 10%, the most likely outcome is to escalate to dose level 2. For DLT rates in the range of 20-25%, the most likely outcome is to proceed with the formal evaluation of pazopanib at dose level 1. For a DLT rate of 45%, the most likely outcome is to de-escalate to dose level 0.

Additional criteria for feasibility: The expected number of pazopanib doses a patient should receive during the first 6 weeks of therapy is 6 weeks x 7 doses/week = 42). The total number of full dose pazopanib doses a patient actually receives will be collected using a patient diary and recorded on the case report forms. Irrespective of the DLT rule above, if 3 or more patients out of 8 (> 25%) receive less than 75% of full dose pazopanib doses during the first 6 protocol weeks, a dose reduction (or dose non-escalation) will be considered. So, for instance, if 1 DLT was observed, but 5 patients received less than 75% of the protocol specified full dose pazopanib, the dose might remain at dose level 1 and the study proceed. Should 2-3 DLTs be observed and 3 or more patients receive less than 75%

of the protocol specified full dose pazopanib, the dose might be reduced to dose level 0 and up to 10 additional patients treated.

If the dose is escalated or de-escalated after the enrollment of the first up to 10 patients, the heuristic will again be applied for the 8 evaluable patients treated at dose level 2 (escalation) or 0 (de-escalation):

At dose level 2, 0-3 DLTs would lead to that dose being used (provided no more than 2 patients received less than 75% of the protocol specified full dose of pazopanib). 4+ DLTs or 3+ patients receiving less than 75% of the protocol specified full dose of pazopanib might lead to dose level 1 being used.

At dose level 0, 0-3 DLTs would lead to that dose being used (provided no more than 2 patients received less than 75% of the protocol specified full dose of pazopanib). 4+ DLTs or 3+ patients receiving less than 75% of the protocol specified full dose of pazopanib would likely lead to reconsideration of the randomized phase of the study.

Applying the criteria: The criteria above are guidelines meant to inform the decision regarding the pazopanib dose to be used in the randomized phase of the study. Depending on the adverse events observed, de-escalation of the pazopanib dose may be required even if fewer than 4 DLTs are observed (for instance 3 cases of Grade 4 left ventricular systolic dysfunction). On the other hand, we may consider escalating the pazopanib dose after observing 4 DLTs (if, for instance they were all Grade 3 ALTs of short duration).

9.3 Monitoring of Dose Limiting Toxicities Following the Dose Finding Phase

After at least 10 patients have been enrolled onto the chemo-radiotherapy plus pazopanib regimen or onto the radiotherapy plus pazopanib regimen, the rate of DLTs will be monitored as follows:

> Should the observed rate of DLTs on either of these treatment regimens at any of the scheduled interim analyses exceed 25% (e.g., > 5 out of 20 patients), study enrollment may be suspended so that the study committee may consider whether a change in the pazopanib dosing is necessary.

The rates of other adverse events will be reported as part of each scheduled study progress report and CTEP-AERS-reportable events will be monitored and reviewed in real time.

9.4 Design and Statistical Considerations for the Phase II Study for Patients With Chemotherapy

This study is designed as a randomized Phase II screening study where the primary endpoint is the protocol Week 13 pathologic response designed to assess the potential benefit for chemoradiotherapy plus pazopanib, compared to chemoradiotherapy alone. Patients randomized to pazopanib will continue to receive it subsequent to the Week 13 evaluation if the patient does not have evidence of progressive disease. Before randomization, patients will be stratified by age (< 18 years versus 18+ years), localized versus metastatic disease and synovial sarcoma versus other sarcomas.

Stage 1: Patients with high risk (> 5 cm, Grade 2 or 3) unresected chemotherapy-sensitive tumors with or without metastatic disease will be eligible for enrollment, provided resection of tumor is planned for the patients with metastatic disease at protocol Week 13.

The expected null (chemotherapy only) pathologic response rate (90%+ necrosis at Week 13) is 40%. The significance level will be set at 20% (1-sided). Seventy (70) eligible patients with Week 13 pathologic response information will provide 80% power to detect a true response rate of 60% with pazopanib. The power calculations were performed assuming that the comparison of pathologic response rates will not be performed using a continuity correction.

From the COG ARST0332 experience, up to 20% of patients may be lost due to ineligibility or off protocol therapy prior to the Week 13 surgical evaluation for reasons other than disease progression (patients off protocol therapy prior to protocol Week 13 for disease progression or non-response will be considered "Week 13" non-responders). We expect to have to randomize up to 100 patients total (50 per treatment) before we have the required 70 eligible patients evaluable for response.

Interim monitoring for efficacy and futility will be performed, starting at about 43% of the expected information (Week 13 response known for 30 eligible patients) and again yearly. Interim monitoring for efficacy will use an O'Brien-Fleming boundary (truncated at 3 standard deviations). For futility monitoring, we will repeatedly test the hypothesis that Prob{Response (ID + pazopanib)} – Prob{Response (ID)} =0.20 versus the alternative the difference is less than 0.20 at a p-value of 0.05.

We will compute estimates of event-free survival (EFS: time to the first occurrence of progression, relapse after response, secondary cancer or death from any cause) for each randomized treatment group, although this will be descriptive only. The Phase II sample size will not be sufficient to provide adequate power to detect relative risks reductions that could be expected with the addition of pazopanib in this patient population.

9.5 Design and Statistical Considerations for the Phase II/III Study for Patients Without Chemotherapy

The structure of this study is that of a two-stage Phase II/III study for patients with chemo-resistant tumors or patients with chemo-sensitive tumors that meet the criteria in Section 3.2.2 and 3.2.3: a randomized Phase II screening study where the primary endpoint is the protocol Week 10 pathologic response; if Stage 1 suggests a potential benefit for radiotherapy plus pazopanib, the study will be extended to a Phase III study with event-free survival as the primary endpoint. Pathologic response results (not EFS) from the Phase II study will be made available if the trial proceeds to the Phase III component. Before randomization, patients will be stratified by age (< 18 years versus 18+ years), grade (French criteria: 2 versus 3) and size of primary (< 5 cm versus 5+ cm).

Stage 1: Patients with unresectable tumors with or without metastatic disease will be eligible for Stage 1 enrollment, provided resection of tumor is planned for the patients with metastatic disease at protocol Week 10. For chemo-resistant tumors, the expected null (radiation therapy only) pathologic response rate (90%+ necrosis at Week 10) is 10%. The significance level will be set at 20% (1-sided). Seventy (70) eligible patients with Week 10 pathologic response information will provide 80% power to detect a response rate of 25%, of sufficient interest to complete the Phase III study (see details below). The power calculations were performed assuming that the comparison of pathologic response rates will not be performed using a continuity correction.

From the COG ARST0332 experience, up to 20% of patients may be lost due to ineligibility or off protocol therapy prior to the Week 10 surgical evaluation for reasons other than disease progression (patients off protocol therapy prior to protocol Week 10 for disease progression or non-response will be considered "Week 10" non-responders. We expect to have to randomize up to 100 patients total (50 per treatment) before we have the required 70 eligible patients evaluable for response.

In the absence of adverse event concerns with radiotherapy + pazopanib, if Stage 1 enrollment continues to 70 patients and is not stopped at interim monitoring, **study enrollment will not be suspended while the final pathologic response data are assembled**. The Week 10 response rates between the randomized treatments will be compared using a chi-square test for contingency tables.

Interim monitoring for efficacy and futility will be performed, starting at about 50% of the expected information (Week 10 response known for 35 eligible patients) and again yearly. Interim monitoring for efficacy will use an O'Brien-Fleming boundary (truncated at 3 standard deviations). For futility monitoring, we will repeatedly test the hypothesis that Prob{Response (RT + pazopanib)} – Prob{Response (RT)} =0.15 versus the alternative the difference is less than 0.15 at a p-value of 0. 05.

Stage 2: Should Stage 1 indicate that the study can proceed to Stage 2, enrollment will then be restricted to patients with localized unresectable tumors (without metastatic disease). Patients with localized disease enrolled in Stage 1 will contribute to the Phase III study analysis. The primary endpoint for the Phase III study will be event-free survival, defined as the first occurrence of progression, relapse after response, a secondary cancer or death as a first event from any cause.

The null (radiation therapy only) 5-year EFS for patients with localized unresectable chemo-resistant tumors is expected to be about 30%. Testing will be performed at the 5% level of statistical significance (1-sided; only an improvement with pazopanib is of interest). The study is designed to have 80% power to detect a 40% reduction is the event risk (0.6:1.0), equivalent to a 5-year EFS improvement to 49%); thus 95 total observed events are required. To assure that 95 events are observed, up to a total of 150 patients will be enrolled.

Interim monitoring of the Phase III study will be performed. Interim monitoring will begin at about 33% of the expected information (which is expected to occur near the time Phase III enrollment begins and will be performed annually. Interim monitoring for efficacy will use an O'Brien-Fleming boundary (truncated at 3 standard deviations) and an alpha-spending function approach to the monitoring. For futility monitoring, we will repeatedly test the hypothesis that the true event relative risk is 0.60 versus the alternative that the relative risk is greater than 0.60 at a p-value of 0.05.

9.6 Statistical Considerations for Study Secondary Objectives

9.6.1 Considerations for Aim 1.2.1

Definitions of failure types:

- Local failure: disease recurrence only at the primary site of disease at diagnosis

- Regional failure: disease recurrence at lymph nodes regional to the primary disease site, with or without local failure but without distant failure (see below)
- Distant failure: disease recurrence at sites other than the primary site and diagnosis and nodes regional to that site (metastatic disease, whether or not present at diagnosis), with or without loco-regional failure.

Failure types will be characterized into these mutually exclusive failure types and the cumulative incidence of these types of failure will be estimated, accounting for the fact that these are competing risks of failure (one type excluding the possibility of observing another type).

9.6.2 Considerations for Aim 1.2.2

The relative risk of specific failure types will be estimated and compared descriptively using the Cox proportional hazard model.

9.6.3 Considerations for Aim 1.2.3 and Aim 1.2.4

The adverse event profile of the treatments delivered (chemo-radiotherapy; radiotherapy) will be characterized using the current CTCAE version and adverse events defined in Section 11.10.

9.7 Statistical Considerations for Exploratory Aims

9.7.1 Statistical Analysis Plan for Actionable Mutations (Aim 1.3.1)

Descriptive statistical analyses, conducted by Dr. Chi and colleagues at the COG Statistics and Data Center, will estimate the relative frequency of actionable mutations across the whole cohort and within more common histological subtypes, like synovial sarcoma and MPNST, as well as the frequency with which combinations of actionable mutations are observed in individual tumor types.

9.7.2 Statistical Analysis Plan for Whole Genome Sequencing (Aim 1.3.1)

Descriptive and exploratory statistical analyses will be carried out as outlined above and will increase the precision with which the rates of actionable mutations are quantified in this population.

9.7.3 Statistical Analysis Plan for Microvessel Density and Circulating Tumor DNA Studies (Aim 1.3.2)

Descriptive analyses will be performed.

9.7.4 Statistical Analysis Plan for Doxorubicin Pharmacokinetics in Combination with Pazopanib (Aim 1.3.3)

Previous pharmacokinetic drug-drug interaction studies have indicated that decreases in the clearance of doxorubicin in adult patients with cancer of 30% are associated with significantly worsened side effects associated with the anthracycline[182] including cardiotoxicity.[183] The mean clearance for doxorubicin used in the power calculation was 25.6 L/h/m^2, estimated from a group of 22 pediatric cancer patients (median age, 15; range, 3.3-21.5 years) that had blood samples collected up to 48 hours after the end of infusion.[184] In this group of patients, the observed SD of the doxorubicin clearance was estimated to be 5.3 L/h/m^2. The present trial is designed to allow detection of statistically

significant changes in the mean clearance of doxorubicin of at least 25% using a one-sample analysis, which concerns testing an observed experimental mean against the expected (historical) mean of 25.6 L/h/m^2. Based on a double-sided analysis for a sample size of 10 for the prospective evaluation, with a significance level of 0.05 (5%), this provides a power of 0.93 (93%). The statistical analysis was performed in the SISA program (Available: http://www.quantitativeskills.com/sisa/; Accessed: November 2013).

9.7.5 Statistical Analysis Plan for FDG-PET Studies (Aim 1.3.4)

FDG PET will be optional but encouraged for all enrolled patients. If done, FDG PET imaging should be performed prior to initiation of chemotherapy and at Week 10 or 13 prior to tumor resection. Based upon ARST0332 and ARST0531, we anticipate 20-25% of patients will undergo FDG PET imaging. Due to the anticipated low percentage of study patients likely to have FDG PET scans performed, the FDG-PET images will be assessed as positive or negative at the primary site and PET response will be descriptively compared to the findings at Week 10 or 13 surgery. SUV_{max} will be determined. This data will provide pilot data regarding the relationship of FDG PET to therapy response. About 30 total events are expected among those patients with PET imaging at Week 10 or 13, too few to say anything definitive unless there is a very large difference in outcome between patients with PET+ and PET- disease, which is not expected. Nevertheless, we will estimate hazard ratios for the association between EFS and change in FDG PET SUV_{max} (or PET response at Week 10 or 13 based upon central review) and also estimate the association between pathologic response and PET response.

9.7.6 Statistical Analysis Plan for Exploratory Aim 1.3.5

We will assess the relative risk of failure comparing CR to PR/NR based on both standard imaging and pathologic assessment using the log-rank test, to see if one response assessment method produces a larger difference in outcome between the response categories.

We expect to observe few radiologic complete responses at the end of initial chemotherapy (the observed rate on ARST0332 was 1%), with a partial response rate of 20-30%, with most of the remaining patients classified as non-responders. We expect to show that imaging response is a poor predictor of subsequent event-free survival, as was shown in rhabdomyosarcoma.[185]

However, we expect to find that the EFS outcome for patients with good pathologic response (90+% necrosis) is better than that for those without a good pathologic response. As detailed in the statistical considerations, up to 20% of patients may not have evaluations of pathologic response at the Week 10 or 13 evaluation). We assume that (if the chemo resistant cohort continues to Phase III) about 250 patients will be available for assessing outcome from definitive surgery (excluding also those with progressive disease). If we restrict to patients with localized disease (N=175) we should expect to observe perhaps 85 events. Testing at the 5% level of statistical significance, we will have about 80% power to detect a relative risk difference of 0.55:1.00 (assuming an overall pathologic response rate of 50%. This corresponds to a long-term EFS of approximately 40% for non-responders and 60% for responders.

9.8 Gender and Minority Accrual Estimates

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

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	27	24	51
Not Hispanic or Latino	153	136	289
Ethnic Category: Total of all subjects	180	160	340*
Racial Category			
American Indian or Alaskan Native	1	3	4
Asian	7	4	11
Black or African American	32	26	58
Native Hawaiian or other Pacific Islander			
White	140	127	267
Racial Category: Total of all subjects	180	160	340*

* These totals must agree

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (ie, v5.02 and all subsequent iterations prior to version 6.0).

10.2 Response Criteria for Patients with Solid Tumors

For the purposes of this study, patients should have imaging performed at baseline and be re-evaluated for response at Week 10 (treatment Regimens C and D) or Week 13 (treatment Regimens A and B).

This study will use volumetric measurements of the primary tumor using an elliptical model (0.5 times the product of the three largest perpendicular diameters) to assess the diagnostic imaging response to neoadjuvant therapy. Response and progression of measurable metastases (including nodal metastases) will be evaluated using the largest unidimensional measurement. These measurements will be correlated with changes in the largest diameter in the (unidimensional measurement) of the primary tumor lesions and the shortest diameter in the case of malignant metastatic lymph nodes according to the new

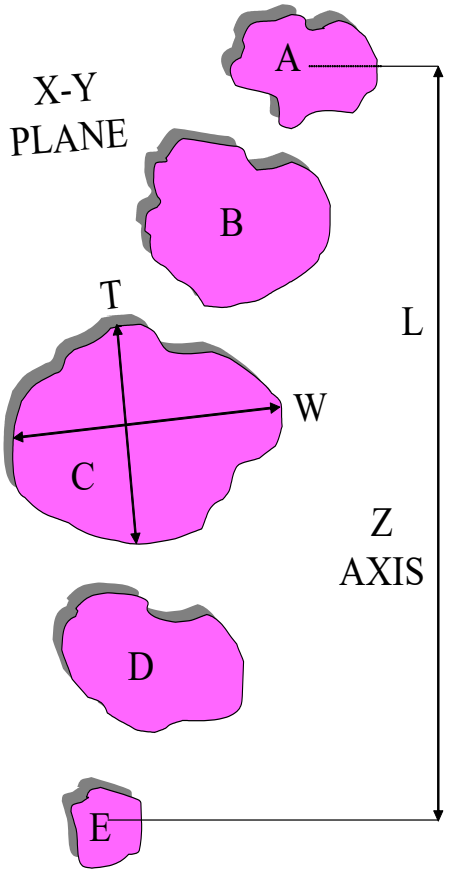
international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[186]

10.2.1 Definitions

The COG guideline (see diagram below) will be used for measurement of the primary tumor on cross-sectional imaging (either computed tomography [CT] or magnetic resonance imaging [MRI]).

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of the first response period will also be considered evaluable.)

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



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor *plus* one *slice* thickness), or [b] the product of ([slice thickness + gap] and the number of slices showing the tumor) *minus* one *gap* distance
- WHO criteria: TxW is used
- RECIST: the larger of the two (T & W) is used (W in this example)
- Elliptical model volume=0.5 LxWxT
- The same modality and measurement method used in the initial imaging should be used in follow ups

TECHNICAL GUIDELINES FOR CROSS-SECTIONAL IMAGING

COMPUTED TOMOGRAPHY (CT)

1. All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle).
2. CT slice thickness should be 5mm or less.
3. The diameter of a "measurable" mass should be at least twice the reconstructed slice thickness. Smaller masses are considered detectable, but will be counted as "non-measurable."
4. Edge-enhanced lung windows, liver, and bone windows should be photographed, if recorded in hard copies. Digital images are submitted either electronically or in CD using DICOM format.

MAGNETIC RESONANCE IMAGING (MRI)

1. Axial images and at least one additional plane are acquired. At least two pulse sequences, such as T1, T2, STIR, or FLAIR-weighted, or in-phase/out-of-phase images are obtained. Post-contrast images are obtained if appropriate. Measurements should be made using the same sequence best showing the tumor in follow up for comparisons.
2. Only axial images will be used for measurement. The cranio-caudal diameter is represented by the distance between the most cranial and caudal slice positions *plus* one *slice* thickness (or [slice thickness + gap] x number of slices showing the tumor *minus* one *gap* distance).

RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST), PRODUCT OF TWO DIAMETERS (WHO), AND THREE PERPENDICULAR DIAMETERS ("VOLUME")
(Modified from Appendix II,Table 2, JNCI 92:213, 2000)

	Diameter, 2R	Product, $(2R)^2$	Volume, $4/3\pi R^3$
Response	**Decrease**	**Decrease**	**Decrease**
	30**%**	50**%**	65%
	50%	75%	87%
Disease Progression	**Increase**	**Increase**	**Increase**
	12%	25**%**	40%
	20**%**	44%	73%
	25%	56%	95%
	30%	69%	120%

Target lesions at baseline must measure greater than 1 cm; if these target lesions decrease in size to below 1 cm, care should be taken in measuring and inadvertently progressing a patient due to minimal changes in measurement from a nadir value below 1 cm, which may be within measurement error. When multiple primary or metastatic masses are present, all masses will be described. However, up to 5 target masses should be measured, using the same method in subsequent follow ups.

10.2.2 Disease Parameters

10.2.2.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. For masses that are smaller than 10 mm, a measurable mass has to be at least twice the slice thickness (< 5 mm) used. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). The maximal perpendicular diameters in all three planes are recorded.

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

10.2.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes

with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

10.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations must be obtained within 3 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

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

10.2.3.1 Clinical lesions: Clinical lesions will only be considered measurable

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible. The utility and potential of diffusion-weighted imaging (DWI) in soft tissue sarcoma diagnosis and therapy response is unknown. If DWI were acquired, they should be submitted with the rest of other MR sequences for central review (ref. Diffusion-weighted imaging (DWI) in musculoskeletal MRI: a critical review.[187]

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

10.2.3.5 Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent

review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

10.2.4 Response Criteria

10.2.4.1 Evaluation of Target Lesions (Primary Tumor)

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

Partial Response (PR): At least 64% decrease in volume compared to the measurement obtained at study enrollment.

Progressive Disease (PD): At least 40% increase in tumor volume compared to the smallest volume obtained since the beginning of therapy. (Note: the appearance of one or more new lesions is also considered progressions.)

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

10.2.4.2 Evaluation of Target Lesions (Metastatic Sites)

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

Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of all target lesions, taking as reference the disease measurement done to confirm measurable disease at study enrollment

Progressive Disease (PD): At least a 20% increase in the sum of the longest diameters of all target lesions, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions.

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

10.2.4.3 Evaluation of Non-Target Lesions

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

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

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

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

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

10.2.4.4 Evaluation of Best Overall Response

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

For Non-Metastatic Patients with Measurable Disease (ie, Target Disease)

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

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

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

For Metastatic Patients with Measurable Disease (ie, Target Disease)

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

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

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

For Patients with Non-Measurable Disease (ie, Non-Target Disease)

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

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

10.2.5 Duration of Response

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

progressive disease the smallest measurements recorded since the treatment started).

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

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

10.2.6 Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10.2.7 Response Review

Central review of imaging studies will be performed in all patients (see Section 16).

10.3 Other Response Parameters

Pathologic response will be assessed at Week 10 (treatment Regimen C and D) or Week 13 (treatment Regimen A and B). Central pathology review will be performed in all patients (see Section 14).

Surgical response will be assessed following the Week 10 (treatment Regimen C and D) or Week 13 (treatment Regimen A and B) definitive surgery (see Section 13).

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

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

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

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

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a

possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

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

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "*Disease progression*" in the system organ class (SOC) "*General disorders and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

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

11.4.4 Secondary Malignancy

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

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

11.4.5 Second Malignancy

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

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

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

11.4.6.1 Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the "***Pregnancy, puerperium and perinatal conditions***" SOC.

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

11.4.6.2 Pregnancy Loss (Fetal Death)

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

11.4.6.3 Death Neonatal

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

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE

terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (eg, elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

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

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

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

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

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

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

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

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

11.6.2 Special Situations as Exceptions to Expedited Reporting

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

11.7 Reporting Requirements - Investigator Responsibility

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

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

11.8 General Instructions for Expedited Reporting via CTEP-AERS

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

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

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.
In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

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

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

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

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

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **301-230-0159** (back-up: 301-897-7404).
Also: Fax or email to COG for **all** IND studies (fax # 626-303-1768; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

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

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

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

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

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

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

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

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

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

11.10 Protocol Specific Additional Instructions and Reporting Exceptions

- **Grades 1- 4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not**

require expedited reporting.

- **Grades 1-2 AST/ALT elevations do not require expedited reporting.**
- **In addition to the defined CTCAE reporting of wound complication adverse events, there is expanded wound complication data submission requirements on the study reporting period and surgery central review case report forms (wound complication grading adapted from Dindo et al. 2004 and characterization of the wound complication adapted from O'Sullivan et al. 2013).[143,144]**

11.11 Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.12 Routine Adverse Event Reporting

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

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 4 and higher Adverse Events with the exception of the events listed in Section 11.10.

12.0 STUDY REPORTING AND MONITORING

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

12.1 CDUS

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

12.2 Data and Safety Monitoring Committee

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

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

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

12.3 CRADA/CTA

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

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

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

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

Email: ncicteppubs@mail.nih.gov

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

13.0 SURGICAL GUIDELINES

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

13.1 Initial Biopsy for Diagnosis and Tissue Submission

An incisional biopsy or core biopsy is preferred. The biopsy should be done in such a way as to permit excision of the biopsy site at the time of formal resection. If the grade and subtype of the tumor cannot be determined from the core biopsy, then an incisional biopsy is required. Fine needle aspiration biopsy is not acceptable to establish the diagnosis. Sufficient tissue must be obtained by either method. The minimum recommended sampling is 8 core biopsies of 2 cm in length. The surgeon should sample heterogeneous areas as determined by prebiopsy imaging. Care must be taken to prevent penetration of the needle through the tumor into unaffected soft tissues.

13.2 Surgery

13.2.1
It is strongly recommended that any eligible patient is seen by the surgeon, pediatric/medical oncologist and radiation oncologist prior to instituting pre-operative therapy. The surgeon should determine and document a high possibility of both primary tumor resection and anticipation of a limb preservation approach after preoperative radiation to obtain local control. After radiation, every effort should be made to have limb preservation surgery unless there is documented evidence of tumor progression during or after the course of radiation that would require amputation for an appropriate negative margin resection. At the discretion of the treating physician(s), plastic and/or vascular surgeons may be consulted.

Upon removal, the tumor specimen should be submitted immediately to the pathologist. It should not be bisected or cut into pieces prior to pathologic evaluation. The tissue should not be placed in formalin, as fresh and snap frozen tissue may be helpful in establishing the diagnosis and providing materials for biology studies and banking. If there will be any delay in transferring the specimen to the pathologist, it should be transported in cytogenetics medium. *The surgeon should note the time of explantation to passing off of the specimen.*

13.2.2
Resection of the sarcoma will occur following combined preoperative radiation and/or chemotherapy per study schema. The resection should be done with the goal of having negative pathologic margins. Quality assurance for surgical resection will be provided by both a review of the operative note and assessment of the specimen by surgical pathology. Microscopic absence of tumor on the inked margins will be accepted as a negative margin

resection (R0).

13.2.3
Definitions of operative procedures will be made after assessment of the operative note and pathologic evaluation of the resected specimen. The definitions include:

13.2.3.1
Amputation: Margin status will still be assessed and categorized if a limb preservation approach is not possible after the preoperative radiation.

13.2.3.2
Limb sparing surgery with the following margin status: R0: No residual tumor- microscopically negative margins; R1: Microscopic residual tumor- microscopic positive margin(s) but no gross tumor; R2: Macroscopic residual tumor. It is strong encouraged that any patient with an R2 margin status following limb sparing surgery should be assessed for surgical re-excision, with a goal of achieving an RO or R1 margin. Any patient left with a R2 margin that is not reresected will be subject to central review.

13.3 Definitive Surgical Procedure

The surgical procedure necessary to resect the tumor with negative margins should be used. The definitions, as noted above, will be recorded in the surgical form. The goal of all surgery should also be limb preservation, if possible, within the realm of an appropriate oncologic resection.

Because the presence or absence of residual tumor following definitive surgery determines whether or not postoperative primary-site radiotherapy is necessary, the goal of definitive tumor resection at Week 10 or 13 should be to achieve negative microscopic margins (R0), if possible. Patients with negative microscopic margins will not receive any postoperative primary-site radiotherapy.

13.4 Principles of Surgery

13.4.1
All lesions of the extremities and trunk should be treated with wide excision after preoperative radiation and/or chemotherapy.

Any incisional biopsy site should be excised *en bloc* with the definitive surgical specimen. Needle biopsy tracks should only be excised if additional morbidity is not anticipated by doing so. Dissection should always be done through grossly normal tissue planes and ideally should be done beyond the fascial plane adjacent to the tumor. If the tumor is close to or displaces major vessels or nerves, these need not be removed if the adventitia or perineurium is removed and the underlying neurovascular structures are not involved with gross tumor. Dissection should include the periosteum if the tumor is adjacent to the bone but not invading. Radical excision or entire anatomic compartment resection is not recommended for patients on this study.

To facilitate the assessment of surgical margins, the surgeon should take care to manipulate the specimen as little as possible to preserve anatomic relationships present at the time of resection; to mark and orient the margins for the pathologist; and to avoid bisecting, bivalving, or cutting the specimen into separate specimens.

If postoperative pathologic evaluation reveals positive soft tissue margins other than bone (periosteum), nerve or large blood vessels, surgical re-resection to obtain negative margins should strongly be considered if it will not have a major impact upon the patient's functionality. If the margin on bone, major blood vessel or nerve is microscopically positive, additional radiation may be given as noted in the protocol.

In general, lymph node dissection is not recommended, but primary tumors overlying major lymph node stations may be treated with surgical resection to include the associated lymph nodes. *Surgical clips (titanium) should be placed to mark the periphery of the surgical field of resection and other relevant structures to help guide the radiation oncologist if postoperative radiation boost is necessary*. Closed suction drainage may be used in all anatomic regions (Hemovac, JP, etc.). The drains should exit the skin close to the edge of the surgical incision and ideally in line with the incision distally.

13.4.2
It is strongly encouraged that the surgeon *clearly state* in the operative note what type of surgical procedure was intended (R0, R1, or R2) and from where the frozen sections of the margins were taken, if any. The final margin status (R status) should be based on the permanent pathology assessment (not frozen section). The surgeon may state that the intent of the procedure was wide resection to obtain a negative oncologic margin. However, the term "radical" should not be used to describe the procedure unless the intent of the surgery was truly to do a complete extracompartmental resection.

13.4.3
Because all patients will have had preoperative radiation, special attention must be given to the skin flaps. Use of muscle flaps, pedicled myocutaneous flaps, and even free flaps are encouraged to fill dead space and provide well-vascularized tissue. These flaps should be used if there is any concern regarding the viability of the skin flaps.

13.4.4
In general, the following principles should be followed in postoperative management of these patients: Maintain staples or skin sutures per surgeon preference. Leave drains in place until the drainage meets the surgeon's criteria for removal. Begin rehabilitation per surgeon's discretion.

13.4.5
Resectability will depend upon the judgment of the operating surgeon. The goal of all surgery for extremity tumors should be limb preservation, if possible within the realm of an appropriate oncologic resection. Every effort should be made to have limb preservation surgery. However, some extremity tumors may require amputation to obtain even grossly negative margins. Only amputation due to treatment complications (not primary intended surgical therapy) will be considered a surgical complication.

13.5 Surgical Management of Patients with Metastasis Prior to Study Enrollment

All distant metastatic sites should be evaluated with appropriate imaging during the initial staging process. Biopsy should be performed whenever there is uncertainty as to the nature of an abnormal mass, particularly if all metastases are < 1 cm in maximal diameter. This may not be necessary in cases where a metastatic tumor growth is documented in a series of consecutive imaging studies including CT and/or MRI, which is highly suggestive of

metastatic disease by the institutional radiologist. The judgment should be made at the discretion of treating physician. These images should be submitted for central review upon request. The surgical approach for patients with metastatic disease should be individualized with the goal of accurately identifying involved sites and minimizing the number of surgical interventions required. If biopsy is required for tissue diagnosis of potential metastasis, the treating team may elect to resect the metastasis prior to study enrollment (for example, resecting pulmonary metastasis via thoracotomy or thoracoscopically). Clinical judgment should dictate the choice of surgical procedure and extent of resection.

If not resected for tissue diagnosis, definitive resection to remove metastatic disease present at study entry should be performed at the completion of all protocol-required chemotherapy. Surgical resection of metastasis at Week 13 (chemotherapy cohort) or Week 10 (non-chemotherapy cohort) (unless the metastasis can be removed via the same incision used for the primary tumor) or at any other time during therapy is prohibited unless there is strong clinical indication for doing so.

13.5.1 Surgical Assessment of Lymph Nodes

Lymph node sampling should be considered (but not required) in patients with epithelioid sarcoma and clear cell sarcoma because the incidence of nodal involvement in these tumors exceeds 15%. Lymph node sampling is recommended in patients with enlarged regional lymph nodes detected by physical exam or diagnostic imaging because this adenopathy may be reactive rather than neoplastic. This should be done prior to starting chemotherapy for staging purposes.

When lymph node biopsy is to be done, the use of sentinel node mapping and biopsy techniques are encouraged (but not required) in cases of nonpalpable lymph nodes, as well as to supplement selective sampling among patients with clinically enlarged nodes. Sentinel node biopsy should be performed with technetium 99m sulfur colloid. The use of isosulfan blue 1% dye is an accepted adjunct to technetium, but is not required, particularly in younger pediatric patients, for whom effective yield of sentinel nodes has been demonstrated with technetium alone and in whom inadvertant tattooing of skin by the dye may be a consideration.

Whether performed by selecting sampling or sentinel node technique, lymph node biopsies have a role in tumor staging and should therefore be done prior to the start of protocol therapy. If lymph node biopsies are positive for tumor (or the lymph nodes are classified as positive by the study radiologist), formal lymph node dissection may be considered at the time of Week 10 or Week 13 definitive surgery, or at completion of therapy when metastatic disease is resected.

13.6 Surgical Adverse Events

13.6.1 Wound Complications

Major wound complications (eg, secondary operations, re-admissions, and/or invasive procedures for wound complications: deep wound packing and prolonged dressing changes) will be reported using the relevant CTCAE version 5.0 criteria.

13.7 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chairs from both COG and NRG Oncology will perform a Quality Assurance Review on a rolling basis once received at COG Statistics and Data

Center (SDC). The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at COG SDC, whichever occurs first.

Surgical quality assurance review will include examination of the formal operative report for the surgical resection, the treating institution's final pathology report (including gross, frozen section, and microscopic pathologic descriptions), and the central pathology review. The reported resection (R) status from the operative note will be assessed and re-evaluated based upon the final pathology report and the central pathology review. The surgical quality assurance review will then assign an official protocol resection status based upon this information. From a clinical treatment and protocol standpoint, an R0 or R1 resection (especially following an attempt to preserve a major neurovascular or bony structure) would be considered an adequate surgical resection. For the purposes of this protocol, an R2 resection would not be considered adequate surgical therapy, even in the context of limb preservation. Any patient left with an R2 resection is subject to central review.

Although every effort should be made to perform limb preservation surgery, some extremity tumors may require amputation to obtain negative margins if a limb preservation approach is not possible after preoperative radiation. In this scenario, amputation would still be considered adequate surgical therapy and margin status will be assessed or categorized based upon the R criteria for limb sparing surgery.

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

14.1 Aims of Retrospective Central Pathology Review

The retrospective central pathology review has several goals:

- To determine whether the addition of pazopanib to neoadjuvant chemoradiation or radiotherapy improves pathologic response in pediatric and adult NRSTS (study objectives 1.2.1 and 1.2.3).
- To determine if pathologic response is predictive of outcome in pediatric and adult NRSTS (study objective 1.3.5).
- To assess whether tumor response based on diagnostic imaging accurately reflects the pathologic response to neoadjuvant therapy in pediatric and adult NRSTS (study objective 1.3.5).
- To confirm that only patients with NRSTS are enrolled on this clinical trial and that each patient was assigned to the appropriate treatment regimen based on the tumor histology and grade.

All patients enrolled on this clinical trial will submit tumor tissue for central pathology review. The diagnosis of NRSTS and the histologic subtype will be confirmed during central pathology review of the percent pathologic necrosis rate. Due to high pathology concordance rates among individual enrolling institutions and central reviewers on ARST0332 and RTOG 0630 (information provided by COG and NRG Oncology), no rapid central review of the sarcoma histologic subtype will be required prior to enrollment or treatment initiation.

14.2 Specimen Submission Requirements

Please note: snap-frozen tissue is not required for study enrollment but should be collected whenever possible for correlative biology studies (see Section 15.1 and 15.2).
COG sites: if a tissue block has been submitted already on APEC14B1, another block is not required for ARST1321.

14.2.1 Pathology Specimens Must be Submitted at the Following Time Points:

- Initial Pretreatment Specimen – The initial diagnostic specimen should be submitted for central review at the same time as the Week 10 or Week 13 specimen.
- Week 10 (treatment arms C and D) or Week 13 (treatment arms A and B) – After the surgical procedure is performed at Week 10 or Week 13, the resulting specimen must be submitted for central pathology review within 4 weeks of the surgery date. If the patient undergoes more than one operation at Week 10 or Week 13, specimens should be submitted from all procedures.
- At the time of tumor progression/recurrence – The specimen obtained at the time of tumor progression/recurrence should be submitted for review to confirm the diagnosis.
- At the time of development of a second malignant neoplasm – The biopsy or resection specimen obtained at the time of diagnosis of a solid second malignant neoplasm should be submitted for review to confirm the diagnosis.

14.2.2 Samples to be Submitted on Study

- Initial Pretreatment Specimen
  - Representative formalin-fixed paraffin blocks

  If blocks are unavailable, submit 1 H & E section of all available blocks and 20 NRSTS plus-charged (polarized) unstained slides for immunoperoxidase studies from 1 or 2 representative blocks and 2 additional H & E slides from the same blocks.

  Note: If a block is not submitted for pathology review, then submission of 10 scrolls of 15 micron thickness is strongly encouraged for biology studies (per Section 15.1.3) in addition to the submission of the materials for central pathology review.

- Week 10 (treatment arms C and D) or Week 13 (treatment arms A and B)
  - Representative formalin-fixed paraffin blocks

  If blocks are unavailable, submit 1 H & E section of all available blocks and 20 NRSTS plus-charged (polarized) unstained slides for immunoperoxidase studies from 1 or 2 representative blocks and 2 additional H & E slides from the same blocks.

Note: in addition to these required samples, it is strongly recommended that the post treatment resections be handled similarly to treated osteosarcoma, and the following also be submitted: a cross section with a specimen map and the percent necrosis calculated accordingly.

- At the time of tumor progression/recurrence
  - Representative formalin-fixed paraffin blocks

  If blocks are unavailable, submit 1 H & E section of all available blocks and 20 NRSTS plus-charged (polarized) unstained slides for immunoperoxidase studies from 1 or 2 representative blocks and 2 additional H & E slides from the same blocks.

- At the time of development of a second malignant neoplasm
  - Representative formalin-fixed paraffin blocks

  If blocks are unavailable, submit 1 H & E section of all available blocks and 20 tumor specimen plus-charged (polarized) unstained slides for immunoperoxidase studies from 1 or 2 representative blocks and 2 additional H & E slides from the same blocks.

14.3 Central Pathology Review Guidelines

14.3.1 The Diagnostic Specimen

No rapid central review of the sarcoma histologic subtype will be required prior to enrollment or treatment initiation. The original pretreatment specimen and the definitive surgical specimen will be reviewed together. The diagnostic specimen will be centrally reviewed by an expert panel of pathologists to determine the histologic subtype of soft tissue sarcoma. Each tumor also will be graded according to the guidelines of the FNCLCC grading systems (see Appendix III). FNCLCC Grade 1, 2 and 3 will be considered low grade, intermediate grade and high grade, respectively. In circumstances where more than one histology is present within a diagnostic specimen, the highest grade component determines the classification (i.e. chemotherapy or non-chemotherapy cohort).

14.3.2 Week 10 or Week 13 Specimen

The definitive resection specimen obtained at Week 10 (treatment arms C and D) or Week 13 (treatment arms A and B) patients will be evaluated for pathologic response. This assessment will include a formal evaluation of percent necrosis according to the guidelines established for osteosarcoma.[188] The pathologic assessment of response (calculated percent necrosis) at Week 10 or Week 13 will be compared with the radiographic assessment of response to assess the degree of correlation between the two methods of measuring tumor response. The tumor response as assessed by central pathology review also will be evaluated to determine whether it predicts clinical outcomes such as local and distant disease control and survival.

14.3.3 Tumor Progression/Recurrence Specimens

The specimen obtained at the time of tumor progression/recurrence will be reviewed to confirm that the diagnosis is the same as at study entry and to document changes in pathologic appearance.

14.3.4 Second Malignant Neoplasm Specimens

The specimen obtained at the time of diagnosis of a second malignant neoplasm will be examined to confirm the diagnosis and to ensure that the new diagnosis differs from the one assigned at the time of original diagnosis.

14.4 Sample Labeling and Shipping

All tumor material must be labeled with the patient's COG ID number and the surgical pathology ID number and block number from the corresponding pathology report.

Please note that ANY tissue sample submission to the BPC for pathology review must include the following documentation:

- Institutional pathology report
- Pathology checklist
- Institutional operative report (Can be provisional as long as final report is sent when available)
- COG Specimen transmittal form

All pathology review material should be sent to the COG Biopathology Center (BPC) at room temperature by regular mail or courier using the submitting institution's courier account. Specimens must be accompanied by the Specimen Transmittal Form and sent to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol ARST1321
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCParaffinTeam@nationwidechildrens.org

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

14.5 Review Pathologists

The central review pathologists for this study are listed below. DO NOT send specimens directly to the review pathologists. Send all materials to the Biopathology Center as directed in Section 14.4.

Jennifer O. Black, MD
Children's Hospital Colorado
Phone: (720) 777-1852
Fax: (720) 777-7119
E-mail: jennifer.black2@childrenscolorado.org

Eduardo Zambrano, MD
Presbyterian St. Luke/Rocky Mountain Hospital for Children
Phone: (650) 498-1031
Fax: (650) 724-6843

E-mail: Eduardo.Zambrano@HealthONEcares.com

Julie C. Fanburg-Smith, MD
Penn State Children's Hospital
Penn State Health/Milton S. Hershey Medical Center
Phone: (703) 623-7013
E-mail: jcfsmd@gmail.com

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

15.1 Analysis of Actionable Mutations and Whole Genome Sequencing

15.1.1 Sample Collection and Processing

Required samples:
Submission of pretreatment paraffin-embedded tumor material (block) or unstained slides (per Section 14.2) is required of all patients.
COG sites: if a block has been submitted already on APEC14B1, additional tissue is not required.

If a block is not submitted for pathology review, then 10 scrolls of 15 micron thickness are strongly encouraged for the biology study. An H&E stained slide cut from the same block should also be submitted for quality control.

The following peripheral blood samples are to be collected pre-treatment and shipped on the day of collection.

- **Peripheral blood (2.5 mL) in a PAXgene RNA tube**
- **Peripheral blood (5 mL) in an EDTA-containing (purple top) tube**

Blood samples are to be processed as follows and shipped per Section 15.1.2 below.

When using the PAXgene RNA tube, blood is placed immediately into the tube, which is then inverted 8-10 times to mix. Blood should be maintained at room temperature if shipped on day of collection. If the tube cannot be shipped immediately then it should be maintained at room temperature for 2-24 hours and then placed in -20ºC (or colder) freezer until shipment. Please note that if tubes are to be kept at temperatures below -20ºC, they must first be stored at -20ºC before being transferred into a -80ºC freezer. Ship frozen tubes on dry ice.

When using the EDTA-containing (purple top) tube, blood is collected in the tube and stored at room temperature until shipped. If specimen cannot be shipped on the day of collection, then it should be stored in a refrigerator until shipment on the next business day.

Optional Samples (Patient Consent Required):
Pre-treatment snap frozen tumor tissue from primary site and any metastatic site is requested.

Snap freeze tissue within 15 minutes after surgery for optimal preservation. Cut at least one specimen from the primary and metastatic areas (if present) into maximum 1 gram aliquots. Foil and zip lock bags are provided in the specimen procurement kit. Place a label inside each zip lock bag stating the tissue type (P for primary or M for metastatic), COG patient ID number and collection date. If available, please also include surgical pathology ID number. If tissue is frozen in a vial instead of foil, all labeling must be on the vial.

Place tissue on a piece of foil and fold the foil around the tissue. Each type of tissue (primary, metastatic) is placed on a separate piece of foil. Snap freeze tissue on dry ice or in vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen). Mark foils as P for primary or M for metastatic and place in separate zip lock bags if both are being submitted. Store snap frozen tissue at -80°C until shipment.

15.1.2 Sample Labeling and Shipping

Labeling

Label biology specimens with the patient's COG patient ID number, specimen type and collection date. Blocks, slides and scrolls must also be labeled with the surgical pathology ID and block number from the corresponding pathology report.

Specimen Procurement Kit

The BPC will provide a specimen procurement kit upon request. This kit is for the shipment of frozen and ambient specimens together in one shipment to the BPC. If you are shipping blood or other ambient specimens alone or shipping to a laboratory other than the BPC, then you must use your own shipping container and supplies.

Kits are ordered via the BPC Kit Management system. To request a specimen procurement kit, access the Kit Management system (https://ricapps.nationwidechildrens.org/KitManagement/).

The Biopathology Center provides Specimen Procurement Kits to institutions in the US and Canada. Institutions outside of the US and Canada are expected to provide their own supplies for submission of samples.

Paperwork to Include

Please note that ANY tissue sample submission to the BPC must include the following documentation:

- Institutional pathology report
- Institutional operative report (Can be provisional as long as final report is sent when available)
- COG Specimen transmittal form

In addition, any material submitted for pathology review must include the pathology checklist.

Packaging and Shipping Specimens

The dual chamber specimen procurement kit is constructed to allow shipment of frozen (**on dry ice**) and ambient temperature tissues in the same container. **Dry ice may be placed in either compartment of the kit, but should not be put in both.** Include a specimen transmittal with every shipment and a pathology report, operative report and pathology checklist when appropriate (see above).

1. Before specimens are placed into the dual chamber specimen procurement kit, they first need to be placed in three separate layers of packaging. Package the frozen specimens and the ambient specimens separately since they will be placed in separate compartments of the kit. Two sets of the biohazard and Tyvek diagnostic envelopes are provided in the kit for this purpose.
    a. Place the specimens in zip lock bags (one bag per specimen type/time point).
    b. Place the zip lock bags in a biohazard envelope with the absorbent material. Expel as much air as possible and seal the envelope.
    c. Place the biohazard envelope inside a Tyvek envelope. Expel as much air as possible and seal the envelope.
2. Frozen specimens should be placed in one of the kit compartments filled with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. Place the foam lid on top to insulate the specimens during shipment.
3. Ambient temperature specimens should be shipped in the other kit compartment at room temperature. Insulate ambient specimens with bubble wrap or similar material.
4. Place the transmittal form(s) and pathology report inside the kit chamber with the ambient specimens.
5. Place a foam cover on top of each kit chamber to insulate the specimens during shipment.
6. Close the outer lid of the specimen procurement kit and secure with filament or other durable sealing tape.
7. Print a shipping label via the BPC Kit Management application and attach to the top of the kit.
8. Complete the dry ice label (UN 1845). Place the dry ice and Exempt Human Specimen labels on the side of the kit.
9. Arrange for FedEx pickup per your usual institutional procedure or by calling 1-800-238-5355.

Shipping Address:
Biopathology Center
Nationwide Children's Hospital
Protocol ARST1321
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

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

Specimens should be shipped Monday through Thursday by FedEx Priority Overnight for delivery Tuesday through Friday. Blood in EDTA and PAXgene tubes (if not frozen) can also be shipped on Friday for Saturday delivery. Please do not ship any other specimens for Saturday Delivery.

15.1.3 Methodology

We aim to gain insight into the disease biology of childhood and adult NRSTS through analysis of actionable mutations and whole genome sequencing. There are two components to this correlative study:

1) We will utilize formalin-fixed, paraffin-embedded (FFPE) material and blood (required) and next-generation sequencing (NGS) technology to assess the status of known or suspected pazopanib targets and a limited panel of other genes that may influence response to this molecularly targeted agent.

2) Using snap-frozen tumor specimens (optional) paired with blood (see above), NGS approaches will be utilized for more comprehensive genomic studies including whole genome sequencing, with the goal to perform this work on ~20 specimens representing major NRSTS categories, such as synovial sarcoma, fibrosarcoma, malignant peripheral nerve sheath tumor, and undifferentiated sarcoma

We will utilize a workflow in which potentially-actionable mutations in patients treated with pazopanib are initially batched; as the project moves forward, we will move toward analysis in "real-time" to facilitate risk group-stratification and treatment assignment.

15.1.3.1 Determining the Prevalence of Actionable Mutations that can be Targeted by Currently Available Drugs Across All NRSTS Subtypes
The following workflow will be used:

Prospective cases collected on ARST1321 will be processed as material is received at the Biopathology Center (BPC)/Nationwide Children's Hospital for research subjects enrolled in this trial. Blocks and pretreatment blood are required.

a. FFPE tissue and blood will be processed in batches by the BPC for 1) diagnosis confirmation and tissue quality assessment, and 2) DNA and RNA extraction with subsequent quality assessment and quantification.
b. Tumor- and blood- derived nucleic acids will be shipped to the Skapek and/or Parsons laboratories for targeted gene panel and/or exome/transcriptome sequencing to evaluate key genes encoding VEGF receptors, PDGF receptors, c-KIT, p53, and N-, K-, and H-RAS.[22,30,32,33,151,189-193] This will be accomplished using Illumina HiSeq and MiSeq platforms and appropriate analysis tools with assistance from the CAP/CLIA-certified Pathology Laboratory at

Children's Medical Center Dallas and the University of Texas Southwestern Medical Center DNA Sequencing Core and/or the Clinical Molecular Pathology Laboratory at Texas Children's Hospital.

c. Data will be stored at the COG Statistics and Data Center and correlated with relevant clinical and pathological features in each case.
d. As the study progresses and potential targets are defined, efforts will be made to transition the analysis to one that can be performed in "real-time" within a CAP/CLIA-certified laboratory, such as at the COG Biopathology Center.

15.1.3.2 Conducting Whole Genome Sequencing in NRSTS in Children and Adults

This aspect of the study is optional as it will be conducted using snap-frozen material, which may not be available on every case. Available snap-frozen material will be paired with the blood collected for component 1 above. The requested snap frozen tumor tissue material is detailed in Section 15.1.3.

a. Snap-frozen tissue and blood will be processed in batches by the BPC for 1) diagnosis confirmation and tissue quality assessment, and 2) DNA and RNA extraction with subsequent quality assessment and quantification.
b. Tumor- and blood-derived nucleic acids will be shipped to the Skapek and/or Parsons laboratories for more comprehensive genomic studies including (in addition to the methods described in Section 15.1.3.1 above) whole genome sequencing. (Note that this experimental initiative is discovery-directed and will not be utilized for patient care decisions, nor will results for sequence analysis be provided to the research subject or enrolling institution.)
c. Sequencing data will be stored on HIPAA-compliant database in the Skapek and/or Parsons laboratories and at the COG Statistics and Data Center; the data will be correlated with relevant clinical and pathological features in each case.

15.2 Microvessel Density and Circulating Tumor DNA as Predictors of Tumor Response and Outcome (Optional)

15.2.1 Kit Ordering, Sample Collection and Processing

Kits for this study can be requested from the NRG Oncology Biospecimen Bank in San Francisco by email at NRGBB@ucsf.edu.

Kits will include instructions, specimen transmittal forms, supplies for FFPE, frozen tumor tissue and plasma processing. One shipping label will be included for batch shipping frozen specimens on dry ice to Dr. Yoon at MSK. Kits are shipped to sites by Fed Ex Ground from the San Francisco bank and can take 4-6 business days to reach the sites.

The following material is requested from all consenting patients. There will be no banking of leftover material.

i) 2 unstained FFPE slides from tumor tissue obtained at diagnosis or pre-treatment.

The slides can be stored for up to 2 months at room temperature. Slides will not be returned to sites.

ii) Snap frozen tumor tissue from primary site obtained at the time of local control surgery (at Week 10 or Week 13).

At least one specimen from the primary at least 1 cm by 1 cm should be cut into 2-3 mm slices and wrapped in foil and snap frozen in liquid nitrogen or cold isopentane. Store snap frozen tissue at -80°C until shipment.

iii) A blood sample (10 mL) is requested at diagnosis/pre-treatment and at the time of local control surgery (at Week 10 or Week 13). Samples are to be processed as follows:

- Collect 10 mL of peripheral blood in purple top (EDTA) tubes. (Blood draw tubes will not be provided in the kits, sites are responsible for providing this).
- Centrifuge tubes at 820 g for 10 minutes.
- Transfer plasma into 15 mL conical tube.
- Store at -80°C.

Blood samples can be stored indefinitely frozen at -80°C and may be batched for shipping.

15.2.2 Sample Labeling and Shipping

Label all specimens with ARST1321, the patient's COG patient ID number, specimen type and collection date.

Include a specimen transmittal form with all sample shipments.

i) The slides can be batched and shipped by regular mail to arrive any day of the week.

ii) Snap frozen tumor tissue and blood plasma samples are to be shipped frozen on dry ice for overnight delivery to arrive Tuesday through Thursday only.

Please contact the lab prior to shipping.

Lab person to contact with questions:

Changhwan Yoon

Email: yoonc1@mskcc.org
Phone: (212) 639-7436

Shipping address:

Sam Yoon Laboratory
Zuckerman Building Z419-G
Memorial Sloan Kettering Cancer Center
408 East 69th Street,
New York NY 10065

15.2.3 Methodology

There are two components to this correlative study:

1) Microvessel Density Study: CD31 immunohistochemistry will be performed on pretreatment tumor tissue, and microvessel density (MVD) will be calculated as previously described.[28] Following combined modality therapy, tumors will be resected and the degree of pathologic necrosis will be determined by an expert sarcoma pathologist. Initial MVD will be correlated to percent tumor necrosis using Kendall's tau coefficients.

2) Plasma levels of circulating tumor DNA: DNA will be collected from plasma using the QIAamp MinElute virus vacuum kit. The amount of total DNA will be quantified by measuring levels of the human long interspersed nuclear element-1 (hLINE-1) retroposon family member by PCR. Determination of chromosomal translocations in frozen tissue from resected STS specimens will be performed. Measurement of ctDNA in plasma will be performed as previously described.[154,155] The levels of ctDNA will be correlated to the degree of pathologic necrosis in resected specimens.

15.3 Doxorubicin Pharmacokinetics in Combination with Pazopanib (Optional)

Accrual to this correlative study ended upon completion of accrual to the dose finding phase of the chemotherapy cohort.

Doxorubicin pharmacokinetics will be performed during the dose-finding phase of the study and in patients enrolled into the chemotherapy cohort only (ie, Regimen A). This is an optional study and patient consent is required.

PK studies will be analyzed in up to 10 patients (minimum of 3 patients < 18 years of age and 3 patients ≥ 18 years of age) non-randomly assigned to receive ifosfamide and doxorubicin with pazopanib at dose level 1. An additional 10 patients may be added for analysis depending on the decision to escalate or de-escalate the pazopanib dose.

Quantitation of doxorubinin and doxorubicinol concentrations will be performed. Using plasma samples, quantitative extraction is achieved by a simple solid phase extraction procedure after the addition of 0.1 M hydrochloric acid. Concentrations of doxorubicin and its metabolite doxorubicinol will be determined by UHPLC-MS/MS.[194]

15.3.1 Sample Collection and Processing

Blood samples will be obtained in Cycle 2 on Day 1-3 at the following 9 time

points related to doxorubicin dosing:

- time 0 (predose)
- 5 minutes after dosing
- 30 minutes after dosing
- 60 minutes after dosing
- 2 hours after dosing
- 4 hours after dosing
- 8 hours after dosing
- 24 ± 3 hours after dosing
- 48 ± 3hours after dosing.

Blood samples (3-5 mL) are to be drawn into tubes containing EDTA (purple top tubes) and immediately placed on ice. Within 30 minutes of collection, centrifuge for 5 min at 3000 g to yield plasma, divide into 2 aliquots and store frozen in polypropylene vials at or below -20°C until shipped.

Samples may be batched and shipped following collection of all 9 samples.

Note: It is strongly recommended the PK samples be collected from a site distant from the injection site. If possible, administer the doxorubicin through a central venous catheter and collect the PK samples from a peripheral i.v. inserted at a distant site. If a peripheral line is not possible, administration of drug and collection of the PK samples via central line may be done utilizing the flushing procedure as per individual institutional policy using normal saline to prevent sample contamination.

15.3.2 Sample Labeling and Shipping

Label all samples with "ARST1321"; patient ID#; date and time the sample was obtained.

Samples are to be shipped overnight frozen on dry ice on Monday - Wednesday for delivery on Tuesday through Thursday only. Include a copy of the PK Data Collection Form with each shipment.

Please contact the laboratory before shipping specimens:

Aksana Vasilyeva or Daelynn Buelow
Email: aksana.vasilyeva@stjude.org
Email: daelynn.buelow@stjude.org
Phone: (901) 595-4759 or (901) 595-5936
Fax: (901) 595-3125

Shipping address:

Sharyn Baker, PharmD, PhD, c/o Aksana Vasilyeva
St. Jude Children's Research Hospital
262 Danny Thomas Place
CCC Room 15503/15504, Mail Stop 313
Memphis, TN 38105-3678

16.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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

16.1 Goals of Diagnostic Imaging

Routine diagnostic imaging will be performed at diagnosis, during treatment and follow-up, and at the time of suspected tumor progression/recurrence to detect and characterize sites of disease involvement.

Central review of baseline and Week 10 (Non-chemotherapy cohort; treatment Regimens C and D) or Week 13 (Chemotherapy cohort; treatment Regimens A and B) imaging will be performed in all patients. This review has the following goals:

- To evaluate change in FDG PET maximum standard uptake value (SUV_{max}) from baseline to Week 10 (treatment Regimens C and D) or Week 13 (treatment Regimens A and B) in patients with unresected tumors and to correlate this change with pathologic response and EFS.
- To compare the rate of response by standard imaging and pathologic assessment to determine which correlates better with local tumor control, distant tumor control, EFS, and overall survival.

Central review of imaging studies also will be performed in patients who experience tumor progression or recurrence while on study and within 4 weeks of completing therapy. In patients who develop a recurrence or progression more than 4 weeks after completing therapy or a second malignant neoplasm imaging studies will be stored for future review. This review will document the pattern of treatment failure (study objective 1.3.5).

16.2 Timing of Diagnostic Imaging

16.2.1 Required Imaging Time Points

- Treatment Arms A and B
  - At study enrollment[#†]
  - At Week 13[†]
  - At end of protocol therapy
  - At the time of suspected tumor progression/recurrence[†]
  - At the time of diagnosis of a second malignant neoplasm[†]

- Treatment Arms C and D
  - At study enrollment[#†]
  - At Week 10[†]
  - At end of protocol therapy
  - At the time of suspected tumor progression/recurrence[†]
  - At the time of diagnosis of a second malignant neoplasm[†]

[#] Baseline imaging studies must be obtained within 4 weeks of study entry and before treatment starts.
[†] Central review of diagnostic imaging studies will only occur at these time points. (Note: in patients who experience tumor progression or recurrence while on study and within 4 weeks of completing therapy, central review of imaging studies will be performed. Imaging for suspected tumor progression/recurrence more than 4 weeks after completing therapy or a second malignant neoplasm should be submitted for future review). Imaging studies done at other time points do not need to be submitted for central review.

16.2.2 Recommended Imaging Time Points Post-Treatment

The following imaging time points are recommended for all patients:

- At 6, 12, 18, 24, 30, 36, 48, and 60 months from "end of therapy" date, defined as the last day of chemotherapy or radiotherapy, or the last date of protocol-required surgery, whichever is latest.

The choice of whether to perform a chest CT or Chest x-ray in follow up is left to institutional preference.

16.3 Required Imaging Studies

- Primary tumor – To be evaluated at the time points specified in Section 16.2.1 using:
  - CT imaging *or*
  - MR imaging.
    In order to standardize target volume definition using better tumor and soft tissue definition, an MRI of the primary site is highly preferred unless a patient has contraindications to MRI (eg, implanted pacemaker, neurostimulator, aneurysm clips, metallic foreign objects, or other contra-indications).
- Metastatic sites
  - CT or MR imaging of the draining lymph node bed for clear cell sarcoma and epithelioid sarcoma only. If a subtotal resection was done, the baseline study of the lymph node bed should be done after this operation. At study enrollment and at the time of suspected tumor progression/recurrence; repeat at each follow-up visit only if adenopathy identified on baseline study
  - Chest CT - At the time points specified in Section 16.2.1
  - Other imaging studies - Any imaging studies in patients other than the above that identify sites of disease that were not detected on other scans should be repeated at Week 10 (treatment arms C and D) or Week 13 (treatment arms A and B), at end of therapy, at the time of suspected tumor progression/recurrence, and at the time of diagnosis of a second malignant neoplasm.

Note: the same imaging modality should be used at each evaluation. If possible, patients should be imaged on the same scanner for the baseline and follow-up studies.

16.4 Recommendations for PET and Diffuse-Weighted MR Imaging Studies

[^{18}F]–Fluorodeoxyglucose Positron Emission Tomography (FDG PET) imaging is optional and requires consent but is encouraged. The primary lesion must be ≥ 1 cm on baseline anatomic imaging in order for a FDG PET scan to be performed. If done, FDG PET imaging should be performed at study enrollment and at Week 10 (Regimen C and D) or Week 13 (Regimen A and B) prior to definitive tumor resection. If insufficient FDG uptake

is seen at baseline, then the follow-up scan should not be performed. FDG PET imaging may also be helpful at the time of suspected tumor recurrence, particularly if a scan was performed at the time of study enrollment. Investigators are encouraged to submit FDG PET scans for central review to allow an assessment of the value of this modality in identifying areas involved by NRSTS and assessing tumor response to treatment.

Diffuse-weighted MR imaging (DWI) is encouraged. If performed, investigators are encouraged to submit DWI (at b-values of 0-50, 400, and 1000 s/mm^2) using spin-echo single shot EPI, parallel imaging factor of 2 slice thickness 5 mm) and ADC (apparent diffusion coefficient in μm^2/s) maps for central review to allow an assessment of the value of this MR sequence in identifying areas involved by NRSTS and assessing tumor response to treatment.

16.5 Central Review of Imaging Studies

For all patients enrolled, one to two central diagnostic imaging reviewers will independently assess the baseline tumor site, size (maximal tumor diameter and tumor volume), invasiveness [non-invasive, neurovascular invasion (touching), neurovascular invasion (surrounding), bone invasion (touching), bone invasion (destroying)], and depth (superficial or deep). Tumors that are located only in the skin or subcutaneous plane are defined as "superficial" and those involving tissues deep to the fascia or in internal organs are defined as "deep". Just prior to definitive surgery at Week 10 (treatment Regimens C and D) or Week 13 (treatment Regimens A and B), tumor dimensions will be re-obtained according to the guidelines in Section 16.7.

One to two central diagnostic imaging reviewers will independently assess the percent tumor necrosis on scans obtained at study enrollment and just prior to definitive surgery at Week 10 (treatment Regimens C and D) or Week 13 (treatment Regimens A and B). Necrosis will be defined as areas not showing contrast enhancement. If the tumor contains a fluid component whose margins are sharply defined, this will be interpreted as a cystic area and will not be included in the calculation of percent necrosis. Four (at 20%, 40%, 60%, and 80% of the distance between the most superior and the most inferior images in the z plane) axial images representing the entirety of the tumor will be selected, and the percent tumor necrosis in each image will be estimated. An "overall percent necrosis" will be estimated based on these 4 images, bearing in mind that a smaller cross-sectional area in the narrower portions of the tumor will contribute proportionally less to the overall percentage in the calculation.

The final calculated tumor dimensions and percent tumor necrosis at study enrollment and at Week 10 or Week 13 will be compared to the pathologic findings (see Section 14) to assess the degree of correlation between these two methods of measuring tumor response. The tumor response as assessed by central imaging review also will be evaluated to determine whether it predicts clinical outcomes such as local and distant disease control and survival.

Note: these reviews will be performed retrospectively and the results will not be returned to the institution.

16.6 Submission of Imaging Studies for Central Review

16.6.1 Requirements for Patients on Treatment Regimen A and B

Central review to assess baseline tumor characteristics and to assess tumor response by diagnostic imaging will be performed on all patients. Studies to be submitted for these patients include:

- Primary site MRI including diffusion-weighted sequences (if acquired) or CT scan (if the patient has a contraindication to MRI) obtained prior to study enrollment. If multiple imaging studies were obtained prior to protocol enrollment, the imaging study showing the largest tumor diameter *and* the study performed closest to the time of enrollment should be submitted. Baseline scans must be obtained within 4 weeks of study entry and before initiation of therapy.
- Primary site MRI including diffusion-weighted sequences (if acquired) or CT scan (if the patient has a contraindication to MRI) obtained at Week 13 prior to definitive tumor resection (required)
- Patients with metastases: All imaging studies that identified metastases at study enrollment and the same scans obtained at Week 13 (required)
- FDG PET scan obtained at study enrollment and at Week 13 prior to definitive tumor resection (optional)

The same imaging modality (CT or MRI) must be used at both study entry and Week 13 so that a valid comparison can be made at the time of central imaging review.

16.6.2 Requirements for Patients on Treatment Regimen C and D

Central review to assess baseline tumor characteristics and to assess tumor response by diagnostic imaging will be performed on all patients. Studies to be submitted for these patients include:

- Primary site MRI including diffusion-weighted sequences (if acquired) or CT scan (if the patient has a contraindication to MRI) obtained prior to study enrollment. If multiple imaging studies were obtained prior to protocol enrollment, the imaging study showing the largest tumor diameter *and* the study performed closest to the time of enrollment should be submitted. Baseline scans must be obtained within 4 weeks of study entry and before initiation of therapy.
- Primary site MRI including diffusion-weighted sequences (if acquired) or CT scan (if the patient has a contraindication to MRI) obtained at Week 10 prior to definitive tumor resection (required)
- Patients with metastases: All imaging studies that identified metastases at study enrollment and the same scans obtained at Week 10 (required)
- FDG PET scan obtained at study enrollment and at Week 10 prior to definitive tumor resection (optional)

The same imaging modality (CT or MRI) must be used at both study entry and Week 10 so that a valid comparison can be made at the time of central imaging review.

16.6.3 Radiotherapy Imaging Requirements

The same imaging studies may be required for both central radiology review and radiotherapy quality assurance review. If submitted with RT QA documentation it is not necessary to resubmit the same scan for the imaging central review. Please see Section 17 for details of radiation planning and required RT studies.

16.6.4 Requirements for Patients with Progressive/Recurrent Disease

Central review of imaging at the time of tumor progression/recurrence, if it occurs while on study and within 4 weeks of completing therapy, is required in all patients who experience this complication. In patients who develop a recurrence or progression more than 4 weeks after completing therapy imaging studies should be submitted and will be stored for future review. At the time of progression/recurrence, submit all of the studies listed below that have not been submitted previously to IROC Rhode Island (formerly QARC):

- Primary site MRI including diffusion-weighted sequences (if acquired) or CT scan (if the patient has a contraindication to MRI) obtained at study enrollment and prior to tumor resection.
- Primary site MRI including diffusion-weighted sequences (if acquired) or CT scan (if the patient has a contraindication to MRI) obtained at the time of tumor recurrence/progression
- All imaging studies that identified metastases at study enrollment and the same scans obtained at the time of tumor recurrence/progression
- All imaging studies that identified metastases at the time of tumor recurrence/progression and the same scans obtained at the time of study enrollment

16.6.5 Requirements for Patients Who Develop a Second Malignant Neoplasm

For patients who develop a second solid tumor, studies should be submitted and will be stored for future review. At the time that a second solid tumor develops, submit the following studies to IROC Rhode Island (formerly QARC):

- Primary site MRI including diffusion-weighted sequences (if acquired) or CT scan (if the patient has a contraindication to MRI) obtained at the time of diagnosis of the second malignant neoplasm
- If the site of the primary tumor is unclear, submit all scans that demonstrate the sites of disease involvement

16.6.6 Submission Guidelines

All imaging studies should be submitted at the time they are acquired along with a copy of the institutional radiologist's report. Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information for obtaining an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC Rhode Island (formerly QARC) at the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using Dicommunicator may submit imaging via that application. Contact IROC Rhode Island (formerly QARC) with questions or for additional information.

IROC Rhode Island QA Center
640 George Washington Highway, Building B, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

16.7 Diagnostic Imaging Guidelines

Note: the guidelines below are recommendations only and are not intended to replace institutional guidelines.

Assessment of the size and features of NRSTS requires cross-sectional imaging such as computed tomography (CT) and/or magnetic resonance (MR) imaging. The optimal imaging modality is selected based on the anatomic site of involvement, with the goal of evaluating the tumor volume and assessing tissue characteristics of the lesion [such as x-ray attenuation or density (CT) or signal intensity (MR)]. Images are acquired in 2 or more planes perpendicular to each other on MR imaging.

In general, MR imaging is superior in evaluating tumors located in the soft tissues of the trunk and extremities, and may also be useful in retroperitoneal and pelvic sites. CT imaging is preferred for evaluation of pulmonary nodules and may be helpful for intraabdominal and pelvic tumors. The same modality should be used at study enrollment and at each follow up visit to allow fair comparisons to be made. ^{18}F-FDG imaging is optional but is encouraged to allow an assessment of the value of this modality in identifying sites of disease and measuring tumor response.

16.7.1 CT Imaging

Breath-hold technique should be used in cooperative patients to reduce motion artifact and spatial misregistration from respiration. In patients incapable of immobilization, conscious sedation should be considered when clinically feasible to minimize image degradation from patient motion.

Use of Contrast Medium

Whether intravenous or enteral (oral and rectal) contrast medium is used is determined by the location and density of the lesion and the surrounding normal tissues. Vascular opacification helps to identify vascular encasement, displacement, and tumor margin. Tumor enhancement is absent in areas of necrosis or cystic degeneration before or after treatment. Enteral contrast helps to differentiate tumor from the surrounding opacified bowel. A dose of 2 mL/kg of ionic or non-ionic contrast is usually given intravenously. The amount of enteral contrast varies with patient's age and tolerance to oral (or nasogastric) or rectal administration.

Technical Guidelines

Technical parameters for CT scans should be chosen to achieve the best compromise between image quality, scan time, and patient radiation dose, and may vary based on the imaging equipment and expertise available at each institution. Image acquisition parameters include beam collimation, detector size configuration, table increment per detector rotation (pitch), gantry rotation time, reconstructed image thickness and spacing, contrast dose, contrast injection rate, image acquisition timing relative to contrast administration, and radiation exposure

factors (kVp and tube current). Image display parameters include field-of-view, window width and level, and hardcopy or softcopy format (eg, film or computer workstation monitors). Follow-up studies should be performed and interpreted with parameters as close as possible to the baseline study. For example, lesions should be measured at the same window width and level settings and reconstruction intervals.

The selection of optimal slice thickness is influenced by the patient's size. For single detector helical (SDCT) or conventional incremental CT, a slice thickness up to 7 - 10 mm is recommended for older children and adolescents, and a slice thickness as thin as 4 or 5 mm is recommended for infants and small children. The use of thinner sections to increase spatial resolution may be valuable in certain settings, such as the evaluation of questionable small lesions, but incurs the expense of increased radiation dose and should be used judiciously. As a general guideline, radiation dose can be minimized and scan coverage maximized with helical/spiral CT by increasing pitch. For SDCT, pitch values in the range of 1.4 - 2.0 are usually optimal, with degradation of longitudinal axis resolution limiting the use of higher values. For MDCT, a more complex relationship between pitch and radiation dose exists and the optimal value will vary with the type of scanner. Reconstruction intervals generally should be set to equal the slice thickness, although overlapping reconstructions with small interscan spacing may be used to increase lesion conspicuity in selected circumstances, such as in the evaluation of small lesions that would otherwise be obscured by volume averaging. The gantry rotation time of scanners can vary, and the more rapid rotation times should be chosen in pediatric patients to reduce scan time and motion artifact. Most pediatric body CT is performed with tube voltage in the range of 100-120 kVp. The use of dual-source and dual-energy CT are allowed and decrease in kVp to 70-100 is encouraged. To keep radiation dose as low as reasonably achievable, the tube current (mA) and gantry rotation time should be set as low as possible while maintaining lesion conspicuity for diagnostic quality images. In general, the smaller and younger the patient, the lower the mAs should be set. The specific settings should be decided for the encountered range of patient sizes and ages at each institution based upon experience with the available CT scanning equipment and published recommendations.

16.7.2 MR Imaging

MR imaging allows a better evaluation of soft tissues than CT imaging by identifying differences in T1, T2, and proton density between normal tissues and tumor tissue. The signal amplitude detected is also affected by the presence of motion (such as flow), system noise, and pulse sequence used. The most commonly used pulse sequences in clinical MRI imaging include T1- and T2-weighted, and fat-suppressed short-tau inversion recovery (STIR) pulse sequences. Fat-suppressed T1-weighted pulse sequence is used in cases where the tumor is surrounded by fat (such as in subcutaneous tissues). The cellularity of a tumor, which may vary with the type of tumor and change in response to therapy, can be studied with diffusion-weighted imaging (optional).

Breathhold techniques can be used for patients who are old enough to cooperate and this technique can reduce the scan time. In patients incapable of immobilization, conscious sedation should be considered when clinically feasible

to minimize image degradation from patient motion. Initial and follow-up studies should use the same pulse sequences, scanning plane, and IV contrast.

Use of Contrast Medium

The use of intravenous contrast agent (0.1 mmol/kg body weight gadolinium-DTPA) may or may not enhance the differentiation of tumor from the surrounding normal tissues. However, IV contrast is required for MRI scans of the primary tumor obtained at study enrollment and at Week 10 (treatment arms C and D) or Week 13 (treatment arms A and B). IV contrast is required in these settings to enable an accurate assessment of tumor necrosis (and therefore tumor response) during central imaging review. In this study, necrosis is defined as the absence of contrast enhancement.

Measurement of Tumor Volume

For assessment of tumor volume, the 2 largest perpendicular diameters are obtained from the image that shows the largest tumor cross-section in an optimal plane. Since multiple planes are possible in MRI imaging, the third diameter is obtained by calculating the distance between the first and the last slices that show the tumor in the same optimal plane used to obtain the first 2 diameters. See Section 10.2.1.

16.7.3 [^{18}F]–Fluorodeoxyglucose Positron Emission Tomography (FDG PET) Imaging

FDG PET imaging is optional, but is encouraged for all patients. If done, FDG PET imaging should be performed prior to initiation of chemotherapy and at Week 10 (treatment Regimens C and D) or at study enrollment and Week 13 (treatment Regimens A and B) prior to tumor resection. Exceptional circumstances may require emergent therapy, and treatment should not be delayed in these cases to perform an FDG PET scan.

Patient Guidelines

The patient should fast for at least 4 hours prior to injection of FDG. FDG PET imaging may follow a MUGA study on the same day, or FDG PET imaging may be performed on the day preceding this study. Plasma glucose should be checked and, if the patient is hyperglycemic (plasma glucose > 250 mg/dL), appropriate treatment with small doses of insulin may be given to bring the plasma glucose into the normal range prior to FDG PET imaging. However, insulin administration may result in excessive muscle uptake of FDG and consequent tumor non-visualization. If possible, the study should be postponed until the plasma glucose is under better control.

Good hydration is required, as the primary route of FDG excretion is renal. The patient should drink water or receive intravenous fluids (not containing dextrose) after FDG injection to promote urinary excretion of the radioactive substrate. After injection, the patient must be kept in a resting state for 45-60 minutes prior to imaging. The patient should empty the bladder immediately prior to imaging.

Imaging Technique

The technique will vary by local institutional guidelines. In general, FDG is administered intravenously at a dose of 0.125-0.200 mCi/kg or by algorithms that adjust the dose by body surface area, within a minimum total dose of 1.0 mCi and maximum total dose of 20.0 mCi. The dose should not exceed 20.0 mCi.

The body should be imaged from the top of the ears to the bottom of the feet. If there is suspicion of involvement of the skull or skull contents, the volume that is imaged should be expanded.

Imaging with a dedicated positron emission tomograph/computed tomography (PET/CT) camera is standard.

The length of time needed to perform head to toe CT will depend on the patient's height but will be approximately 45 seconds. Contiguous axial images should be obtained at 5 mm thickness using 90 mA and 120 Kv and adjusted for local institutional protocol. No oral or IV contrast is required but either or both are permissible and may be of benefit in cases where intraabdominal or pelvic pathology is a specific concern. With regard to patient positioning, the arms can be placed in a comfortable position at the patient's sides as long as they fit into the field of view. If the patient is large it may be necessary to lay the arms across the abdomen and hold in position with a stabilizing device.

FDG-PET done in combination with MRI is also an option (PET/MRI). For an individual patient, it is highly recommended that the same technology (either PET/CT or PET/MRI) be used for protocol studies.

Study Processing

The FDG PET study is processed for display by an iterative reconstruction algorithm. FDG activity should be corrected for attenuation, scatter, and radioactive decay. Attenuation correction is necessary, as apparent uptake will otherwise vary with depth of the lesion in the body and the nature of surrounding tissues. The procedure used for attenuation correction should be recorded. The level of tumor uptake is assessed subjectively by visual inspection and semi-quantitatively by determination of standardized uptake values (SUV). Uptake time, glucose levels, and partial volume effects influence both methods. The SUV method is also dependent on body weight, and correction of SUV by normalizing for body surface area (BSA) reduces this dependency on body weight. SUVs should be calculated for lesions known to be 1.2 cm or larger in diameter. Smaller lesions may have underestimated SUVs due to partial volume averaging effects at typical scanner resolutions (0.6-1.2 cm).

To calculate the SUV, a region of interest (ROI) should be carefully drawn around as much of the area of elevated FDG uptake as can be done. The SUV should be calculated as SUV_{BSA} = ROI activity concentration (nCi/cc) x BSA / injected activity (nCi). SUV_{MAX} is obtained by determining the activity of the pixel with the highest FDG uptake.

The BSA is calculated from body mass (kg) and height (cm) using an appropriate algorithm. The SUV_{BSA} for each measured lesion should be recorded and the technique for assessing SUV_{BSA} should be consistent on follow-up studies.

16.8 Growth Plate Evaluation

If patients are found to have a closed tibial growth plate, no further radiographs will be required. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained at the end of therapy and in post treatment follow-up as necessary. Consideration should be given towards obtaining

bilateral AP radiographs of the tibial growth plate during follow-up, only in patients with open growth plates, since end of therapy x-rays may not reflect recovery after pazopanib is stopped. These could be done at 6 months or a year off therapy, and perhaps repeated annually until normalization or complete fusion of the growth plates. The baseline radiograph will be compared with each radiograph performed during follow-up.

17.0 RADIATION THERAPY GUIDELINES

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

Radiation therapy (RT) for pediatric patients on COG or NRG Oncology protocols can only be delivered at approved COG RT facilities or NRG Oncology RT facilities.

17.1 General Guidelines

17.1.1 The radiation therapy guidelines for this study were developed specifically for patients with newly diagnosed, localized non-rhabdomyosarcoma soft-tissue sarcoma (NRSTS) or patients with limited metastatic NRSTS for whom resection of the primary is planned. This protocol is a successor study to RTOG 0630 and ARST0332 but only includes patients with an unresected primary site in the truncal and extremity sites with the exception of embryonal liver sarcoma for whom the protocol treatment will only consist of preop chemotherapy +/- pazopanib (without radiation).

17.1.2 All primary NRSTS tumors must be deemed potentially resectable with limb-preserving approach in discussion with surgical oncologist (see Section 13). The goal of combined modality preoperative therapy is to make surgery feasible and improve the extent of resection.

17.1.3 All patients should be seen by a Radiation Oncologist at the time of study enrollment. The purpose of the consultation is to participate in risk classification and to review the adequacy of the initial diagnostic imaging studies that will be used for RT planning. **All treatment plans and supporting data for the primary site must be submitted to IROC Rhode Island (formerly QARC) for pre-treatment review and approval prior to the start of radiotherapy. See Section 17.10 for submission instructions.**

17.1.4 This study requires credentialing dependent on the treatment techniques and/or treatment modalities to be used. See Section 17.4.3 for an outline of credentialing requirements.

17.2 Treatment Overview

17.2.1 Chemotherapy Cohort

Patients eligible for the Chemotherapy Cohort will be randomized to neoadjuvant combined modality therapy with ifosfamide and doxorubicin (ID) and 45 Gy RT at 1.8 Gy per fraction starting at Week 4 plus or minus concurrent pazopanib. Definitive surgery will be done at Week 13, with postoperative completion of the assigned ID/pazopanib or ID regimen starting at Week 16. For patients with gross residual disease, a postoperative boost radiotherapy of 21.6 Gy at 1.8 Gy per fraction is required (cumulative dose 66.6 Gy). For patients with microscopic margins, postoperative boost radiotherapy to the tumor bed is highly recommended but optional based on the discretion of the treating physician. The recommended dose is 16.2 Gy at 1.8 Gy per fraction (cumulative dose 61.2 Gy). Equivalent boost with brachytherapy is allowed. Delay of the postoperative radiotherapy boost should be documented. Omission of the optional postoperative radiotherapy boost (positive microscopic margins) should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10). No boost is to be given for negative margins. Negative margin is defined as the microscopic absence of tumor on the inked margins following resection regardless of the proximity of tumor cells to the margin. Patients will receive postoperative chemotherapy plus or minus pazopanib based on the initial randomization. Patients randomized to the pazopanib regimen will resume pazopanib no sooner than 2 weeks after surgery. If postoperative RT boost is given, doxorubicin will be held during the postoperative RT. Ifosfamide plus or minus pazopanib will be given concurrently with the postoperative RT and continued thereafter with doxorubicin for a total of 3 cycles.

17.2.2 Non-Chemotherapy Cohort

Patients enrolled in the Non-Chemotherapy cohort will be randomized to preoperative 50 Gy RT at 2 Gy per fraction with and without pazopanib. Those patients randomized to receive pazopanib will begin concurrently with RT at Week 1. Preoperative radiation will be completed by the end of Week 5. Definitive surgery will be done at Week 10. For patients with gross residual disease, postoperative boost radiotherapy to a dose of 20 Gy at 2 Gy per fraction is required (cumulative dose 70 Gy). For patients with microscopic margins, postoperative boost radiotherapy to the tumor bed is highly recommended but optional based on the discretion of the treating physician. The recommended dose is 16 Gy at 2 Gy per fraction (cumulative dose 66 Gy). Equivalent boost with brachytherapy is allowed. Those patients randomized to receive pazopanib will resume the agent no sooner than 2 weeks after surgery; followed by radiation once wound has adequately healed (starting 3 weeks after surgery). Delay of the postoperative radiotherapy boost should be documented. Omission of the optional postoperative radiotherapy boost (positive microscopic margins) should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10). No boost is to be given for negative margins. Negative margin is defined as the microscopic absence of tumor on the inked margins following resection regardless of the proximity of tumor cells to the margin.

17.2.3 Patients with Metastatic Disease in Either Cohort

These patients will undergo surgical resection of metastases at the completion of therapy, with additional RT for incompletely resectable or unresectable lesions.

17.2.4 Special Considerations:

Hepatic primary tumors: *Patients with liver primaries will not receive pre-operative RT. Postoperative radiotherapy is optional at Week 16 for the chemotherapy cohort or Week 13 for the non-chemotherapy cohort.*

17.3 Timing of RT

17.3.1 Timing for RT to Primary Site:

17.3.1.1 Chemotherapy Cohort

Patients in the chemotherapy cohort will receive preoperative RT to the primary site starting at Week 4. Week 4 radiotherapy should be started at least 24 hours after completion of the Week 4 doxorubicin. Doxorubicin should be withheld at Weeks 7 and 10 during radiation therapy. If needed, Week 16 radiotherapy should be started at least 24 hours after completion of the Week 16 doxorubicin.

Postoperative boost radiotherapy for gross residual disease (required) or microscopic positive margins (optional) should begin at Week 16 (3 weeks after surgery). If there is inadequate wound healing at Week 16, postoperative RT can be delayed until Week 19. If wound complications preclude initiating postoperative RT by Week 19 (6 weeks from surgery), the rationale for the delay should be documented by the treating physician. If radiotherapy for microscopic positive margins is omitted the rationale for omission should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10).

17.3.1.1.1 Criteria to Start Radiation Therapy with Chemotherapy

Radiation should not begin until the ANC $\geq 500/\mu L$ and platelets $\geq 75{,}000/\mu L$ for patients in the Chemotherapy Cohort.

17.3.1.1.2 Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for any life threatening infection. However, radiation therapy interruption should be strongly considered for ANC $< 300/\mu L$ or platelets less than $20{,}000/\mu L$ until the counts have recovered above these levels. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. If any area has been previously treated (emergently), care should be taken not to exceed normal tissue tolerance levels.

17.3.1.2 Non-Chemotherapy Cohort

Patients in the nonchemotherapy cohort will receive preoperative RT starting at Week 1. Resection takes place during Week 10.

Postoperative boost radiotherapy for gross residual disease (required) or microscopic positive margins (optional) should begin at Week 13 (3 weeks after surgery). If there is inadequate wound healing at Week 13,

postoperative RT can be delayed until Week 16. If wound complications preclude initiating postoperative RT by Week 16 (6 weeks from surgery), the rationale for the delay should be documented by the treating physician. If radiotherapy for microscopic positive margins is omitted the rationale for omission should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10).

17.3.2 Metastatic Sites:

For patients in the high risk group with metastatic sites of disease, radiation therapy will be delivered at the completion of all planned therapy and following surgical removal of resectable metastases.

17.3.3 Emergency Radiation Therapy

In the case of a neurologic compromise, uncontrolled tumor bleeding or life or function-threatening situations, RT may be administered early.

17.4 Radiation Treatment Planning and Delivery Techniques

17.4.1 Simulation Including Patient Positioning and Immobilization

17.4.1.1 Patient Positioning

Patients should be immobilized in stable and comfortable positions to allow accurate repositioning from treatment to treatment and to prevent movement during treatments. A variety of immobilization devices may be utilized, including Alpha Cradle and thermoplastic casts. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches. Positioning of the involved extremity to avoid variations in soft tissue distortion from day to day positioning is recommended. The contralateral limb should be positioned to avoid interference with optimal beam angles for the treatment limb. Whenever possible, skin folds should be minimized.

17.4.1.2 Special Considerations for Immobilization and Simulation.

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily radiation therapy treatments.

17.4.2 Equipment Allowed and Methods of RT Delivery/Verification

Radiation therapy using photons, electrons or protons, 3D-conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) will be allowed in this study. Use of both LDR and HDR brachytherapy is allowed for boost treatment (see Section 17.6.1 for dose prescription). Intraoperative radiation therapy is allowed (see Section 17.6.1 for dose prescription).

IMRT or protons may be used in the thoracic region or for treatment of tumors affected by respiratory motion when the degree of motion can be limited to 0.5 cm using breath hold or abdominal compression techniques. Use of IMRT in conjunction with gating or tracking techniques requires credentialing by the IROC Houston QA Center (RPC), see Section 17.4.3 below. The Motion Management

Reporting Form shall be submitted with the Quality Assurance Documentation materials whenever motion management techniques are used (see Section 17.10).

Equipment	Photons (4-15MV)**	Electrons (4-20 MeV)	IMRT (4-10MV)	Protons	Brachytherapy*
Linear Accelerator	X	X	X		
Proton Beam				X	
Intraoperative Radiation Therapy* **	X	X			
Brachytherapy - high or low dose rate					X

* Permanent radioactive implants are *not allowed* on this protocol. The dose prescription for brachytherapy is given in Section 17.6.1.
** For tumors adjacent or included in lung tissue, beam energy should be < 10 MV.
*** The dose prescription for intraoperative radiation therapy is given in Section 17.6.1.

17.4.3 Credentialing Requirements

- All therapy units used on this protocol must have their calibrations verified by the IROC Houston QA Center (RPC). The table above indicates allowable modes of treatment delivery.
- IMRT: Those treating with IMRT and not previously credentialed for its use in clinical trials must update their Facility Questionnaire on the IROC Houston website and complete either the IMRT Benchmark (available at www.QARC.org) or IROC Houston's head and neck phantom. Contact IROC Houston (http://rpc.mdanderson.org/rpc/) for information about their phantoms.
- Proton Therapy: The Proton Questionnaire (available at http://rpc.mdanderson.org/rpc/) must be completed. Each beam line used to treat patients on this study must be credentialed for clinical trial use by IROC Houston.
- Motion Management: If patients are treated with IMRT and gating or tracking methods are used to compensate for respiratory motion, IROC Houston's Thorax-Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion.
- IGRT: Standard PTV margins for this protocol are 1.0 cm. Reducing this margin to as little as 0.5 cm is possible with use of IGRT provided that IGRT credentialing has been completed. Prior credentialing for RTOG 0630 or other IGRT credentialing for soft tissue will be accepted. See www.QARC.org under "Benchmarks" for instructions on IGRT credentialing. Use of IGRT is not required if PTV margins of 1.0 cm are to be used.

17.4.4 Guidelines and Requirements for the Use of IMRT

Investigators using IMRT will be required to comply with the guidelines developed for the use of IMRT in National Cancer Institute sponsored cooperative group trials. These guidelines are available through www.qarc.org. These guidelines

require that the protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

17.4.5 Guidelines and Requirements for the Use of Proton Beam Therapy

Investigators using proton beam therapy will be required to comply with current guidelines for the use of protons in National Cancer Institute sponsored cooperative group trials. These guidelines shall be available through www.qarc.org. These guidelines specify the following for the participating institution: dose reporting will be in Cobalt Gy equivalent (1 CGE = 1 proton Gy * 1.1) which is the same as ICRU 78 DRBE; radiation doses shall be prescribed to protocol specified definitions for gross (GTV) and clinical (CTV). For set-up uncertainties and target motion, additional margin, smearing, range of modulation will be added on a per beam basis. The proton institution is required to participate in on-site and remote review according to COG requirements.

17.4.6 Guidelines and Requirements for the Use of Brachytherapy or Intraoperative Irradiation

Brachytherapy or intraoperative radiation therapy may be used for conformal irradiation of residual disease in the operative bed.

Brachytherapy, using either high dose rate or low dose rate radioactive sources may be used on this protocol as a boost to the positive tumor margin. Brachytherapy should not start until Day 5 after the surgery. Typically, brachytherapy catheters are placed at an interval of 0.5 -1.0 cm on the residual tumor bed (positive margin) plus a margin of 1 cm during surgery. Skin surface dose should be kept below 50% of the prescription dose unless positive margins occur in cutaneous or subcutaneous tissues. It is not necessary to include the entire surgical bed, drain sites and wound. The details of the dose prescription for brachytherapy are given in Section 17.6.1.

Intraoperative radiation therapy may be used on this protocol. The details for the prescription for intraoperative radiation therapy are given in Section 17.6.1.

17.4.7 Image Guidance Procedures (IGRT)

IGRT is defined in this protocol as use of computer-assisted systems that provide detailed information on shifts of the patient support system based on image registration software. The institution's procedure to register treatment day imaging datasets with a reference dataset should comply with the following recommendations:

Imaging must be done each day if using reduced margins with IGRT. MV, KV and CBCT are all acceptable forms of daily image guidance. Sites treating young children should contact a Radiation Oncology member of the study committee if daily imaging cannot be performed.

Region-of-Interest (ROI) or "clip box" for image registration should be set to encompass the high dose PTV and adjacent bony anatomy; If the image

registration software allows the user to create an irregular ROI (eg, ExacTrac), treatment room objects (eg, patient support system structure) seen on in room X-rays should be excluded from the registration; Both manual (eg, based on bony anatomy) and automatic (eg, based on mutual information) types of registration can be used; the result of the image registration must be visually checked for the alignment of the bony anatomy.

Institutions are encouraged to include closest joints in the imaging process in order to increase the information used in the image registration process for long bone image registration.

The daily pretreatment images for each case should be archived at each treating institution and should be available for central review by NRG Oncology/COG upon request.

17.4.7.1 Management of Radiation Dose to the Patient from IGRT

The estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scan on a Tomotherapy unit were estimated to be in range from 1 to 3 cGy, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT vary from 1 cGy to 10 cGy depending on the field size. Thus, the doses for 3D imaging systems are in the range from 1 to 10 cGy for sarcoma imaging and can contribute from 0.5 to 5% to the daily dose of 2.0 Gy. As a technique of controlling patient dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. The QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging by ensuring that the registration software functions properly when a shift in patient position is carried out.

17.5 Radiation Treatment Targets

17.5.1 CT (Volumetric)-Based Planning

CT (volumetric)-based planning is required to optimize dose to the PTV while protecting normal tissues. Organs within the irradiated volume should be contoured including those required by treatment site (see Section 17.8.2). A dose volume histogram (DVH) is necessary to determine target coverage and evaluate dose to normal tissues.

17.5.2 MRI of the Affected Site

MRI of the affected site is required unless a patient has contraindications for an MRI. When possible, direct fusion of the MRI with CT planning is recommended but is optional. For the best registration, MRI obtained in similar orientation as the planning CT is preferred. For example, for upper extremity lesions, same supination/pronation is preferable.

17.5.3 Standard Tumor and Target Volume Definitions

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62 and 78 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study. Treatment planning will be based on the following definitions:

Photons

Gross tumor volume (GTV) is the volume occupied at diagnosis by visible or palpable disease.

Clinical target volume (CTV) includes the GTV and sites with potential occult tumor involvement including lymph nodes adjacent to the GTV that may be clinically involved.

Planning target volume (PTV) is the CTV surrounded by a geometric margin to account for variability in set-up, breathing or motion during treatment.

Protons

GTV is the same for protons and photons.

CTV is the same for protons and photons.

The planning target volume (PTV) for proton therapy will include a margin which is added to the CTV in 3-dimensions. The margin should be consistent with the motion control and setup accuracy for the particular type of treatment (scattered versus scanning) at the treating proton center.

When proton therapy is used, the PTV will be used for dose reporting and not specifically for treatment planning. The goal of treatment planning will be CTV coverage at 100% directly with specific measures taken for each specific uncertainty.

The PTV will vary with each individual field and will require additional adjustment including (1) the lateral margins, (2) smearing of compensator, (3) range of beam (depth of penetration) and, (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 2-7 mm) will be based on the range uncertainty, CT number uncertainty, internal motion, and set up error determined for the particular body site at the individual proton institution. The following parameters must be explicitly reported for each beam: range, modulation, smearing radius of the compensator, set-up margin (SM) and PTV margin. The specifics of dose reporting for the proton PTV and recommendations regarding the PTV margin are discussed in Section 17.6.3. As stated above in Section 17.4.3 describing credentialing requirements, the use of IGRT with protons will allow a reduction of the setup margin from 1.0 cm to as low as 0.5 cm.

Brachytherapy

GTV is the same as for photons.

CTV is the same as for photons.

PTV is equal to *CTV*

17.5.4 GTV Definitions:

GTV
The GTV is defined as the visible and/or palpable disease defined by physical examination, computed tomography (CT), magnetic resonance imaging (MRI, usually the T1 post gadolinium sequence, highly preferred) or operative notes and pathology reports. The GTV must include all infiltrative disease detected at initial presentation. However, contouring GTV must respect anatomic boundary of tumor extension. Examples include truncal tumors which compress but not invade the lung, intestine or bladder that radiographically return to normal anatomic position following neoadjuvant chemotherapy plus/minus pazopanib.

GTV boost postoperative radiation (external beam or brachytherapy [low-dose-rate or high-dose-rate], or intraoperative radiation therapy) is required for gross residual tumor and highly recommended but optional for microscopic positive margin based on the discretion of the treating physician. Metallic clips or gold seeds are recommended to be placed during surgery to aid in defining the high-risk tumor bed (a positive margin or residual tumor). The GTV boost for postoperative RT will be the residual tumor bed and any residual gross tumor as defined by the surgical and pathological findings. If there is gross residual tumor, postoperative MRI is encouraged to visualize the residual tumor. It should be noted that the entire surgical bed, drain site, and wound are not required to be in the GTVboost for postoperative radiation because the patients will have received preoperative RT.

17.5.5 CTV Definition: CTV is Defined Based on Skeletal Maturity.

17.5.5.1 For > 18 year old Skeletally Mature Patients: Based on RTOG 0630

CTV for Intermediate-to-High Grade Tumors ≥ 5 cm: Include gross tumor and clinical microscopic extension. CTV = GTV plus a 3 cm longitudinal margin. Using MRI (preferably with image fusion), the CTV will also include suspicious peritumoral edema as defined on T2 weighted MR sequences beyond the T1 post-gadolinium gross tumor. If this causes the field to extend beyond the involved anatomic compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1.5 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

CTV for All Other Tumors (intermediate to high grade tumors < 5 cm): Include gross tumor and clinical microscopic extension. CTV = GTV plus at least a 2 cm longitudinal margin. Using MRI (preferably with image fusion), the CTV will also include suspicious peritumoral edema as defined on T2 weighted MR sequences beyond the T1 post-gadolinium gross tumor. The radial margin from the lesion should be 1 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

Special Considerations: Tumors located in subcutaneous tissues or in areas along the trunk and extremity where there are multiple potential high risk margins along different muscles/neurovascular bundles, the longitudinal margin should be expanded in all the planes that may be at high risk of spread. For example, CTV for subcutaneous sarcomas should include a minimum 1.5 cm (in patients ≤ 18) and 3 cm (in patients > 18 years old) of the subcutaneous space in all planes except radially; radially it should include the fascia but not the muscles deep to the fascia. (see Appendix XVI) CTV also includes regional lymph node chains found to be involved. A treating physician is encouraged to discuss these special considerations with radiation oncology chairs in this protocol.

17.5.5.2 For ≤ 18 year old Skeletally Immature Patients: Based on ARST0332

CTV
The CTV is defined as GTV + 1.5 cm (but not extending outside of the patient). Using MRI (preferably with image fusion), the CTV will also include suspicious peritumoral edema as defined on T2 weighted MR sequences beyond the T1 post-gadolinium gross tumor. CTV also includes regional lymph node chains that are known to harbor pathologically involved nodes. CTV is modified to account for specific anatomic barriers to tumor spread. Skin surfaces should not be contoured in CTV unless these are involved by gross tumor. If the incisional biopsy scar is small and will be resected at the time of surgery, it may not be contoured as CTV at the discretion of the treating radiation oncologist. Use of bolus on the skin surfaces is not encouraged when IMRT is used. A strip of normal tissue should be spared from high dose irradiation to avoid severe lymphedema if it is extremity sarcoma.

For all patients:

CTV boost for postoperative radiation if given (required for gross residual disease; optional for microscopic positive margins):

The CTV boost is defined as GTV boost (as defined in Section 17.5.4) plus a 1 cm margin.

PTV
The PTV is defined as CTV with an additional standard margin of 1.0 cm. Smaller margins can be used after the institution is credentialed for the use of IGRT. If some portion or all of the standard margin is reduced from 1.0 cm to a value that is no less than 0.5 cm, then daily image-guided radiotherapy (IGRT) will be required. In the absence of IGRT, the PTV margin must be 1.0 cm. The PTV margin does not need to be uniform in all dimensions, particularly if normal tissues are compromised. Beam specific PTV expansions may be required for proton planning, particularly in the axis of the beam. This treatment delivery technology can also take advantage of IGRT for margin reduction. Skin surfaces should not be contoured in PTV unless these are involved by gross tumor. If the incisional biopsy scar is small and will be resected at the time of surgery, it may not be contoured as CTV at the discretion of the treating radiation

oncologist. Use of bolus on the skin surfaces is not encouraged when IMRT is used. A strip of normal tissue should be spared from high dose irradiation to avoid severe lymphedema if it is extremity sarcoma.

17.5.6 Site-Specific Modifications

Nodal Radiation

For tumors with no evidence of nodal involvement (N_0), the draining regional lymph nodes should not be irradiated. When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain may be included in the CTV at the discretion of treating physician.

Metastatic Sites

Radiation is recommended to all metastatic sites when feasible at the completion of all protocol treatment. Feasibility diminishes as the number of metastatic sites increases and will be determined by the treating radiation oncologist. Surgical resection of metastases is encouraged prior to considering irradiation if it can be done with reasonably low or acceptable morbidity. Surgery and/or radiation should be used such that morbidity from treatment is minimized. Radiation therapy to a focal lung or liver metastases can be considered if surgery is not acceptable or possible.

Targeting of Metastases

The GTV for metastatic sites is the area of residual tumor defined on CT, PET, and/or MRI (post-chemotherapy/surgery). In cases where there is a discrepancy in volume between the scans, the larger volume will be irradiated. A CTV is not required for the treatment of metastatic lesions. The appropriate PTV should be the GTV with a geometric margin (approximately 1 cm at the discretion of treating physician).

17.6 Radiation Treatment Dose

17.6.1 Prescribed Dose and Fractionation

17.6.1.1 **Preoperative Radiation:**

In the non-chemotherapy cohort, the total preoperative dose to the primary tumor on the non-chemotherapy regimen will be 50 Gy (PTV) in 2 Gy fractions.

In the chemotherapy cohort, the total preoperative dose to the primary tumor will be 45 Gy (PTV) in 1.8 Gy fractions. This reflects a 10% reduction in radiation dose because of concurrent chemotherapy.

Table 17.6 **Prescribed RT doses and fractionation**

	Target Dose (Gy)	Dose per fraction (Gy)	Cumulative Dose (Gy)
Chemotherapy Regimen			
Preoperative RT	45	1.8	45
Postoperative RT			
Positive microscopic margins (optional)	16.2	1.8	61.2
Gross residual disease (required)	21.6	1.8	66.6
Non-Chemotherapy Regimen			
Preoperative RT	50	2	50
Postoperative RT			
Positive microscopic margins (optional)	16	2	66
Gross residual disease (required)	20	2	70
Metastases*			

* Metastases: Resection and/or irradiation is recommended at the discretion of the treating team. The radiation dose and fractionation for metastases will be at the discretion of treating physician.

17.6.1.2 **Postoperative Boost (if applicable)**

For patients with gross residual tumor after the resection, a boost is required. For patients with microscopic positive margin, postoperative radiation is controversial; it is highly recommended but optional. Delay of postoperative RT OR omission of postoperative RT for microscopic margin should be documented. Delay or omission documentation should be submitted with the RT QA materials (see Section 17.10). No boost is to be given for negative margins. Negative margin is defined as the microscopic absence of tumor on the inked margins following resection regardless of the proximity of tumor cells to the margin. Postoperative boost may be given with the following techniques:

17.6.1.2.1 **External Beam Radiotherapy**

In the Chemotherapy Cohort:

For gross residual disease (required) the boost dose is 21.6 Gy in 12 fractions for a cumulative dose of 66.6 Gy. For positive margins (optional), the recommended boost dose is 16.2 Gy in 9 fractions for a cumulative dose of 61.2 Gy.

In the Non-Chemotherapy Cohort:

For gross residual disease (required), the boost dose is 20 Gy in 10 fractions once a day for a cumulative dose of 70 Gy. For positive margins (optional), the boost dose is 16 Gy in 8 fractions once a day for a cumulative dose of 66 Gy

Postoperative external beam boost RT (required for gross residual and optional for microscopic positive margins) should begin 3 weeks following resection, if the healing of the surgical wound is satisfactory at

the discretion of the surgeon. If wound complications preclude initiating postoperative RT by 6 weeks from surgery, the reasons for a delay in boost treatment or omission of boost for microscopic margin should be documented and reported with the QA documentation (Section 17.10). Bolus should be avoided unless positive margins occur in cutaneous or subcutaneous tissues. Because preoperative radiation therapy has been delivered, it is not necessary to include the entire surgical bed, drain sites, and wound. Unless brachytherapy or intraoperative RT is to be used, postoperative RT should be consistent with the technique used for the patient's preoperative RT, ie, if image-guided 3D-CRT was used for preoperative RT, it should be used for postoperative RT; if image-guided IMRT was used for preoperative RT, it should be used for postoperative RT.

Brachytherapy

Either low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy as a boost to the positive tumor margin is acceptable as an alternative to external beam radiotherapy. Brachytherapy should not start until Day 5 after the surgery (Day 0) and must be completed within 2 weeks following surgery. Typically, brachytherapy catheters are placed at an interval of 0.5 -1.0 cm on the residual tumor bed (positive margin) plus a margin of 1 cm during surgery. Skin surface dose should be kept below 50% of the prescription dose unless positive margins occur in cutaneous or subcutaneous tissues. It is not necessary to include the entire surgical bed, drain sites and wound. For LDR brachytherapy, the dose is 16 Gy at no more than 80 cGy per hour. For HDR brachytherapy, 4 fractions of 3 to 3.4 Gy are delivered in a b.i.d. fashion, with an interval of at least 6 hours between fractions.

Intraoperative Radiotherapy Boost

Intraoperative radiation therapy (electron therapy or high-dose-rate interstitial brachytherapy) in a single fraction is allowed. For chemotherapy cohort, a dose of 7.5-10 Gy to microscopic margin and a dose of 12.5 Gy to macroscopic disease (gross residual disease). For non-chemotherapy cohort, a dose of 10-12.5 Gy to microscopic margin and a dose of 15 Gy to macroscopic disease (gross residual disease). **Note**: A frozen section diagnosis of positive margin must be obtained prior to intraoperative radiotherapy. Typically the dose is prescribed to 1 cm depth or 90% isodose line. However, prescription depth or isodose line coverage should be decided at the discretion of the treating radiation oncologist based on the consideration of boost target volume, surgical/pathological findings, and adjacent normal tissue structure tolerance.

17.6.2 Dose Definition

Photon dose is to be specified in Gray (Gy)-to-muscle. For proton beam, the absorbed dose is specified in Gy RBE, which is the same as ICRU 78 DRBE using a standard RBE of 1.10 with respect to Cobalt-60.

17.6.3 Dose Uniformity

At least 95% of the PTV/PTVBoost and 100% of the CTV/CTVBoost should be encompassed by 95% of the protocol-specified dose. No more than 10% of the PTV (PTVBoost for patients with a volume reduction) should receive greater than 110% of the protocol dose as evaluated by DVH. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

It is recognized that in some cases it may be difficult to achieve full coverage of the PTV. This may be the case, for example, in extremity sarcomas in young children where the PTV extends into the buildup region. Cases such as this will be considered per protocol if 95% of the protocol dose encompasses 100% of the CTV.

Proton Specific Guidelines: For protons, treatment planning does not specifically use a traditionally defined PTV for treatment planning. All uncertainties are taken into account explicitly to create a robust plan that provides full dose coverage of the CTV, generally from each beam – proton plans should be evaluated for adequate coverage provided by each individual beam and for PTV coverage from the summation of all beams. For passive scattering and uniform scanning, the aperture margin must include the appropriate beam penumbra for the selected beam energy, and setup and internal margins (SM and IM). These margins depend on the patient setup techniques used at the treating proton center. The aperture margin may be expanded further if a cold spot occurs near the edge of CTV due to insufficient lateral scatter. The smearing radius for the range compensator must be equal to the setup and internal margins (SM and IM). The beam range should be equal to the maximum water equivalent depth of the CTV plus a range margin. The main part of the range margin comes from uncertainty in CT accuracy and the conversion of the Hounsfield units to proton stopping power ratios. Most proton centers are expected to use 3.5% of the maximum water-equivalent depth of the CTV and then add another millimeter to account for uncertainties in beam range calibration and compensator fabrication. Additional range margin should be applied if internal motion could increase the water equivalent depth of the CTV. The modulation width should be increased consistently to ensure proximal coverage of the target volume. The beam range may be adjusted at the discretion of the treating radiation oncologist based on normal tissue dose concerns. A PTV should be created by a uniform expansion from CTV for reporting purposes. The expansion margin should be consistent with SM and IM and is typically 3 mm for a static target volume when daily imaging is performed. With the planning guidelines provided herein, no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. In most cases, at least 95% of the protocol-specified dose should encompass 100% of the PTV. A potential exception is when the range margin is smaller than the PTV expansion (eg, 3mm). As a result, the beam may not penetrate deep enough to sufficiently cover the distal portion of the PTV. This may occur for shallow target volumes where the maximum depth of the CTV is small and the range margin is small. This scenario is not expected for this protocol; however, such incomplete coverage of the PTV will not constitute a planning deviation because the plan should be sufficiently robust to cover the CTV with the protocol specified dose accounting for all uncertainties.

17.6.4 Tissue Heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. When treatment beams traverse lung, planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. When protons are used, correlation between the institutional CT treatment planning system Hounsfield Units and "relative proton stopping power" must be established and documented. Proton therapy should be used with extreme caution when any of the treatment beams traverse normal lung parenchyma. Please see explicit planning guidelines for this situation in Section 17.8.3.

17.7 Treatment Technique

17.7.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar), IMRT or proton therapy is required to minimize dose to normal tissues.

17.7.2 Selection of Proton Beam Arrangements

There are uncertainties (1-3 mm) in the distal range of the proton beam in which the RBE may be greater than 1.1; therefore, single proton beam plans which stop in a critical organ will not be allowed. Critical organs include, but are not limited to, spinal cord, trachea, and mainstem bronchus. Individual proton beams which are a component of a multi-field proton beam, which stop within such an organ, will be allowed.

17.7.3 Field Shaping

Field shaping for photons will be done with multileaf collimation. Use of customized cerrobend blocking is allowed when needed. Field shaping for protons will be done with either brass or cerrobend apertures or proton-specific multileaf collimation.

17.7.4 Motion Management and Margins to Account for Target Volume and Organ Motion

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the internal motion (IM) component of the PTV and is meant to account for potential motion of the CTV. If adequate clinical data do not exist to define the IM component of the PTV margin, the following suggestions are provided:

- For a CTV susceptible to physiologic motion, a margin of at least 0.5 cm should be added to the CTV prior to PTV margin expansion or a PTV margin of 1.0 cm should be chosen.
- For tumors of the thorax or abdomen, an assessment should be made to determine the extent of motion present. PTV margins should include this motion as a component.

- IMRT may be used for tumors of the thorax only if the degree of tumor motion is assessed and can be limited to 0.5 cm in any direction. IMRT can also be used in combination with gating or tracking when appropriate credentialing is performed for this type of treatment. Techniques for managing or suppressing tumor motion shall be applied as needed.

- Protons may be used for tumors of the thorax only if the degree of tumor motion is assessed and can be limited to 0.5 cm in any direction. Motion should be accounted for in an ITV. Motion of the target volume in three dimensions (cranial, caudal, anterior to posterior, and lateral) may be determined by 4-dimensional CT, respiratory gated CT, or other accepted techniques.

- A description of the method used and evidence (ie, observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4-D CT) of the remaining tumor motion should be submitted on the Motion Management Reporting Form with the Quality Assurance Documentation materials as noted in Section 17.10.

  NOTE: For patients treated with IMRT, use of gating or tracking methods to compensate for respiratory motion requires irradiation of IROC Houston's Thorax-Lung Phantom with accompanying reciprocating platform to simulate motion. Contact IROC Houston's (http://rpc.mdanderson.org/rpc/) for information about their phantoms.

17.7.5 Special Considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

17.8 Organs at Risk (OAR)

17.8.1 General Principles

Radiation dose to normal tissues should be kept within the accepted normal tissue tolerances when using standard 1.8 to 2 Gy fractionation schedules. All critical structures appropriate for each anatomic site must be contoured consistently and dose to normal structures should be strictly limited. Exceptions based on the site of the sarcoma should be documented to avoid a deviation.

Every effort should be made to avoid treating the full circumference of an extremity. No more than 50% of a longitudinal stripe of skin and subcutaneous tissue of an extremity should receive 20 Gy. This stripe of normal tissue is contoured at the discretion of treating radiation oncologist. Full prescription dose to skin over areas commonly traumatized (eg, the elbow, knee, shin) should be avoided. Efforts should be made to avoid treating anus, vulva and scrotum, lung, spinal cord, femoral head/neck.

If the tumor is close to the following structures, typically less than 50% volume of anus and vulva should receive 30 Gy, the testes should be kept to < 1 Gy and the ovaries to < 5 Gy, the V20 lungs should be <30%, and less than 5% of femoral head/neck should receive 60 Gy. Less than 50% of any joints (including shoulder, elbow and knee) should receive 50 Gy. Kidney dose > 20 Gy should be kept to < 30%.

For any other normal tissue structures, no radiation dose more than the established TD5/5 limit should be given. The above criteria must be met in the CT based plan.

No more than 50% of normal weight-bearing bone within the radiation field (contoured for full length covered by PTV plus 2 cm to both ends) should receive 50 Gy except when the tumor invades the bone or when there is circumferential involvement of the tumor more than a quarter of the bone or when the bone will be resected in a subsequent surgical resection after radiation with plans for plating/prosthetic/graft placement to strengthen the bone.

We recommend that skin surface (5 mm thickness) including scar from incision biopsy is not included in CTV or PTV and is not bolused for IMRT, unless (1) the biopsy scar is not subsequently resected after radiotherapy (resection of the biopsy scar is highly recommended) (2) the tumor is subcutaneous and within 5 mm of the skin; or (3) the tumor infiltrates or ulcerates through the skin based on clinical exam and/or imaging.

17.8.2 Organs at Risk (OAR) Dose Constraints

OAR and planning organ at risk volumes (PRV) and dose guidelines are cumulative dose limits. These limits are adapted from Quantitative Analyses of Normal Tissue Effects in the Clinic QUANTEC[195] and adjusted based on potential increased effect from concurrent therapy. OARs include additional structures specific to extremity sarcomas. Contouring of normal structures should be based on the atlas available on the RTOG web site. http://www.rtog.org/CoreLab/ContouringAtlases.aspx.

Primary Tumor Site	DVH required if structure is in path of or near any treatment beam	Required DVH Metric	Per Protocol Cumulative Dose	Variation Acceptable	Deviation Unacceptable	Toxicity Endpoint
Trunk/ Chest wall	Brachial Plexus	Max	63 Gy	<= 65 Gy	> 65 Gy	Brachial plexopathy
	Esophagus	Mean Max	<30 Gy < 70 Gy	<= 33 Gy <= 74 Gy	> 33 Gy	Esophagitis
	Heart	Mean V30	<26 Gy <40%	<= 30 Gy <= 50%	> 30 Gy > 50%	Pericarditis
	Lung	Mean V5 V20	7 Gy < 60% < 30%	<= 8 Gy <= 65% <= 35%	> 8 Gy > 65% > 35%	Symptomatic pneumonitis
	Spinal cord (if receiving any dose)	Max	45 Gy	<=48 Gy	> 48 Gy	Myelopathy
	PAR-cord (see Section 17.8.3)	Max	50 Gy	<=52 Gy	> 52 Gy	Myelopathy
Abdominal wall	Liver	Mean	<30 Gy	<= 33 Gy	> 33 Gy	RILD in normal function liver
	R & L Kidneys	Mean V20	< 14.4 Gy < 30%	<= 16 Gy <= 33%	> 16 Gy > 33%	Renal dysfunction
	Small bowel (peritoneal cavity)	V45	< 20% (or max volume 195 cc)	<= 30% (or max volume 205 cc)	> 30% (or max volume > 205 cc)	Grade 3+ toxicity
	Stomach	Max	<45 Gy	<= 47 Gy	> 47 Gy	Ulceration

Pelvis	Anus	V30 V50	<50% < 20%	<= 60% <= 25%	> 60% > 25%	Grade 3+ toxicity
	Bladder	V50 V70	<50% <20%	<= 60% <= 25%	> 60% > 25%	Grade 3+ toxicity
	Rectum	V50 V70	<50% <20%	<= 60% <= 25%	> 60% > 25%	Grade 3+ toxicity
	Vulva**	V30	< 50%	<= 60%	> 60%	Moist desquamation
	Testes (if fertility preservation desired)	V1	<50%	<= 60%	> 60%	Infertility
	Ovaries (if fertility preservation desired)	V5	<50%	<= 60%	>60%	Infertility
Paraspinal	Spinal Cord	Max	<45 Gy	<=48	>48	Myelopathy
	PAR-Cord (see Section 17.8.3)	Max	50 Gy	<= 52 Gy	>52 Gy	Myelopathy
Extremity	Femur within the field*	V50	<50%	<= 60%	>60%	Fracture
	Joints*	V50	<50%	<= 60%	>60%	Joint stiffness
	Total skin within field (5 mm thickness)**	V20	<50%	<= 60%	>60%	Wound healing/lymph-edema

* Exception allowed for tumor infiltrating the femur or joints.

** Exception allowed for primarily subcutaneous tumors or tumor infiltrating the skin for which the subcutaneous fat/skin lymphatics is the high risk margin.

17.8.3 Use of Proton Therapy in Treatment of Thoracic Tumors

During treatment of truncal tumors that may require beams to traverse normal lung tissue, proton therapy should be used with extreme caution. The following specific constraints will apply in this situation:

- When considering the total lung volume less the PTV:
  - The volume of lung receiving 20 Gy (V20) should be less than 30%
  - The volume of lung receiving 5 Gy (V5) should be less than 60%
  - The mean lung dose should be less than 7 Gy
- When considering the spinal cord:
  - The maximum dose should be 45 Gy
  - A structure called PAR-Cord should be created, and consist of the contoured spinal cord plus a 5 mm expansion. The maximum dose to the PAR-Cord structure should be 50 Gy.
- Additionally, the distal end of the Bragg peak of a single beam should not stop in a critical structure, such as the spinal cord, trachea, or mainstem bronchus due to uncertainty with regard to dose deposition at the distal end of the beam. Individual proton beams which are a component of a multi-field proton beam, which stop within such an organ, will be allowed.

17.9 Dose Calculation and Reporting

17.9.1 Prescribed Dose

The monitor units required to deliver the prescribed dose shall be calculated and submitted using the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The daily and total prescribed dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record.

17.9.2 Required Normal Tissue DVH Data According to Primary Tumor Site

The dose to the critical organs indicated in Section 17.8.2 should be calculated whenever any beam traverses the structure. The dose shall be reported on the RT-2 Radiotherapy Total Dose Record form and the appropriate dose-volume histograms shall be submitted. If IMRT is used, a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

17.10 Quality Assurance and Documentation

Primary Site: One week prior to the start of radiation therapy, detailed treatment data shall be submitted for pre-treatment review and approval.

Postoperative Boost (when done): Detailed treatment data shall be submitted at the end of treatment to the boost.

Metastatic Site(s): Data may be submitted at the end of treatment. Only the RT-2 form and a copy of the radiotherapy record (treatment chart) are required.

Digital Submission:
Submission of treatment plans as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either sFTP or CD. Instructions for data submission are on the IROC Rhode Island (formerly QARC) web site at www.qarc.org under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

Please submit the following for the Primary Site Target Volume (and postoperative boost, if applicable):

External beam Treatment Planning System

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.

- Digitally reconstructed radiographs (DRR) for each treatment field. DRR's are not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- All diagnostic imaging used to plan the target volume. Digital format is preferred. This includes CT or MRI PRIOR to attempted surgical resection of the primary tumor.
- Copies of reports (radiology, operative, pathology, cytology) and any other information used in defining the target volumes.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC Rhode Island (formerly QARC) and the radiation oncology reviewers.
- If modifications are made for patients with age < 24 months, documentation should be provided.
- Documentation of any emergency RT administered prior to the protocol prescribed course of RT. Documentation should be provided in the form of the radiotherapy record (treatment chart).
- Documentation of postoperative boost delay or omission of postoperative boost for positive margins.

Forms

- RT-1 Dosimetry Summary Form.
- Proton Reporting Form (if applicable).
- Motion Management Reporting Form (if applicable).

Submit the following items within 1 week following the completion of each treatment phase

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- RT-2 Radiotherapy Total Dose Record Form.

Please submit the following for Metastatic Sites

Forms

- RT-2 Radiotherapy Total Dose Record Form.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

Please submit the following additional information for brachytherapy, if used:

- Treatment planning CT used for post-implant dosimetry
- Computer printouts of the isodose distribution and associated CT-based calculations.
- Dose volume histograms for the GTV, CTV, and PTV.
- A completed Brachytherapy Physics Reporting Form.
- A copy of the written directive.

Please submit the following additional information for intra-operative radiation therapy, if used:

- Radiotherapy record (treatment chart) including prescription doses to all required areas and organs at risk
- Physician's note describing the procedure, dose calculation and description of the applicator along with any relevant dosimetric characteristics (ie, percent depth dose for the prescribed energy)
- Documentation of approval by a Radiation Oncology Study Committee Member.

These data should be forwarded to IROC Rhode Island (formerly QARC).

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
IROC Rhode Island QA Center
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865-4207
Tel: (401) 753-7600
Fax: (401) 753-7601
Email: physics@qarc.org

Definitions of Deviation in Protocol Performance

The Per Protocol definition of the dose prescription is given in Sections 17.6.1 and 17.6.3.

	Variation Acceptable	Deviation Unacceptable
Dose		
External beam	10% PTV receives > 110% of protocol dose but ≤ 115% *or* < 95% but ≥ 90% of the protocol dose covers 95% of PTV or 100% of CTV*	10% PTV receives > 115% of protocol dose *or* < 90% of the protocol dose covers 95% of PTV or 100% of CTV*
Brachytherapy	< 95% but ≥ 90% of the protocol dose covers 100% of CTV	< 90% of the protocol dose covers 100% of CTV
Volume	Margins for CTV/PTV less than specified or excessively large	A portion of the GTV or potentially tumor bearing area (CTV) is not included in the treated volume
Organs at Risk	Dose to any required OAR exceeds the goal stated in Section 17.8.2	Dose to any required OAR exceeds the variation acceptable limit in Section 17.8.2

* See Section 17.6.3 for handling targets near the skin surface.

17.11 Adverse Effects of Radiation and Management

17.11.1 Radiotherapy related treatment effects are both location- and time-dependent and clearly related to the dose delivered to specific organs or structures. Effects are divided into acute reactions, early delayed reactions and late reactions divided by arbitrary time periods indicated below.

17.11.2 Acute reactions (during radiotherapy): Fatigue, regional alopecia, skin erythema, desquamation, reduction in blood counts, cough, shortness of breath, nausea, diarrhea, swelling of the limb dependent on location of the tumor in the trunk or extremity.

17.11.3 Subacute reactions (6 weeks to 3 months after irradiation): Soft tissue edema, wound healing complications.

17.11.4 Late reactions (more than 3 months after irradiation): Fibrosis of soft tissues including muscle, injury to muscle or bone, including changes in bone growth, and changes in tissue vascularity, lymphedema, joint stiffness, bowel injury, osteoradionecrosis, bone fracture, and radiation associated second malignancy.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

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

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

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

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

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

CTSU REGISTRATION PROCEDURES

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the ARST1321 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the COG link to expand, then select trial protocol #ARST1321
  Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for ARST1321 Site Registration:

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

Submitting Regulatory Documents:

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

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

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

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

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

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

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

APPENDIX II: ANATOMIC SITE DEFINITIONS

The determination of the anatomic site of the primary tumor should be based on the location of the epicenter of the tumor as defined by muscle and/or bony landmarks. Tumors that arise in subcutaneous tissues should be considered to belong to the closest anatomic site.

Head and Neck Sites (NOT eligible for this study)

Head – Tumors arising in the facial and sub-mandibular structures, the mouth and pharynx, and in all sites superior to the skull base. This site is excluded in this study.

Neck – Tumors that arise above the level of the inferior aspect of cervical vertebra 7 and below the skull base, but not arising from the face, sub-mandibular structures, mouth, or pharynx. Tumors arising within the trapezius above the level of the clavicle are also included. Tumors within the paraspinal muscle complex in the neck should be classified as *paraspinal*. Tumors arising within the spinal canal should be categorized as *intraspinal*.

Body Wall Sites (Eligible for this Study)

Anterior chest wall – Tumors arising within intercostal muscles in proximity to the anterior ribs, and tumors arising superficial to the pectoralis muscles that do not involve the breast. This site is bordered superiorly by the top of the first rib and sternal notch, inferiorly by the cartilage and bone forming the rib cage, and laterally by the mid-axillary line. Tumors that arise within the pleural space and those with an associated pleural effusion should be classified as *intrathoracic*. Tumors arising within the pectoralis muscle and all axillary tumors except those originating in the intercostal muscles of the chest wall should be classified as *shoulder*. Tumors arising within the fibroglandular tissue of the breast should be classified as *breast*.

Breast - Tumors arising anterior to the pectoralis muscles and within the fibroglandular tissue of the breast. Tumors superficial to the pectoralis muscles that do not involve either the breast tissue or the pectoralis muscles themselves should be classified as *anterior chest wall*.

Posterior chest wall – Tumors arising within the intercostal muscles in proximity to the posterior ribs. This site is bordered superiorly by the top of the first rib, inferiorly by the 12th rib, and laterally by the mid-axillary line and includes only sites deep to the scapular musculature. Tumors arising within the musculature of the scapula should be categorized as *shoulder*. All axillary tumors except those originating in the intercostal muscles of the chest wall also should be classified as *shoulder*.
Note that tumors that arise within the pleural space and those with an associated pleural effusion should be classified as *intrathoracic*.

Paraspinal – Tumors located within the paraspinal muscle complex (transversospinalis muscle group and the erector spinae muscles) that arise superior to the upper aspect of the sacrum and outside of the spinal canal. The erector spinae muscles occupy the vertebrocostal groove of the back and lie just deep to the thoracolumbar fascia. This muscle group is composed of three longitudinally oriented groups of fasicles extending from a common tendinous origin from the sacrum to variable attachments on the ribs and spinous processes. The transversospinalis muscle group is deep to the erector spinae muscles and consists of the multifidus and rotatores muscles which extend obliquely upward two to four levels and one to two levels, respectively, from the transverse processes to the spinous processes of the vertebrae. Tumors arising within the musculature of the scapula should be categorized as *shoulder*. Tumors that arise within the pleural space and those with an associated pleural effusion or ascites should be classified as *intrathoracic* or *intraperitoneal*, as appropriate. Tumors with their epicenter at or below the upper aspect of the sacrum should be classified as *hip*. Tumors arising within the spinal canal should be categorized as *intraspinal*.

Intraspinal – Tumors with their epicenter within the spinal canal and between the skull base and the upper aspect of the sacrum. Tumors extending intraspinally but with their epicenter within the paraspinal muscle complex should be classified as *paraspinal*. Tumors with their epicenter at or below the upper aspect of the sacrum should be classified as *hip*.

Abdominal wall – Tumors within extraperitoneal soft tissues bordered superiorly by the cartilage and bone forming the rib cage, posteriorly by the lateral edge of the paraspinal muscle complex, and inferiorly by a line running anteriorly from the lateral margin of the paraspinal muscle complex along the iliac crests and the inguinal ligaments to the superior pubic rami. Tumors arising more inferiorly should be classified as *hip*. Tumors with their epicenter within the peritoneal space or that are associated with ascites should be classified as *intraperitoneal* or *pelvis*, as appropriate.

Visceral Sites (NOT eligible for this study))

Intrathoracic – Tumors with their epicenter in the area between the apical lung pleura/superior mediastinum and the diaphragms. All contents of the pleural space and mediastinum are included. Tumors of the diaphragms are included.

Intraperitoneal – Tumors with their epicenter within the peritoneal cavity between the dome of the diaphragms and a plane defined by the superior aspect of the iliac crests and the sacrum. Tumors of the diaphragms should be classified as *intrathoracic.* Intra-abdominal tumors with their epicenter inferior to the uppermost aspect of the iliac crests and sacrum should be classified as *pelvis*. Tumors arising in retroperitoneal structures (as defined below) should be classified as *retroperitoneal*. Retroperitoneal tumors that invade the peritoneal space as defined above should be classified as *intraperitoneal*.

Retroperitoneal – Tumors with their epicenter in the space bounded superiorly by the diaphragm, inferiorly by a plane defined by the superior aspect of the iliac crests and the sacrum, anteriorly by the posterior layer of the peritoneum, and posteriorly by the muscles of the back. This space includes the intra-abdominal aorta and inferior vena cava, psoas muscle, pancreas, kidneys, ureters, perirenal space, and adrenal glands. Tumors of the diapharagms should be classified as *intrathoracic.* Tumors with their epicenter inferior to the uppermost aspect of the iliac crests should be classified as *pelvis*. Tumors within the muscles of the back should be classified as *paraspinal* or *abdominal wall.* Note that retroperitoneal tumors that invade the peritoneal space should instead be classified as *intraperitoneal* or *pelvic*, as appropriate (tumors that invade the peritoneal space in both locations should be classified as *intraperitoneal*).

Pelvis – Tumors within the confines of the bony pelvis and internal to the sciatic notch with their epicenter below the plane defined by the superior aspect of the sacrum and iliac crests and extending inferiorly to the urogenital diaphragm. Tumors arising within muscles that course through the pelvis (iliopsoas complex, piriformis) are included if the epicenter falls within the anatomic confines noted above. Tumors arising in an extraperitoneal location in the anterior abdominal wall should be classified as *abdominal wall.* Tumors with their epicenter superior to the iliac crests should be classified as either *intraperitoneal* or *retroperitoneal.* Retroperitoneal tumors that invade the peritoneal space within the anatomic confines of the pelvis as defined above should be classified as *pelvis*. Tumors arising inferior to the urogenital diaphragm should be classified as *perineum* (tumors of the prostate should be classified as *pelvis*). Tumors arising external to the sciatic notch and those external to the bony pelvis should be classified as *hip*. Paratesticular sarcomas involving the scrotum or spermatic cord are not eligible for this study as postoperative radiotherapy may be preferable due to the difficulty of wound healing in this region with preoperative radiotherapy.

Perineum – Tumors with their epicenter in the space below the urogenital diaphragm bounded anteriorly by the pubic symphysis, laterally by the inferior pubic rami and ischial tuberosities, and posteriorly by the

coccyx. This space includes the urethra (in males, only the portion inferior to the prostate), levator ani muscles, ischiorectal fossa, and other periurethral and perianal structures. Tumors arising immediately outside of this space should be classified as either *pelvis* or *hip*, as appropriate.

Upper Extremity Sites (Eligible for this Study)

Shoulder – Tumors arising in or around the periscapular musculature (rhomboids, teres major/minor, supraspinatus, infraspinatus, subscapularis), deltoid, and pectoralis major/minor. This region also includes tumors arising in or around the following muscles above the insertion of the deltoid: biceps, triceps, corachobrachialis. All axillary sites except sites originating in the intercostal muscles of the chest wall are also included. Note that the superior boundary of the axilla is T1; sites above T1 should be considered to be *neck* sites. Tumors arising within the trapezius muscle are included if the epicenter is inferior to level of the clavicles (tumors of the trapezius muscle whose epicenter is superior to the level of the clavicles are included in the *neck* site).

Upper arm – Tumors that arise in or around the following muscles below the deltoid insertion: biceps, triceps, corachobrachialis, brachialis (including their insertion points about the elbow). Tumors arising in the elbow joint proper are classified in this group.

Lower arm – Tumors with their epicenter in or around the forearm musculature from the elbow to the level of the radiocarpal joints. Tumors arising in the elbow joint proper should be classified as *upper arm*. Tumors that arise in tendons that pass through the wrist into the hand are considered *hand* tumors when the epicenter is distal to the radiocarpal joint.

Hand – Tumors arising within or around the intrinsic muscles of the hand and tumors with their epicenter in the forearm tendons distal to the radiocarpal joint. Tumors arising around the carpus proper are classified in this group. Tumors of the fingers are included.

Lower Extremity Sites (Eligible for this Study)

Hip – Tumors arising external to the bony pelvis inferior to a line running from the upper aspect of the sacrum along the iliac crests and the inguinal ligaments to the superior pubic rami and external to the sciatic notch, above the level of the lesser trochanter of the femur. This site includes the neurovascular and related structures in the inguinal canal and muscles that originate, insert, or course through this anatomic region (gluteus maximus/medius/minimus, piriformis, superior/inferior gemelli, obturator internus/externus, iliopsoas, tensor fascia latae, adductor brevis/longus/magnus, gracilis, sartorius, quadriceps femoris, rectus femoris, biceps femoris, semimembranosus, and semitendinosus). Tumors arising in the perineal space or pelvis (as defined in this appendix) are excluded.

Thigh – Tumors arising within or around the following muscles (adductor brevis/longus/magnus, gracilis, sartorius, quadriceps femoris, rectus femoris, biceps femoris, semimembranosus, and semitendinosus) below the level of the lesser trochanter. Tumors arising from the knee joint proper are classified in this group.

Leg – Tumors arising within or around the gastrocnemius, soleus, popliteus, and plantaris muscles, and tumors arising at or above the malleoli in or around the following muscles: tibialis posterior, flexor digitorum longus, flexor hallucis longus, tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneus longus/brevis. Tumors arising from the ankle joint proper are classified in this group.

Foot – Tumors arising within or around the extensor digitorum brevis and the instrinsic muscles of the foot, and tumors arising in or around tendons of the following muscles below the malleoli: tibialis posterior, flexor digitorum longus, flexor hallucis longus, tibialis anterior, extensor digitorum longus, extensor hallucis longus, peroneus longus/brevis. Tumors of the toes are included.

APPENDIX III: THE FNCLCC SARCOMA GRADING SYSTEM[196,197]

Tumour differentiation • Score 1: Sarcomas closely resembling normal adult mesenchymal tissue and potentially difficult to distinguish from the counterpart benign tumor (eg, well-differentiated liposarcoma, well-differentiated leiomyosarcoma) • Score 2: Intermediate recognition known histologic type, myxoid (eg, myxoid liposarcoma, myxofibrosarcoma) • Score 3: Embryonal and undifferentiated sarcomas, synovial sarcomas, sarcomas of doubtful phenotype, synovial sarcomas
Mitotic count (established on 10 high-power field – HPF; a HPF measures 0.1734 mm^2) • Score 1: 0 to 9 mitoses per 10 HPF • Score 2: 10 to 19 mitoses per 10 HPF • Score 3: ≥ 20 mitoses per 10 HPF
Tumour necrosis • Score 0: no necrosis • Score 1: < 50% of tumour necrosis • Score 2: ≥ 50% of tumour necrosis
Histologic grade • Grade 1: total score 2, 3 • Grade 2: total score 4, 5 • Grade 3: total score 6, 7, 8

APPENDIX IV: WORLD HEALTH ORGANIZATION CLASSIFICATION OF SOFT TISSUE TUMOURS: INTERMEDIATE (RARELY METASTASIZING) AND MALIGNANT TUMOURS, 2013

Adapted from Fletcher CD, et al. World Health Organization Classification of Tumours, Pathology, and Genetics. Tumours of Soft Tissue and Bone. IARC Press, Lyon, 2013

Intermediate (Rarely Metastasizing)	Malignant
ADIPOCYTIC TUMORS	
Atypical lipomatous tumour / Well differentiated liposarcoma	
	Dedifferentiated liposarcoma
	Myxoid liposarcoma*
	Pleomorphic liposarcoma
	Liposarcoma, not otherwise specified
FIBROBLASTIC/MYOFIBROBLASTIC TUMORS	
	Adult fibrosarcoma
Solitary fibrous tumour	Malignant solitary fibrous tumour
Inflammatory myofibroblastic tumour	Myxofibrosarcoma
Dermatofibrosarcoma protuberans*	Low grade fibromyxoid sarcoma
Fibrosarcomatous dermatofibrosarcoma protuberans*	
Pigmented dermatofibrosarcoma protuberans*	
Low grade myofibroblastic sarcoma	Sclerosing epithelioid fibrosarcoma
Myxoinflammatory fibroblastic sarcoma	
Atypical myxoinflammatory fibroblastic tumour	
Infantile fibrosarcoma*	
SO-CALLED FIBROHISTIOCYTIC TUMORS	
Plexiform fibrohistiocytic tumour	
Giant cell tumour of soft tissues	
SMOOTH MUSCLE TUMORS	
	Leiomyosarcoma
PERICYTIC (PERIVASCULAR) TUMORS	
	Malignant glomus tumour
SKELETAL MUSCLE TUMORS	
	Embryonal rhabdomyosarcoma*
	Alveolar rhabdomyosarcoma*
	Pleomorphic rhabdomyosarcoma*
	Spindle cell/sclerosing rhabdomyosarcoma*
VASCULAR TUMORS	
Retiform hemangioendothelioma*	Epithelioid hemangioendothelioma*
Papillary intralymphatic angioendothelioma*	Angiosarcoma of soft tissue
Composite hemangioendothelioma*	
Pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma*	
Kaposi sarcoma*	

(con't)

Intermediate (Rarely Metastasizing)	Malignant
CHONDRO-OSSEOUS TUMORS	
	Mesenchymal chondrosarcoma
	Extraskeletal osteosarcoma
NERVE SHEATH TUMORS	
	Malignant peripheral nerve sheath tumor
	Epithelioid malignant peripheral nerve sheath tumour
	Malignant Triton tumour
	Malignant granular cell tumor
	Ectomesenchymoma*
TUMORS OF UNCERTAIN DIFFERENTIATION	
Atypical fibroxanthoma	
Angiomatoid fibrous histiocytoma	Synovial sarcoma
Ossifying fibromyxoid tumor	Malignant ossifying fibromyxoid tumour
	Epithelioid sarcoma
Mixed Tumour NOS	Malignant mixed tumour
Myoepithelioma	Myoepithelial carcinoma
Phosphaturic mesenchymal tumour	Malignant phosphaturic mesenchymal tumour
	Alveolar soft part sarcoma
	Clear cell sarcoma of soft tissue
	Extraskeletal myxoid chondrosarcoma
	Extraskeletal Ewing sarcoma*
	Desmoplastic small round cell tumor*
	Extra-renal rhabdoid tumor*
	Neoplasms with perivascular epithelioid cell differentiation (PEComa)
	Intimal sarcoma
VISCERAL TUMORS	
	Embryonal sarcoma (undifferentiated sarcoma) of the liver
UNDIFFERENTIATED SARCOMAS	
	Undifferentiated round cell sarcoma
	Undifferentiated pleomorphic sarcoma
	Undifferentiated epithelioid sarcoma
	Undifferentiated spindle cell sarcoma
	Undifferentiated sarcoma NOS

*These tumor types are NOT eligible for ARST1321, but may be eligible for other COG or NRG Oncology studies sponsored by the Soft Tissue Sarcoma, Bone Tumors, Renal Tumors, and Rare Tumors committees.

APPENDIX VA: 90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN GIRLS AGE 1-17 YEARS

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

APPENDIX VB: 90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN BOYS AGE 1-17 YEARS

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

APPENDIX VC: ORAL ANTIHYPERTENSIVE MEDICATIONS

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with pazopanib through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

APPENDIX VI: CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

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

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5]	atazanavir	aprepitant	barbiturates	bosentan
alfentanil[4,5]	boceprevir	conivaptan	carbamazepine	dabrafenib
amiodarone[4]	clarithromycin	crizotinib	enzalutamide	efavirenz
aprepitant/fosaprepitant	cobicistat	diltiazem	fosphenytoin	etravirine
atorvastatin	darunavir	dronedarone	phenobarbital	modafinil
axitinib	delavirdine	erythromycin	phenytoin	nafcillin
bortezomib	graperfruit[3]	fluconazole	primidone	rifapentin
bosutinib[5]	grapefruit juice[3]	fosamprenavir	rifampin	
budesonide[5]	idelalisib	grapefruit[3]	St. John's wort	
buspirone[5]	indinavir	grapefruit juice[3]		
cabozantinib	itraconazole	imatinib		
calcium channel blockers	ketoconazole	isavuconazole		
cisapride	lopinavir/ritonavir	mifepristone		
citalopram/escitalopram	nefazodone	nilotinib		
cobimetinib[5]	nelfinavir	verapamil		
conivaptan[5]	posaconazole			
copanlisib	ritonavir			
crizotinib	saquinavir			
cyclosporine[4]	telaprevir			
dabrafenib	telithromycin			
dapsone	voriconazole			
darifenacin[5]				
darunavir[5]				
dasatinib[5]				
dexamethasone[2]				
diazepam				
dihydroergotamine				
docetaxel				
doxorubicin				
dronedarone[5]				
eletriptan[5]				
eplerenone[5]				
ergotamine[4]				
erlotinib				
estrogens				
etoposide				
everolimus[5]				
fentanyl[4]				
gefitinib				
haloperidol				
ibrutinib[5]				
idelalisib				
imatinib				
indinavir[5]				
irinotecan				
isavuconazole[5]				
itraconazole				
ivacaftor				
ketoconazole				

lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2] Refer to Section 4.1.6 regarding use of corticosteroids.
[3] The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4] Narrow therapeutic range substrates
[5] Sensitive substrates (drugs that demonstrate an increase in AUC of ≥ 5-fold with strong inhibitors)

APPENDIX VII: MEDICATIONS ASSOCIATED WITH PROLONGED QTC

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

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

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

APPENDIX VIII: SUPPORTIVE CARE GUIDELINES

These supportive care guidelines are provided for institutional consideration but are not intended to supplant institutional practices. Investigator discretion should be used, and certain clinical situations and institutional guidelines may suggest other approaches. Investigators may wish to refer to Supportive Care of Children with Cancer, Arthur Ablin ed., 2004, for further recommendations.

Central Venous Access

Placement of a central venous catheter is recommended for patients receiving chemotherapy to facilitate simultaneous administration of doxorubicin and ifosfamide/mesna. Selected patients receiving radiotherapy also may be candidates for a central venous access device if daily intravenous sedation is required for radiotherapy.

Dental Evaluation

A baseline dental examination is recommended prior to initiation of chemotherapy and/or radiotherapy to document dental development at baseline and identify potential foci of infection. Significant caries or other problems that pose an infectious risk should be treated prior to initiation of antineoplastic therapy, if possible. All patients and their families should be educated about dental hygiene and mouth care during treatment.

Since chemotherapy is associated with abnormal dental development and a greater risk for tooth loss and decay, patients receiving chemotherapy (particularly young children) should be seen for regular follow-up to identify problems and reinforce dental hygiene. Regular post-treatment dental follow-up is important for patients receiving radiotherapy that involves the jaw, as these patients are at risk for abnormal dental development, severe caries, and oral infections.

Anti-Emetics

Routine use of anti-emetics is recommended for patients receiving chemotherapy and those receiving radiotherapy to a field that includes abdominal/pelvic contents. Due to the highly emetogenic nature of the chemotherapy regimen, a serotonin antagonist (eg, ondansetron, granisetron) may be considered for all patients receiving chemotherapy. Other medications may be helpful in combination with the seratonin antagonists. Dexamethasone may be warranted for patients who remain symptomatic despite combinations of other anti-emetics. Aprepitant interacts with CYP3A4 and may not be given during either ifosfamide or doxorubicin chemotherapy and should be avoided with the use of pazopanib.

Fever and Neutropenia

All patients should be evaluated promptly for fever of 38°C (oral) three times in a 24-hour period or a single temperature of 38.5°C. If the ANC is < 500/µL, appropriate cultures should be obtained to rule out an occult invasive bacterial or fungal infection and broad spectrum antibiotics should be administered.

Specific infections identified should be managed according to institutional guidelines. Even in the absence of an identified infection, broad spectrum antibiotics should be continued until the patient is afebrile for more than 24 hours and has an ANC > 200/µL. If fever without an obvious source persists for more than 5 days or recurs after defervescence while on broad-spectrum antibiotics, systemic antifungal coverage should be considered.

Mucositis

Mucositis following doxorubicin-containing chemotherapy is common, and may be exacerbated by herpes simplex infection. Pazopanib may result in mucositis as well. Consideration should be given to herpes simplex prophylaxis in patients with a history of herpetic stomatitis. Patients with significant mucositis during chemotherapy should have a viral culture of the oral lesions performed, and anti-viral therapy should

be started if herpes simplex virus is identified. Patients with documented herpes simplex infection during therapy should receive antiviral prophylaxis throughout the remainder of chemotherapy.

Oral swish-and-swallow glutamine suspension at a dose of 2 g/m² BID has been shown to reduce the severity and duration of mucositis associated with chemotherapy and radiotherapy in a randomized controlled clinical trial.[198] Sucralfate swish-and-swallow may reduce the symptoms or severity of chemotherapy- and radiotherapy-induced mucositis.[199] Sucralfate blocks the oral absorption of many medications. Pazopanib should be given at least 2 hours before or 4 hours after a dose of sucralfate.

Cardiotoxicity
Dexrazoxane is required for all doxorubicin-containing cycles. Dexrazoxane has been shown to provide short- and medium-term protection from cardiotoxicity induced by anthracyclines in children and adults with sarcomas.[200,201] Although recommended that dexrazoxane be considered in adults receiving more than 300 mg/m^2 doxorubicin-based therapy,[202] no such recommendations exist for pediatric patients. Due to the concern of added cardiac toxicity of pazopanib and doxorubicin, the use of dexrazoxane is required. To facilitate direct comparison of the randomization arms and to limit cardiotoxicity, all patients in the chemotherapy cohort will receive dexrazoxane for all doxorubicin-containing cycles. Hypertension may result with the use of pazopanib. Anti-hypertensive management is detailed in Section 5.6.

Blood Product Support
Indications
There are no standardized guidelines for blood product support, and decisions should be based on the patient's symptoms, examination findings, medical history, and the clinical setting.

Depending on the particular setting, red blood cell transfusions may be appropriate in the following situations:

- Hgb < 8 gm/dL and an expectation that a rise in Hgb is not imminent
- Symptoms of anemia present and Hgb < 10 g/dL
- Hgb < 10 gm/dL in a patient receiving radiotherapy (theoretical considerations suggest that radiotherapy may be more efficacious in patients with adequate tissue oxygenation)
- Acute blood loss estimated at > 10% of blood volume
- Hgb < 12 gm/dL in a patient with respiratory insufficiency not corrected by supplemental oxygen or ventilatory support

Platelet transfusions may be indicated in the following settings, depending on the particular situation:
Platelet count < 10,000/µL

- Active bleeding in a patient with a normal PT/PTT/fibrinogen and a platelet count < 50,000/µL or dysfunctional platelets
- Platelet count < 50,000/µL in a patient who requires a surgical procedure

Leukocyte Depletion
Leukocyte depleted blood products are recommended to decrease the likelihood of alloimmunization and prevent febrile, non-hemolytic transfusion reactions. Leukocyte depletion may be accomplished via leukocyte depletion filters or blood product washing.

Irradiation
All blood products should be irradiated as per institutional and national guidelines.

Platelet Products
Platelet apheresis products should be used, if available. If single-donor products are not available, random-donor pooled platelets are acceptable.

Growth Factor Administration
Administration of growth factor is required after all chemotherapy cycles except when doxorubicin is administered alone. Use of growth factor after doxorubicin alone is optional. Selection of growth factor is based on patient body weight and physician preference:

- Filgrastim (G-CSF): 5 mcg/kg subcutaneous daily (max 480 mcg) starting on the day after the last dose of chemotherapy until ANC > 2,000/μL after the nadir. Use of intravenous filgrastim is permitted, but discouraged. Filgrastim should not be administered within 24 hours of chemotherapy.
- Pegfilgrastim (Neulasta™): Patients ≤ 45 kg: 100 mcg/kg subcutaneous x 1 dose on the day after the last dose of chemotherapy.[203] Patients > 45 kg: 6 mg subcutaneous x 1 dose on the day after the last dose of chemotherapy. Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy.
- The use of exogenous erythropoietin (ie, epoetin, darbepoetin) is at the investigator's discretion.

Pneumocystis (carinii) jirovecii Prophylaxis
Consideration should be given for all patients receiving chemotherapy to receive prophylaxis against Pneumocystis (carinii) jirovecii infection. If used, treatment should begin with the initiation of chemotherapy and continue for 12 weeks after chemotherapy finishes. Co-trimoxazole [trimethoprim (TMP) and sulfamethoxazole (SMX)] 1:5 drug combination at 75 mg/m^2/dose of TMP twice daily on 3 consecutive days each week is recommended. An alternate form of prophylaxis also should be used for patients who experience excessive myelosuppression during chemotherapy administration, as TMP/SMX can enhance bone marrow suppression.

Patients who are allergic to or intolerant of TMP/SMX should receive an alternate form of prophylaxis:

- Dapsone 2 mg/kg daily (max 100 mg) OR
- Atovaquone
    - Patients 12 - 24 months old: 45 mg/kg once daily with food
    - Patients > 24 months old: 30 mg/kg once daily with food
    - Adolescents ≥ 13 years and adults: 1500 mg once daily with food

Pentamidine should be avoided due to the risk of QT prolongation and should only be used if the patient is intolerant to or has failed all other agents.

Nutritional Support
Adequate nutritional status is critical for wound healing and tolerance of therapy. Supplemental enteral or parenteral nutrition should be considered for patients who have lost 10% or more of body weight before or during therapy and for those who have persistent hypoalbuminemia (albumin < 3 g/dL). Parenteral support also should be considered for patients receiving abdominal and/or pelvic radiotherapy who experience significant gastrointestinal toxicity.

Issues for Postmenarchal Females
Postmenarchal females receiving chemotherapy are at risk for excessive menstrual bleeding. Thus, consideration should be given to suppressing menses with hormonal interventions in these patients. In addition, sexually active females should be counseled to avoid sexual intercourse during periods of neutropenia/thrombocytopenia. All postmenarchal females receiving chemotherapy or radiotherapy should be counseled about the risks of fetal exposure and the need for contraception.

Sperm Banking
Adolescent males receiving chemotherapy or radiotherapy to a field involving the testes should be provided with information regarding sperm banking prior to initiation of treatment.

Recommendations for Specific Anatomic Sites of Tumor
Chest Wall/Intrathoracic Sites
Baseline evaluations that may be useful, depending on the specific anatomic sites of tumor involvement, include:

- Echocardiogram with doppler and/or MUGA (multiple gated acquisition) scan
- Pulmonary function tests
- Upper airway endoscopy/bronchoscopy
- Barium esophagram
- Esophagoscopy

Abdominal/Retroperitoneal/Pelvic Sites
Depending on the particular anatomic sites of tumor involvement, the following evaluations may be useful:

- Endoscopic examination of the bowel
- Female pelvic examination
- Cystoscopy/vaginoscopy/proctoscopy with examination under anesthesia
- Ultrasound examination of the urinary or biliary tract to assess need for decompression

Oophoropexy to move the ovaries out of the radiotherapy field may be considered in female patients with pelvic tumors who will receive radiotherapy.

Extremity Sites
A baseline rehabilitation evaluation is recommended for identifying functional limitations and initiating rehabilitation.

Rash
Suggested products for the treatment of skin reactions for patients on pazopanib have been adapted from Bracarda et al.[204] and includes:

- Non foaming cleansing cream containing taurate and sarcosinate detergents
- Polydecene based highly emollient ointment
- Glycolic salicylic peeling cream
- Zinc oxide and magnesium silicate lenitive cream without vaseline
- Benzalkonium chloride 0.2% aqueous solution
- Cicatrizing PEG and allantoin ointment
- Potassium permanganate (tablet 250 mg)
    - To prepare, dissolve a 250 mg tablet in 2L of boiling water, cool and keep in a dark glass bottle
- Sulfosalicylic cream without vaseline

All products for external use compress ONLY

Hand-Foot Syndrome
Oral administration of vitamin B6 (pyridoxine) should be administered for patients on pazopanib who develop hand-foot syndrome:

- BSA < 0.5 m^2: 50 mg per day

- BSA 0.5-1.0 m^2: 100 mg per day
- BSA 1.1-1.5 m^2: 200 mg per day
- BSA > 1.5 m^2: 300 mg per day

APPENDIX IX: THERAPY DELIVERY MAPS FOR REGIMEN A

Regimen A: Neoadjuvant Chemotherapy and Radiotherapy with Pazopanib

<table>
<tr><th colspan="9">Regimen A</th></tr>
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<tr><td>I</td><td>I</td><td>I</td><td>I</td><td rowspan="4">Surgery</td><td>I</td><td>I</td><td></td><td></td></tr>
<tr><td>D</td><td>D</td><td></td><td></td><td>D</td><td>D</td><td>D</td><td></td></tr>
<tr><td colspan="4">Pazopanib Weeks 1-12</td><td colspan="4">Pazopanib Weeks 16-25</td></tr>
<tr><td></td><td colspan="3">Radiotherapy</td><td colspan="3">Radiotherapy</td><td></td><td></td></tr>
</table>

See Section 4.2 and Section 17 for complete details of protocol therapy.

The therapy delivery maps relating to Induction and Continuation therapy for patients on Regimen A are provided in the following 7 pages.

Regimen A Induction (Weeks 1-12): This therapy delivery map relates to Cycle 1 of therapy, Weeks 1-3 Induction consists of 12 weeks of therapy (84 days in total) made up of four 21-day cycles. This therapy delivery map presents Induction therapy on 4 pages.	_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/μL and platelet count ≥ 75,000/μL post nadir (without transfusion). If the ANC has risen to ≥ 750/μL after the nadir but then falls the next cycle should be given despite ANC < 750/μL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Dexrazoxane (DXRZ)	Slow IV push/infusion over 5-15 mins	375 mg/m^2/dose	1 and 2 of Week 1	Give immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.2.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose*	1 and 2 of Week 1	*75 mg/m^2/cycle. If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days. See Section 4.2.1 for details.
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Wk 1	See Section 4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Wk 1	Administer with IFOS, see Section 4.2.1
Pazopanib IND# 118613	PO	350 mg/m^2 (pediatric) 600 mg (adult)	1-7 of Wk 1-3	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII.
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of myelosuppressive chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/μL post nadir (continue without regard to pazopanib administration) and discontinue at least 24 hours prior to next cycle of chemotherapy.				

OBSERVATIONS

a. History, PE with VS, Ht, Wt, BSA
b. Blood pressure**
c. CBC, differential, platelets
d. Electrolytes, including Ca, Mg, PO_4
e. Creatinine, ALT, Total bilirubin
f. Amylase**, Lipase**, Urinalysis +/- UPC**
g. EKG and ECHO or MUGA
h. Pulmonary function tests**
i. Imaging studies**
j. Pregnancy test
k. Optional sperm banking
l. Required & optional biology studies

**See Section 7.1.1 for full details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	DXRZ ___mg	DOXO ___mg	IFOS ___mg	MESNA (with IFOS) _____mg/day%	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						Growth factor used:_____
		1	1	___mg	___mg	___mg	_____mg/day%	_____mg	(a-d, e$, f)#, g-k, lα	End date:_____
			2	___mg	___mg	___mg	_____mg/day%			
			3			___mg	_____mg/day%			
			4	Start growth factor. Record type and end date.						
			5							
			6							
			7							
		2	1						b, c, d, e$	
			2-7							
		3	1						b, c, d, e$	
			2-7					_____mg		
The therapy delivery map for Induction continues on the next page.										

% **Enter total daily mesna dose as mg/day by CI or intermittent infusion.**

Obtain within 4 days prior to the start of each cycle.
$ Obtain direct bilirubin if total bilirubin is abnormally elevated.
α Blood is required; slides, tumor tissue and blood are requested (see Sections 15.1 & 15.2).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen A Induction Continued: Cycle 2 of therapy, Weeks 4-6
Induction consists of 12 weeks of therapy (84 days in total) made up of four 21-day cycles.
This therapy delivery map presents Induction therapy on 4 pages.

Patient ID _____ DOB _____

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Dexrazoxane (DXRZ)	Slow IV push/infusion over 5-15 mins	375 mg/m^2/dose	1 and 2 of Week 4	Give immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.2.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose*	1 and 2 of Week 4	*75 mg/m^2/cycle. If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days. See Section 4.2.1 for details.
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Wk 4	See Section 4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Wk 4	Administer with IFOS, see Section 4.2.1
Pazopanib IND# 118613	PO	350 mg/m^2 (pediatric) 600 mg (adult)	1-7 of Wk 4-6	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII.
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of myelosuppressive chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/µL post nadir (continue without regard to pazopanib administration) and discontinue at least 24 hours prior to next cycle of chemotherapy.				

OBSERVATIONS

a. History, PE with VS, Ht, Wt, BSA
b. Blood Pressure**
c. CBC, differential, platelets
d. Electrolytes, including Ca, Mg, PO_4
e. Creatinine, ALT, Total bilirubin
f. Amylase**, Lipase**, Urinalysis +/- UPC**
g. Optional biology study (DOXO PK)

**See Section 7.1.1 for full details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	DXRZ ___mg	DOXO ___mg	IFOS ___mg	MESNA (with IFOS) ___mg/day%	Pazopanib ___mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						Growth factor used:_____
		4†	1	___mg	___mg	___mg	___mg/day%	___mg	(a, b, c, d, e$, f)#, g β	End date:_____
			2	___mg	___mg	___mg	___mg/day%		g β	
			3			___mg	___mg/day%		g β	
			4	Start growth factor. Record type and end date.						
			5							
			6							
			7							
		5	1						b, c, d, e$	
			2-7							
		6	1						b, c, d, e$	
			2-7					___mg		
The therapy delivery map for Induction continues on the next page.										

% **Enter total daily mesna dose as mg/day by CI or intermittent infusion.**
† Begin RT. Note: omit RT at Week 4 for patients with hepatic primary tumors (see Sec. 17).
# Obtain within 4 days prior to the start of each cycle.
$ Obtain direct bilirubin if total bilirubin is abnormally elevated.
β Blood is requested; see Section 15.3 for a list of time points.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen A Induction Continued Cycle 3 of therapy, Weeks 7-9 Induction consists of 12 weeks of therapy (84 days in total) made up of four 21-day cycles. This therapy delivery map presents Induction therapy on 4 pages.	_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Week 7	See Section 4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Week 7	Administer with IFOS, see Section 4.2.1.
Pazopanib IND# 118613	PO	350 mg/m^2 (pediatric) 600 mg (adult)	1-7 of Wk 7-9	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII.
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of myelosuppressive chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/µL post nadir (continue without regard to pazopanib administration) and discontinue at least 24 hours prior to next cycle of chemotherapy.				

OBSERVATIONS

a. History, PE with VS, Ht, Wt, BSA
b. Blood Pressure**
c. CBC, differential, platelets
d. Electrolytes, including Ca, Mg, PO_4
e. Creatinine, ALT, Total bilirubin
f. Amylase**, Lipase**, Urinalysis +/- UPC**
g. EKG and ECHO or MUGA

**See Section 7.1.1 for full details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	IFOS _____mg	MESNA (with IFOS) _____mg/day%	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				Growth factor used:_____ End date:_____
		7	1	_____mg	_____mg/day%	_____mg	(a, b, c, d, e$, f)#, g	
			2	_____mg	_____mg/day%			
			3	_____mg	_____mg/day%			
			4	Start growth factor. Record type and end date.				
			5					
			6					
			7					
		8	1				b, c, d, e$	
			2-7					
		9	1				b, c, d, e$	
			2-7			_____mg		
The therapy delivery map for Induction continues on the next page.								

% Enter total daily mesna dose as mg/day by CI or intermittent infusion.

Obtain within 4 days prior to the start of each cycle.
$ Obtain direct bilirubin if total bilirubin is abnormally elevated.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen A Induction Continued, Cycle 4 of therapy, Weeks 10-12 Induction consists of 12 weeks of therapy (84 days in total) made up of four 21-day cycles. This therapy delivery map presents Induction therapy on 4 pages.	_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Week 10	See Section 4.2.1 for details.	a. History, PE with VS, Ht, Wt, BSA b. Blood Pressure** c. CBC, differential, platelets d. Electrolytes, including Ca, Mg, PO_4 e. Creatinine, ALT, Total bilirubin f. Amylase**, Lipase**, Urinalysis +/- UPC** **See Section 7.1.1 for full details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Week 10	Administer with IFOS, see Section 4.2.1	
Pazopanib IND# 118613	PO	350 mg/m^2 (pediatric) 600 mg (adult)	1-7 of Wk 10-12	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII. Pazopanib will be held pre- and post-surgery. See Section 4.2.1 for details.	
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of myelosuppressive chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/µL post nadir (continue without regard to pazopanib administration) and discontinue at least 24 hours prior to next cycle of chemotherapy. Note: Use of GM-CSF (sargramostim) is not permitted.					

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	IFOS _____mg	MESNA (with IFOS) _____mg/day%	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				Growth factor used:_____ End date of growth factor:_____ End date of pazopanib:_____
		10	1	_____mg	_____mg/day%	_____mg	(a, b, c, d, e$, f)#	
			2	_____mg	_____mg/day%			
			3	_____mg	_____mg/day%			
			4	Start growth factor. Record type and end date.				
			5					
			6					
			7					
		11	1				b, c, d, e$	
			2-7					
		12^	1			▼	b, c, d, e$	
			2-7			_____mg		
				Surgery will follow Induction during Week 13; see Section 13 for details. See Section 7.1.1 for observations required prior to surgery.				

% Enter total daily mesna dose as mg/day by CI or intermittent infusion.

^ Pazopanib is to be held at least 7 days prior to surgery. This may mean stopping pazopanib before the end of Week 12 and will depend upon the timing of surgery.

Obtain within 4 days prior to the start of each cycle. $ Obtain direct bilirubin if total bilirubin is abnormally elevated.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen A **Continuation (Weeks 16-25): This therapy delivery map relates to Cycle 1, Weeks 16-18** Continuation phase consists of 10 weeks of therapy (70 days in total) made up of three 21-day cycles plus one further week of pazopanib. The therapy delivery map presents Continuation phase on 3 pages.	_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexrazoxane (DXRZ)	Slow IV push/infusion over 5-15 mins	375 mg/m^2/dose	1 and 2 of Week 16@	Give immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.2.2.	a. History, PE with VS, Ht, Wt, BSA b. Blood Pressure** c. CBC, differential, platelets d. Electrolytes, including Ca, Mg, PO_4 e. Creatinine, ALT, Total bilirubin f. Amylase**, Lipase**, Urinalysis +/- UPC** **See Section 7.1.1 for full details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose*	1 and 2 of Week 16@	*75 mg/m^2/cycle. If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days. See Section 4.2.2 for details.	
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Wk 16	See Section 4.2.2 for details.	
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Wk 16	Administer with IFOS, see Section 4.2.2.	
Pazopanib IND# 118613	PO	350 mg/m^2 (pediatric) 600 mg (adult)	1-7 of Wk 16-18	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII. Pazopanib will be held at least 14 days post-surgery prior to starting Continuation (see Section 4.2.2).	
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of myelosuppressive chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/µL post nadir (continue without regard to pazopanib administration) and discontinue at least 24 hours prior to next cycle of chemotherapy. Note: Use of GM-CSF (sargramostim) is not permitted.					

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	DXRZ ___mg	DOXO ___mg	IFOS ___mg	MESNA (with IFOS) _____mg/day%	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						Growth factor used:_____
		16@	1	___mg	___mg	___mg	_____mg/day%	_____mg	(a, b, c, d, e$, f)#	End date:_____
			2	___mg	___mg	___mg	_____mg/day%			
			3			___mg	_____mg/day%			
			4	Start growth factor. Record type and end date.						
			5							
			6							
			7							
		17	1						c	
			2-7							
		18	1						c	
			2-7					_____mg		
The therapy delivery map for Continuation continues on the next page.										

% Enter total daily mesna dose as mg/day by CI or intermittent infusion.

@ Begin RT, if postoperative RT given (see Section 17.2). This may delay DOXO administration (see Section 4.2.2).

$ Obtain direct bilirubin if total bilirubin is abnormally elevated. # Obtain within 4 days prior to the start of each cycle.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen A **Continuation Continued: Cycle 2 of therapy, Weeks 19-21** Continuation phase consists of 10 weeks of therapy (70 days in total) made up of three 21-day cycles plus one further week of pazopanib. The therapy delivery map presents Continuation phase on 3 pages.	_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Dexrazoxane (DXRZ)	Slow IV push/infusion over 5-15 mins	375 mg/m^2/dose	1 and 2 of Week 19@	Give immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.2.2.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose*	1 and 2 of Week 19@	*75 mg/m^2/cycle. If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days. See Section 4.2.2 for details.
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Wk 19	See Section 4.2.2 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Wk 19	Administer with IFOS, see Section 4.2.2.
Pazopanib IND# 118613	PO	350 mg/m^2 (pediatric) 600 mg (adult)	1-7 of Wk 19-21	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII.
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of myelosuppressive chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/µL post nadir (continue without regard to pazopanib administration) and discontinue at least 24 hours prior to next cycle of chemotherapy. Note: Use of GM-CSF (sargramostim) is not permitted.				

OBSERVATIONS

a. History, PE with VS, Ht, Wt, BSA
b. Blood Pressure**
c. CBC, differential, platelets
d. Electrolytes, including Ca, Mg, PO_4
e. Creatinine, ALT, Total bilirubin
f. Amylase**, Lipase**, Urinalysis +/- UPC**
g. EKG and ECHO or MUGA

**See Section 7.1.1 for full details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	DXRZ mg	DOXO mg	IFOS mg	MESNA (with IFOS) mg/day%	Pazopanib mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						Growth factor used:_____
		19@	1	____mg	____mg	____mg	_____mg/day%	_____mg	(a, b, c, d, e$, f)#, g	End date:_____
			2	____mg	____mg	____mg	_____mg/day%			
			3			____mg	_____mg/day%			
			4	Start growth factor. Record type and end date.						
			5							
			6							
			7							
		20	1						c	
			2-7							
		21	1						c	
			2-7					_____mg		

The therapy delivery map for Continuation continues on the next page.

% Enter total daily mesna dose as mg/day by CI or intermittent infusion.
@ RT administration may delay DOXO administration (see Sec 4.2.2).
# Obtain within 4 days prior to the start of each cycle.
$ Obtain direct bilirubin if total bilirubin is abnormally elevated.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen A **Continuation Continued: Cycle 3 of therapy + 1 week of pazopanib alone, Weeks 22-25**
Continuation phase consists of 10 weeks of therapy (70 days in total) made up of three 21-day cycles plus one further week of pazopanib alone. The therapy delivery map presents Continuation phase on 3 pages.

_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/μL and platelet count ≥ 75,000/μL post nadir (without transfusion). If the ANC has risen to ≥ 750/μL after the nadir but then falls the next cycle should be given despite ANC < 750/μL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Dexrazoxane (DXRZ)	Slow IV push/infusion over 5-15 mins	375 mg/m^2/dose	1 and 2 of Week 22	Give immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.2.2.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose*	1 and 2 of Week 22	*75 mg/m^2/cycle. If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days. See Section 4.2.2 for details.
Pazopanib IND# 118613	PO	350 mg/m^2 (pediatric) 600 mg (adult)	1-7 of Wk 22-25	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII. Pazopanib is to be held at least 7 days prior to any surgery planned at the end of Continuation therapy. See Section 4.2.2 for details.
The use of growth factor support is optional for this cycle, see Section 4.2.2.				

OBSERVATIONS

a. History, PE with VS, Ht, Wt, BSA
b. Blood Pressure**
c. CBC, differential, platelets
d. Electrolytes, including Ca, Mg, PO_4
e. Creatinine, ALT, Total bilirubin
f. Amylase**, Lipase**, Urinalysis +/- UPC**
g. EKG and ECHO or MUGA

**See Section 7.1.1 for full details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	DXRZ _____mg	DOXO _____mg	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					End date of pazopanib:_____
		22	1	_____mg	_____mg	_____mg	(a, b, c, d, e$^{\$}$, f)$^{\#}$, g	
			2	_____mg	_____mg			
			3					
			4					
			5					
			6					
			7					
		23	1				c	
			2-7					
		24	1				c	
			2-7					
		25$^{\%}$	1				c	
			2-7			_____mg		
				See Section 7.1.1 for observations required at the end of protocol therapy.				

Obtain within 4 days prior to the start of each cycle. $ Obtain direct bilirubin if total bilirubin is abnormally elevated.
% Dexrazoxane/Doxorubicin should be given at week 25 if omitted in weeks 16 or 19.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

APPENDIX X: THERAPY DELIVERY MAPS FOR REGIMEN B

Regimen B: Neoadjuvant Chemotherapy and Radiotherapy

Regimen B							
Induction Phase				**Surgery**	**Continuation Phase**		
Week 1	Week 4	Week 7	Week 10	Week 13	Week 16	Week 19	Week 22
I	I	I	I	Surgery	I	I	
D	D				D	D	D
	Radiotherapy				Radiotherapy		

See Section 4.3 and Section 17 for complete details of protocol therapy.

The therapy delivery maps relating to Induction and Continuation therapy for patients on Regimen B are provided in the following 3 pages.

Regimen B **Induction (Weeks 1-12): This therapy delivery map relates to Cycles 1 and 2 of therapy, Weeks 1-6.**
Induction consists of 12 weeks of therapy (84 days in total) made up of four 21-day cycles.
The therapy delivery map presents Induction therapy on 2 pages.

Patient ID _____ DOB _____

Criteria to start each cycle: ANC ≥ 750/μL and platelet count ≥ 75,000/μL post nadir (without transfusion). If the ANC has risen to ≥ 750/μL after the nadir but then falls the next cycle should be given despite ANC < 750/μL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Dexrazoxane (DXRZ)	Slow IV push/infusion over 5-15 mins	375 mg/m^2/dose	1 and 2 of Weeks 1 and 4	Give immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.3.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose*	1 and 2 of Weeks 1 and 4	*75 mg/m^2/cycle. If BSA > 2 m^2, maximum dose is 75 mg/day and total dose is 150 mg over 2 days. See Section 4.3.1 for details.
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Weeks 1 and 4	See Section 4.3.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Weeks 1 and 4	Administer with IFOS, see Section 4.3.1
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/μL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy. Note: Use of GM-CSF (sargramostim) is not permitted.				

OBSERVATIONS

a. History, PE with VS, Ht, Wt, BSA
b. Blood Pressure
c. CBC, differential, platelets
d. Electrolytes, including Ca, Mg, PO_4
e. Creatinine, ALT, Total bilirubin
f. Urinalysis
g. ECHO or MUGA
h. Pulmonary function tests**
i. Imaging studies**
j. Pregnancy test
k. Optional sperm banking
l. Required & optional biology studies

**See Section 7.1.2 for full details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 1: Ht_____cm Wt_____kg BSA_____m^2 **Cycle 2: Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Week	Day	DXRZ mg	DOXO mg	IFOS mg	MESNA (with IFOS) mg/day[%]	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below						Cycle 1, Growth factor used:_____ End date:_____ Cycle 2, Growth factor used:_____ End date:_____
		1	1	mg	mg	mg	mg/day[%]	(a-d, e[$], f)[#], g-k, l[α]	
			2	mg	mg	mg	mg/day[%]		
			3			mg	mg/day[%]		
			4-7	Start growth factor. Record type and end date.					
		2	1-7						
		3	1-7						
		4†	1	mg	mg	mg	mg/day[%]	(a-d, e[$], f)[#]	
			2	mg	mg	mg	mg/day[%]		
			3			mg	mg/day[%]		
			4-7	Start growth factor. Record type and end date.					
		5	1-7						
		6	1-7						

The therapy delivery map for Induction continues on the next page.

[%] **Enter total daily dose as mg/day by CI or intermittent infusion.**
† Begin RT. Note: omit RT at Week 4 for patients with hepatic primary tumors (see Sec. 17).
α Blood is required; slides, tumor tissue and blood are requested (see Sections 15.1 & 15.2)
Obtain within 4 days prior to the start of each cycle.
$ Obtain direct bilirubin if total bilirubin is abnormally elevated.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII SUPPORTIVE CARE

Regimen B **Induction Continued: Cycles 3 and 4 of therapy, Weeks 7-12.** Induction consists of 12 weeks of therapy (84 days in total) made up of four 21-day cycles. The therapy delivery map presents Induction therapy on 2 pages.	_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m^2/dose	1-3 of Weeks 7 and 10	See Section 4.3.1 for details.	a. History, PE with VS, Ht, Wt, BSA b. Blood Pressure** c. CBC, differential, platelets d. Electrolytes, including Ca, Mg, PO_4 e. Creatinine, ALT, Total bilirubin f. Urinalysis g. ECHO or MUGA** **See Section 7.1.2 for full details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m^2/day	1-3 of Weeks 7 and 10	Administer with IFOS, see Section 4.3.1.	
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/µL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy. Note: Use of GM-CSF (sargramostim) is not permitted.					

Cycle 3: Ht_____cm Wt_____kg BSA_____m^2 Cycle 4: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	IFOS _____mg	MESNA (with IFOS) _____mg/day%	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				Cycle 3, Growth factor used:_____
		7	1	_____mg	_____mg/day%	(a-d, e$, f)#, g^	End date:_____
			2	_____mg	_____mg/day%		Cycle 4, Growth factor used:_____
			3	_____mg	_____mg/day%		End date:_____
			4-7	Start growth factor. Record type and end date.			
		8	1-7				
		9	1-7				
		10	1	_____mg	_____mg/day%	(a-d, e$, f)#	
			2	_____mg	_____mg/day%		
			3	_____mg	_____mg/day%		
			4-7	Start growth factor. Record type and end date.			
		11	1-7				
		12	1-7				
Surgery will follow Induction at Week 13; see Section 13 for details. See Section 7.1.2 for observations required prior to surgery.							

% Enter total daily dose as mg/day by CI or intermittent infusion.

Obtain within 4 days prior to the start of each cycle.

$ Obtain direct bilirubin if total bilirubin is abnormally elevated.

^ Obtain for patients < 21 years. For patients ≥ 21 years obtain only if clinically indicated.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen B **Continuation, Weeks 16-24**
Continuation phase consists of 9 weeks of therapy (63 days in total) made up of three 21-day cycles.
The therapy delivery map presents Continuation phase on 1 page.

Patient ID _____ DOB _____

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Dexrazoxane (DXRZ)	Slow IV push/infusion over 5-15 mins	375 mg/m²/dose	1 and 2 of Weeks 16, 19@ and 22	Give immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.3.2.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m²/dose*	1 and 2 of Weeks 16, 19@ and 22	*75 mg/m²/cycle. If BSA > 2 m², maximum dose is 75 mg/day and total dose is 150 mg over 2 days. See Section 4.3.2 for details.
Ifosfamide (IFOS)	IV over 2-4 hours	2500 mg/m²/dose	1-3 of Weeks 16 and 19	See Section 4.3.2 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 2500 mg/m²/day	1-3 of Weeks 16 and 19	Administer with IFOS, see Section 4.3.2.
Begin myeloid growth factor support (filgrastim or pegfilgrastim) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 2000/µL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy. Note: Use of GM-CSF (sargramostim) is not permitted. The use of growth factor after doxorubicin alone is optional.				

OBSERVATIONS

a. History, PE with VS, Ht, Wt, BSA
b. Blood Pressure
c. CBC, differential, platelets
d. Electrolytes, including Ca, Mg, PO_4
e. Creatinine, ALT, Total bilirubin
f. Urinalysis
g. ECHO or MUGA**

**See Section 7.1.2 for full details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 1: Ht_____cm Wt_____kg BSA_____m² **Cycle 2: Ht_____cm Wt_____kg BSA_____m²**
Cycle 3: Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Week	Day	DXRZ mg	DOXO mg	IFOS mg	MESNA (with IFOS) mg/day%	Studies
			Enter calculated dose above and actual dose administered below					
		16@	1	____mg	____mg	____mg	____mg/day%	(a-d, e$, f)#
			2	____mg	____mg	____mg	____mg/day%	
			3			____mg	____mg/day%	
			4-7	Start growth factor. Record type and end date.				
		17	1-7					
		18	1-7					
		19@	1	____mg	____mg	____mg	____mg/day%	(a-d, e$, f)#, g
			2	____mg	____mg	____mg	____mg/day%	
			3			____mg	____mg/day%	
			4-7	Start growth factor. Record type and end date.				
		20	1-7					
		21	1-7					
		22	1	____mg	____mg			(a-d, e$, f)#, g
			2	____mg	____mg			
			3-7					
		23	1-7					
		24	1-7					
		25^						

Comments (Include any held doses, or dose modifications)
Cycle 1, Growth factor used:_____
End date:_____
Cycle 2, Growth factor used:_____
End date:_____

See Section 7.1.2 for observations required at the end of protocol therapy.

% Enter total daily mesna dose as mg/day by CI or intermittent infusion. may delay DOXO administration (see Sec 4.3.2)

Obtain within 4 days prior to the start of each cycle.

$ Obtain direct bilirubin if total bilirubin is abnormally elevated.

@ Begin RT, if postoperative RT given (see Section 17.2). RT

^ Dexrazoxane/Doxorubicin should be given at week 25 if omitted in weeks 16 or 19.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

APPENDIX XI: THERAPY DELIVERY MAPS FOR REGIMEN C

Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

Regimen C: Neoadjuvant Radiotherapy and Pazopanib

<table>
<tr><th colspan="8">Regimen C</th></tr>
<tr><th colspan="3">Induction Phase</th><th>Surgery</th><th colspan="4">Continuation Phase</th></tr>
<tr><td>Week 1</td><td>Week 4</td><td>Week 7</td><td rowspan="3">Week 10
Surgery</td><td>Week 13</td><td>Week 16</td><td>Week 19</td><td>Weeks 22- 25</td></tr>
<tr><td colspan="3">Pazopanib Weeks 1-9</td><td colspan="4">Pazopanib Weeks 13-25</td></tr>
<tr><td colspan="3">Radiotherapy</td><td colspan="2">Radiotherapy</td><td colspan="2"></td></tr>
</table>

See Section 4.4 and Section 17 for complete details of protocol therapy.

The therapy delivery maps relating to Induction and Continuation therapy for patients on Regimen C are provided in the following 3 pages.

Regimen C Induction, Weeks 1-9 Induction consists of three 21-day cycles of daily pazopanib therapy (63 days in total). This therapy delivery map presents Induction phase on 1 page. Repeat this TDM for each cycle of pazopanib therapy.	_____ Patient ID _____ DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Pazopanib IND# 118613	PO	450 mg/m^2 (pediatric) 800 mg (adult)	1-7 of Weeks 1-9	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII. Pazopanib will be held pre- and post-surgery. See Section 4.4.1 for further details.	a. History, PE with VS, Ht, Wt, BSA b. Blood Pressure** c. CBC, differential, platelets d. Electrolytes, including Ca, Mg, PO_4 e. Creatinine, ALT, Total bilirubin f. Amylase**, Lipase**, Urinalysis +/- UPC** g. EKG and ECHO or MUGA h. Pulmonary function tests** i. Imaging studies** j. Pregnancy test k. Optional sperm banking l. Required & optional biology studies **See Section 7.1.3 for full details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Cycle: _____ Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below		End date of pazopanib:_____
		1[@]/4/7	1	_____mg	(a-d, e[$], f)[#], (g-k)[&], 1[α]	
			2-7	↓		
		2/5/8	1		b, c, d, e[$]	
			2-7			
		3/6/9^	1		b, c, d, e[$], g[%]	
			2-7	_____mg		
Surgery will follow Induction at Week 10; see Section 13 for details. **See Section 7.1.3 for observations required prior to surgery.**						

\# Obtain within 4 days prior to the start of each cycle. $ Obtain direct bilirubin if total bilirubin is abnormally elevated. & Prior to Cycle 1 only.
α Blood is required; slides, tumor tissue and blood are requested (see Sections 15.1 & 15.2). % Obtain EKG before stopping pazopanib prior to surgery (see Section 7.1.3).
@ Begin RT. Note: omit at Week 1 for patients with hepatic primary tumors (see Section 17).
^ Pazopanib is to be held at least 7 days prior to surgery. This may mean stopping pazopanib before the end of Week 9 and will depend upon the timing of surgery.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen C **Continuation Phase (Weeks 13-25): This therapy delivery map relates to Cycles 1 and 2, Weeks 13-18.** Continuation phase consists of 13 weeks of therapy (91 days in total) made up of four 21-day cycles plus one extra week of pazopanib therapy. This therapy delivery map presents the Continuation phase on 2 pages.	_____ Patient ID _____ DOB

DRUG	**ROUTE**	**DOSAGE**	**DAYS**	**IMPORTANT NOTES**	**OBSERVATIONS**
Pazopanib IND# 118613	PO	450 mg/m^2 (pediatric) 800 mg (adult)	1-7 of Weeks 13-18	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII. Pazopanib will be held at least 14 days post-surgery prior to starting Continuation. See Section 4.4.2 for further details.	a. History, PE with VS, Ht, Wt, BSA b. Blood Pressure** c. CBC, differential, platelets d. Electrolytes, including Ca, Mg, PO_4 e. Creatinine, ALT, Total bilirubin f. Amylase**, Lipase**, Urinalysis +/- UPC** g. EKG **See Section 7.1.3 for full details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Cycle 1: Ht_____cm Wt_____kg BSA_____m^2 Cycle 2: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
		Enter calculated dose above and actual dose administered below				
		13@	1	_____mg	(a-d, e$, f)#	
			2-7	↓		
		14	1	↓		
			2-7	↓		
		15	1	↓	g%	
			2-7	↓		
		16	1	_____mg	(a-d, e$, f)#	
			2-7	↓		
		17	1	↓		
			2-7	↓		
		18	1	↓		
			2-7	_____mg		
The therapy delivery map for Continuation continues on the next page.						

Obtain within 4 days prior to the start of each cycle.

$ Obtain direct bilirubin if total bilirubin is abnormally elevated.

@ Begin RT, if postoperative RT given (see Section 17.2).

%Obtain EKG 2-4 weeks after the start of the Continuation phase (see Section 7.1.3).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

Regimen C Continuation Phase Continued Weeks 19-25: Cycles 3 and 4 plus 1 week of pazopanib Continuation phase consists of 13 weeks of therapy (91 days in total) made up of four 21-day cycles plus one extra week of pazopanib therapy. This therapy delivery map presents the Continuation phase on 2 pages.	_____ Patient ID _____ DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Pazopanib IND# 118613	PO	450 mg/m^2 (pediatric) 800 mg (adult)	1-7 of Weeks 19-25	For pediatric patients (<18 years of age) use dosing tables for pazopanib provided in Appendix XVII. Pazopanib is to be held at least 7 days prior to any surgery planned at the end of Continuation therapy. See Section 4.4.2 for further details.	a. History, PE with VS, Ht, Wt, BSA b. Blood Pressure** c. CBC, differential, platelets d. Electrolytes, including Ca, Mg, PO_4 e. Creatinine, ALT, Total bilirubin f. Amylase**, Lipase**, Urinalysis +/- UPC** **See Section 7.1.3 for full details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Cycle 3: Ht_____cm Wt_____kg BSA_____m^2 Cycle 4: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	Pazopanib _____mg	Studies	Comments (Include any held doses, or dose modifications)
		Enter calculated dose above and actual dose administered below				End date of pazopanib:_____
		19	1	_____mg	(a-d, e$^{\$}$, f)$^{\#}$	
			2-7	↓		
		20	1-7	↓		
		21	1-7	↓		
		22	1	_____mg	(a-d, e$^{\$}$, f)$^{\#}$	
			2-7	↓		
		23	1-7	↓		
		24	1-7	↓		
		25	1-7	_____mg		
See Section 7.1.3 for observations required at the end of protocol therapy.						

Obtain within 4 days prior to the start of each cycle. $ Obtain direct bilirubin if total bilirubin is abnormally elevated.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE APPENDIX VIII FOR SUPPORTIVE CARE

APPENDIX XII: URINE PROTEIN TO CREATININE (UPC) RATIO

Clinical Meaning of UPC

There is a good correlation between the ratio of urine protein to creatinine concentrations (UPC) in a random urine sample and the amount of protein excreted in a 24-hour urine collection period.[205] Thus the UPC allows for an estimation of the 24-hour urine protein excretion from a random sample. The creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate:

- Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day
- Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day

Normal protein excretion is <100 mg to 150 mg per 24 hours.

- The UPC ratio is roughly equal to the 24 hour urine protein excretion in g/day

Calculating UPC Ratio

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

Example: If a subject has a urine protein of 90 mg/dL and urine creatinine of 30 mg/dL,

then UPC ratio = $\frac{90\ (mg/dL)}{30\ (mg/dL)} = 3$

Result UPC is 3 correlating to roughly 3g of protein excretion in a 24-hour period.

Units for UPC ratio

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

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

APPENDIX XIII: REFERENCE GUIDE FOR REQUIRED AND RECOMMENDED CORRELATIVE STUDIES

Note: in addition to the specimens below, this study includes a retrospective central pathology review with additional specimen requirements (see Section 14.0).

	At Diagnosis/Pre-treatment	Induction Cycle 2, Day 1-3	Local Control Surgery (Week 10 or Week 13)	Suspected Tumor Recurrence	Lab Receiving Specimens
Analysis of actionable mutations* (Section 15.1)	• Peripheral blood (2.5 mL) in a PAXgene RNA tube • Peripheral blood (5 mL) in purple top (EDTA) tube				BPC
Whole genome sequencing^ (Section 15.1)	Snap frozen tumor tissue from primary site and any metastatic site				BPC
Microvessel density and circulating tumor DNA^ (Section 15.2)	• 2 unstained slides from tumor tissue • Peripheral blood (10 mL) in purple top (EDTA) tubes		• Snap frozen tumor tissue from primary site • Peripheral blood (10 mL) in purple top (EDTA) tubes		Yoon
Doxorubicin pharmacokinetics^ (Section 15.3) **NOTE:** Accrual to this correlative study ended upon completion of accrual to the dose finding phase of the chemotherapy cohort		Blood (3-5 mL) in tubes containing sodium citrate at the following 9 time points pre- and post-doxorubicin: • time 0 (predose) • 5 min after dosing • 30 min after dosing • 60 min after dosing • 2 hours after dosing • 4 hours after dosing • 8 hours after dosing • 24 ± 3 hours after dosing • 48 ± 3 hours after dosing.			Baker
Imaging Aims^ (Section 16)	**FDG PET**		**FDG PET (pre-surgery)**	**FDG PET**	IROC RI

* Required of all patients.
^ Recommended (option for participation embedded in main study consent).

APPENDIX XIV: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ARST1321
(for children from 7 through 12 years of age)

A study to compare treatments for a type of cancer called Soft Tissue Sarcoma (STS)

1. We have been talking with you about your Soft Tissue Sarcoma (STS). STS is a type of cancer that grows in the soft tissues of the body like the muscles. It can grow in many places in the body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have STS. A research study is when doctors work together to try out new ways to help people who are sick.
   The usual treatment for STS includes surgery, radiation therapy and chemotherapy.
   - Radiation therapy is like using high energy x-rays.
   - Chemotherapy is a name for drugs that fight cancer.

   Not all STS tumors are alike; some do respond to chemotherapy and some do not.

   We want to see if giving pazopanib along with the usual therapy is safe without bad side effects. We also want to see how well each of the study treatments works against the type of cancer that you have.

   In this study, we will test whether adding a drug called pazopanib to the usual therapy will improve the treatment for the type of cancer that you have.

3. Children who are part of this study will be treated in one of 2 ways.

   If you have a type of STS that we think will respond to chemotherapy, you will be treated with

   - Chemotherapy + Radiation therapy + Surgery + pazopanib

   or

   - Chemotherapy + Radiation therapy + Surgery

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is that you get rid of the cancer for a long time. But we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that the study treatment may not work as well as other therapies. Also, the study treatment may cause more side effects than other therapies. Other things may happen to you that we don’t yet know about.

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

7. We are asking your permission to use leftover tumor tissue and to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. These samples

would be taken when surgery or standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples and use tumor tissue for research.

8. Also, if you are to be treated with pazopanib, we may ask your permission to collect extra blood for biology research tests. These samples would be taken when you would not usually have blood drawn. These samples are likely to be taken from your central line and should not cause pain. You can still take part in this study even if you don't allow us to collect the extra blood samples for this research.

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

A study to compare treatments with and without pazopanib for soft tissue sarcoma (STS)

1. We have been talking with you about your Soft Tissue Sarcoma (STS). STS is a type of cancer that grows in the soft tissues of the body like the muscles. It can occur in many places in the body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have STS. A research study is when doctors work together to try out new ways to help people who are sick.

   The usual treatment for STS includes surgery, radiation therapy (high energy x-rays), and chemotherapy (anti-cancer drugs). Not all STS tumors are alike; some do respond to chemotherapy and some do not.

   We want to see if giving pazopanib along with the usual therapy is safe without bad side effects. We also want to see how well each of the combinations works against the type of cancer that you have.

   In this study, we will test whether adding an experimental drug, called pazopanib, to the usual therapy will improve the treatment for the type of cancer that you have.

3. Children and teens who are part of this study will be treated in one of 2 ways.

   If you have a type of STS that is sensitive to chemotherapy, you will be treated with

   - Chemotherapy + Radiation therapy + Surgery + pazopanib

   or

   - Chemotherapy + Radiation therapy + Surgery

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is that you get rid of the cancer for a long time. But we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that the study treatment may not work as well as other therapies. Also, the study treatment may cause more side effects than other therapies. Other things may happen to you that we don’t yet know about.

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

7. This study includes required biology research tests. We want to see if there are ways to tell how the cancer will respond to treatment. For this test we will use some of the tumor tissue that was removed to make the diagnosis of NRSTS. You will not have an extra procedure to collect tumor tissue for this test. In addition, we will collect about 1½ teaspoons of blood for these tests. This

blood will be taken when other standard blood tests are being performed, so there would be no extra procedures.

8. This study also includes optional biology research tests. We are asking your permission to use leftover tumor tissue and to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when surgery or standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples and use tumor tissue for research.

9. Also, if you are to be treated with pazopanib, we may ask your permission to collect additional blood. We want to examine the effect pazopanib might have on one of the standard chemotherapy drugs. These samples would be taken when you would not usually have blood drawn. These samples are likely to be taken from your central line and should not cause pain. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

APPENDIX XV: SUBJECT'S MEDICATION DIARY - PAZOPANIB

Today's date: _____ **Agent:** **Pazopanib**

Subject Name: _____ (*initials acceptable)* **Subject Study ID:** _____

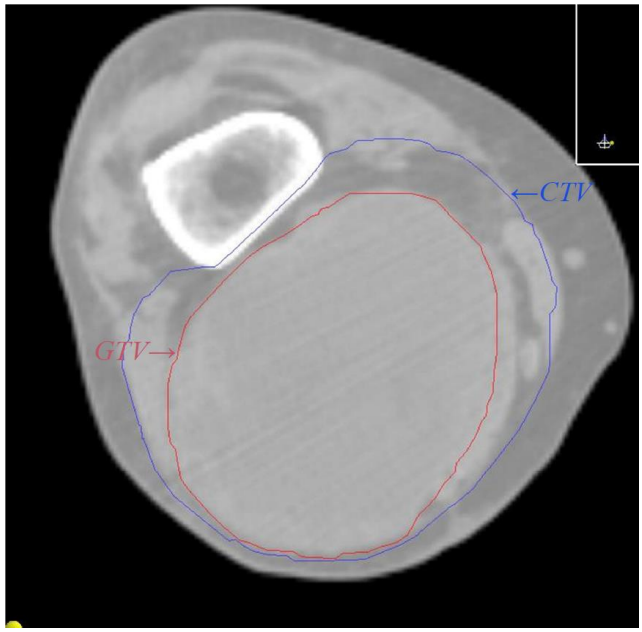
		INSTRUCTIONS TO THE SUBJECT: 1. Complete one form for each 21 day cycle. 2. Take your dose of pazopanib each day in the morning either 1 hour before or 2 hours after you eat with about 1 cup (240 mL) of water. You will take the tablets as instructed by your provider. You should swallow the tablets whole. **Do not chew, crush, or break the tablets.** 3. If a dose is missed, do not take or "make up" the dose unless there is at least 12 hours until the next scheduled dose. If you vomit within 30 minutes of taking the dose, the dose may be repeated. If more than 30 minutes have elapsed, do not repeat the dose. 4. Record the date, the number of tablets you took, and when you took them. 5. If you have any comments or notice any side effects, please record them in the Comments column. 6. Please return the forms to your provider when you go for your next appointment.		
		Starting Week: ____ BSA: ____m^2 Weekly Dose: ____mg/m^2		
Day	**Date**	**What time was dose taken?**	**Number of 200 mg tablets taken**	**Comments**
1			# prescribed: ___ # taken: ___	
2			# prescribed: ___ # taken: ___	
3			# prescribed: ___ # taken: ___	
4			# prescribed: ___ # taken: ___	
5			# prescribed: ___ # taken: ___	
6			# prescribed: ___ # taken: ___	
7			# prescribed: ___ # taken:	
8			# prescribed: ___ # taken: ___	
9			# prescribed: ___ # taken:	
10			# prescribed: ___ # taken: ___	
11			# prescribed: ___ # taken: ___	
12			# prescribed: ___ # taken: ___	
13			# prescribed: ___ # taken: ___	
14			# prescribed: ___ # taken:	
15			# prescribed: ___ # taken: ___	

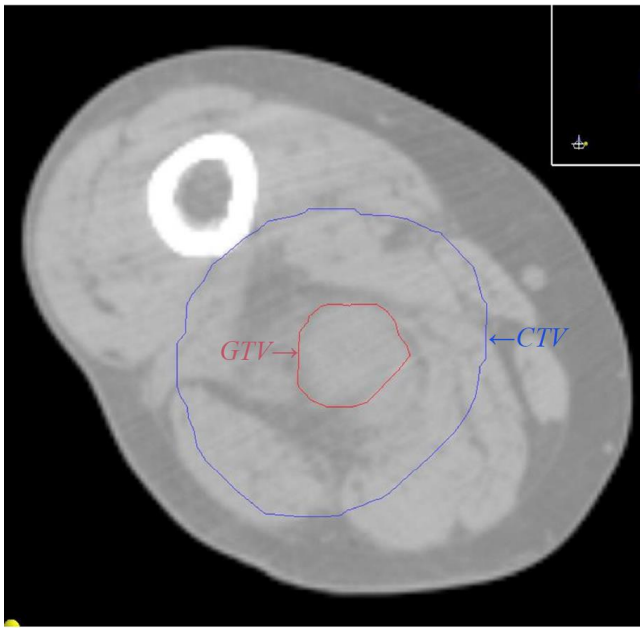
16			# prescribed: ___ # taken: ___	
17			# prescribed: ___ # taken: ___	
18			# prescribed: ___ # taken: ___	
19			# prescribed: ___ # taken: ___	
20			# prescribed: ___ # taken: ___	
21			# prescribed: ___ # taken: ___	
		Physician's Office will complete this section: 1. Date subject started protocol treatment_____ 2. Date subject was removed from study _____ 3. Subject's planned total daily dose _____ 4. Total number of pills taken this month _____ 5. Physician/Nurse/Data Manager's Signature _____		

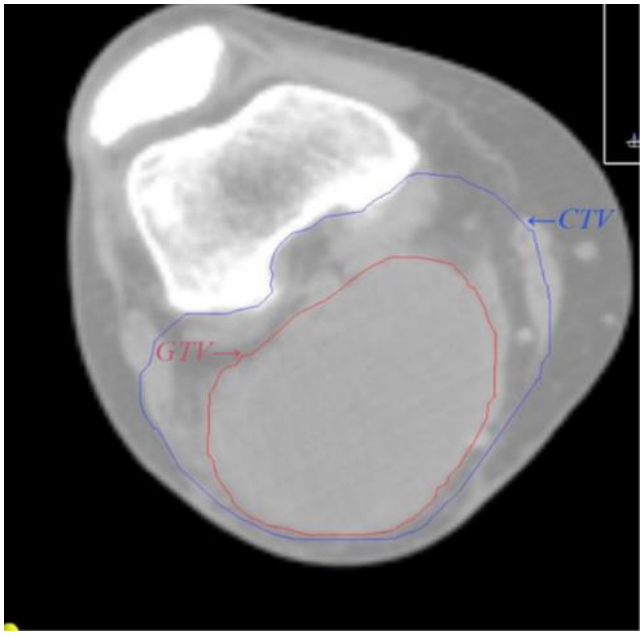
Subject's signature: _____

APPENDIX XVI: RADIATION TREATMENT TARGET VOLUME

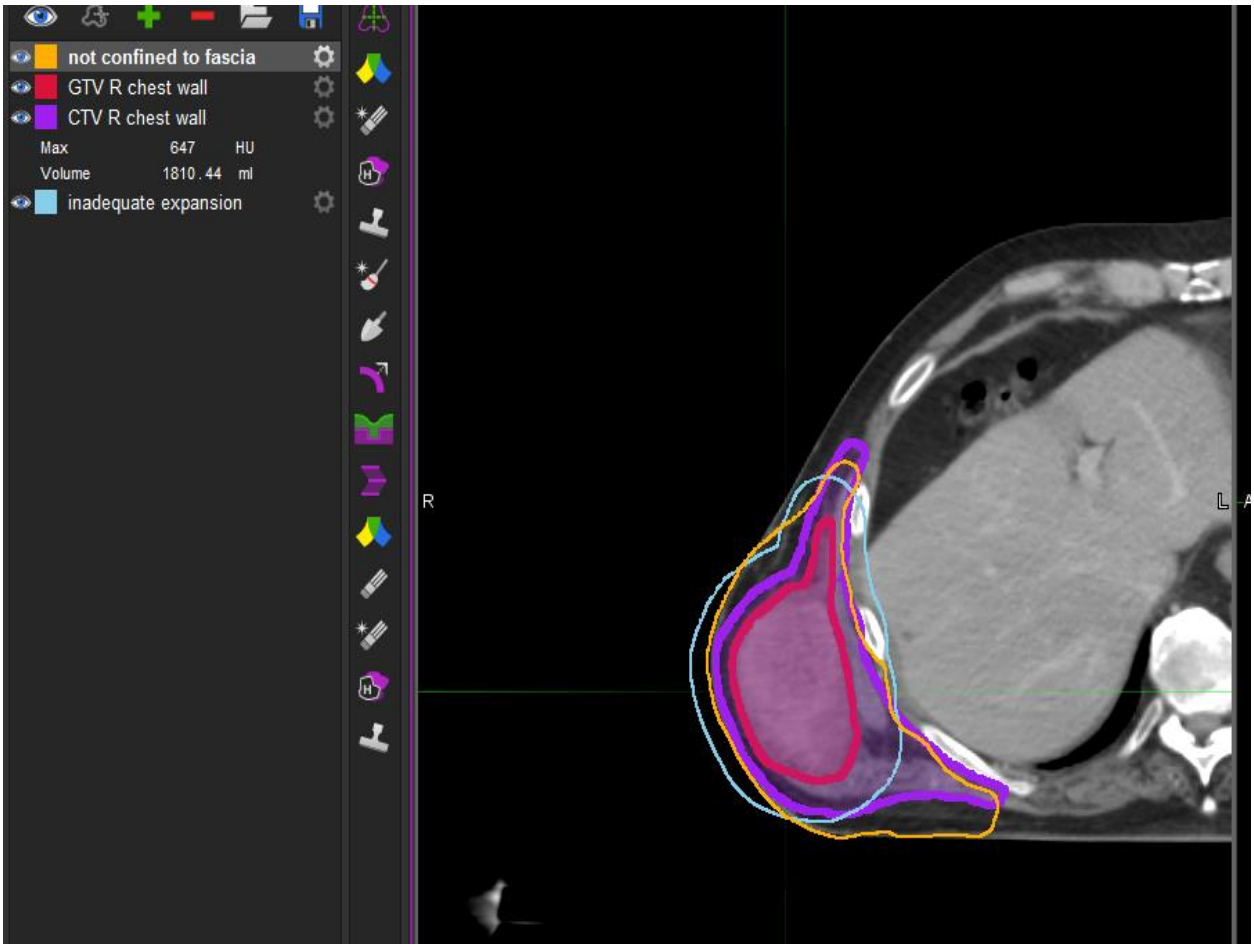
Example 1:
From RTOG Lower Extremity Sarcoma Atlas (https://www.rtog.org/LinkClick.aspx?fileticket=AThtvc6dabE%3d&tabid=356, accessed 5/1/2016): CTV for intermediate to high grade tumors ≥ 5 cm should include 3 cm longitudinal margin and 1.5 cm radial margin, confined by anatomic barriers. Note the trimming of the CTV at the cortex of the abutting femur and deep fascia rather than extend to the skin.







Example 2:
Grade 3 sarcoma along chest wall involving latissimus dorsi. The thickened red volume is the GTV and the thickened purple line indicates the correct expansion for the involved muscle. The thin orange volume shows overexpansion into the subcutaneous space and extension to skin. The thin light blue volume is a strict 1.5 cm radial expansion of the GTV along the X-Y axis, which would be inadequate for the longitudinal spread along the involved muscle along the chest wall.



APPENDIX XVII: PEDIATRIC (< 18 YEARS OF AGE) DOSING TABLES FOR PAZOPANIB

Chemotherapy Cohort
Pazopanib 350 mg/m^2

Body Surface Area (m^2)	Daily dose (d) for 7 days (1 tablet = 200 mg)	Cumulative Weekly Dose
0.3 – 0.36	1 tab / d QOD x 4	800 mg/wk
0.37 – 0.44	1 tab / d x 5	1000 mg/wk
0.45– 0.53	1 tab / d x 6	1200 mg/wk
0.54 – 0.61	1 tab / d x 7	1400 mg/wk
0.62 – 0.69	1 tab / d x 6; 2 tab / d x 1	1600 mg/wk
0.7 – 0.77	1 tab / d x 5; 2 tab / d x 2	1800 mg/wk
0.78 – 0.85	1 tab / d x 4; 2 tab / d x 3	2000 mg/wk
0.86 – 0.93	2 tab / d x 4; 1 tab / d x 3	2200 mg/wk
0.94 – 1.02	2 tab / d x 5; 1 tab / d x 2	2400 mg/wk
1.03 – 1.1	2 tab / d x 6; 1 tab / d x 1	2600 mg/wk
1.11 – 1.18	2 tab / d x 7	2800 mg/wk
1.19 – 1.26	2 tab / d x 6; 3 tab / d x 1	3000 mg/wk
1.27 – 1.34	2 tab / d x 5; 3 tab / d x 2	3200 mg/wk
1.35 – 1.42	2 tab / d x 4; 3 tab / d x 3	3400 mg/wk
1.43 – 1.51	3 tab / d x 4; 2 tab / d x 3	3600 mg/wk
1.52 – 1.59	3 tab / d x 5; 2 tab / d x 2	3800 mg/wk
1.6 – 1.67	3 tab / d x 6; 2 tab / d x 1	4000 mg/wk
1.68 and greater	3 tab / d x 7	4200 mg/wk

For dose modifications to the chemotherapy cohort (350 mg/m^2), please see Section 5.2.

Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

Non-Chemotherapy Cohort
Pazopanib 450 mg/m^2

Body Surface Area (m2)	Daily dose (d) for 7 days (1 tablet = 200 mg)	Cumulative Weekly Dose
0.3 – 0.34	1 tab / d x 5	1000 mg/wk
0.35– 0.41	1 tab / d x 6	1200 mg/wk
0.42 – 0.47	1 tab / d x 7	1400 mg/wk
0.48 – 0.53	1 tab / d x 6; 2 tab / d x 1	1600 mg/wk
0.54 – 0.6	1 tab / d x 5; 2 tab / d x 2	1800 mg/wk
0.61 – 0.66	1 tab / d x 4; 2 tab / d x 3	2000 mg/wk
0.67 – 0.73	2 tab / d x 4; 1 tab / d x 3	2200 mg/wk
0.74 – 0.79	2 tab / d x 5; 1tab / d x 2	2400 mg/wk
0.8 – 0.85	2 tab / d x 6; 1 tab / d x 1	2600 mg/wk
0.86 – 0.92	2 tab / d x 7	2800 mg/wk
0.93 – 0.98	2 tab / d x 6; 3 tab / d x 1	3000 mg/wk
0.99 – 1.04	2 tab / d x 5; 3 tab / d x 2	3200 mg/wk
1.05 – 1.11	2 tab / d x 4; 3 tab / d x 3	3400 mg/wk
1.12 – 1.17	3 tab / d x 4; 2 tab / d x 3	3600 mg/wk
1.18 – 1.23	3 tab / d x 5; 2 tab / d x 2	3800 mg/wk
1.24 – 1.3	3 tab / d x 6; 2 tab / d x 1	4000 mg/wk
1.31 – 1.36	3 tab / d x 7	4200 mg/wk
1.37 – 1.42	3 tab / d x 6; 4 tab / d x 1	4400 mg/wk
1.43 – 1.49	3 tab / d x 5; 4 tab / d x 2	4600 mg/wk
1.5 – 1.55	3 tab / d x 4; 4 tab / d x 3	4800 mg/wk
1.56 – 1.61	4 tab / d x 4; 3 tab / d x 3	5000 mg/wk
1.62 – 1.68	4 tab / d x 5; 3 tab / d x 2	5200 mg/wk
1.69 – 1.74	4 tab / d x 6; 3 tab / d x 1	5400 mg/wk
1.75 and greater	4 tab / d x 7	5600 mg/wk

For dose modifications to the non-chemotherapy cohort (450 mg/m^2), please see Section 5.2.

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173. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.,
174. Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.,

175. Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC. ,
176. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC. ,
177. Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. ,
178. Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC. ,
179. Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).
180. These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications. ,
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