COG-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)

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. 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). See Section 3.1.3. Randomization will take place at the time a patient is enrolled via OPEN.

___2. 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**.

___3. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated below.

___4. 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.

___5. 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).

___6. 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.

___7. 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
- Patients meeting the above criteria (histology, size, and grade) with the EXCEPTION of histologies noted in the next bullet point 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 the next bullet point but medically deemed unable to receive chemotherapy or who elect not to receive chemotherapy are eligible for the non-chemotherapy cohort.
- 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

___8. Eligibility for non-chemotherapy cohort:
Note: The Non-Chemotherapy Cohort is closed to further accrual, effective October 12, 2017.

___9. Extent of Disease

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

___10. Specimen Submission - Sufficient tissue and blood must be available to submit for required biology studies (see Section 15.1.1).

___11. Performance Level

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

___12. Organ Function Requirements

- 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.

- 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	1.7	1.4

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

- 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
- Adequate cardiac function defined as:
  - Shortening fraction of ≥ 27% by echocardiogram OR Ejection fraction of ≥ 50% by radionuclide angiogram.
  - QTc < 480 msec
- 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.

___13. Anticoagulation - Patients on low molecular weight heparin or coumadin (with a stable INR) are eligible.
___14. Life Expectancy - Patient must have a life expectancy of at least 3 months with appropriate therapy.
___15. Assent – Assent of children 14 and older is a necessary condition for proceeding with the research. Verbal assent should be documented.

EXCLUSION CRITERIA:

___1. Patients with Grade 1 NRSTS tumors of any size are not eligible.

___2. Patients with known CNS metastases are not eligible.
Note: Brain imaging is not an eligibility requirement.

___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).

___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.

___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.

___6. PRIOR THERAPY
- Patients must have had no prior anthracycline (eg, doxorubicin, daunorubicin) or ifosfamide chemotherapy.
- Patients must have had no prior use of pazopanib or similar multi-targeted TKI.
- 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 in #7 below 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.

___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.

___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.

___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.

___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.

___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.

___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

___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

___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.

___15. History of serious or non-healing wound, ulcer, or bone fracture.

___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.

___17. Patients who are unable to swallow whole tablets are not eligible.

___18. Patients with a Body Surface Area $< 0.5\ m^2$ are not eligible.

___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.

___20. Patients who are receiving any other investigational agent(s).

___21. Pregnancy and Breast Feeding
- Female patients who are pregnant are ineligible due to risks of fetal and teratogenic adverse events as seen in animal/human studies.
- 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.
- Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

___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.

REQUIRED OBSERVATIONS:

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

Regimen A: CHEMORADIOTHERAPY + Pazopanib

Observation

- History, Physical Exam, Ht, Wt, BSA, Vital Signs
- Blood Pressure [A]
- CBC with differential and platelets
- Electrolytes including Ca, Mg, PO4
- Creatinine, ALT, Total bilirubin [B]
- Amylase and lipase
- Urinalysis +/- UPC [C]
- Pregnancy test (females of childbearing potential)
- Sperm banking (optional)
- EKG and Echocardiogram or MUGA
- Pulmonary function tests [D]
- MRI or CT scan of primary site [E]
- CT chest
- Growth plate evaluation [M]
- FDG PET scan (optional, see Sec 16.4)
- Metastatic site imaging [F]
- Central imaging review [G]
- Operative notes & pathology reports [H]
- Central pathology review [I]
- Central radiotherapy review [J]
- Required biology studies [K]
- Optional biology studies [L]

A 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.

B Obtain direct bilirubin if total bilirubin is abnormally elevated.

C 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).

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

E 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).

F Metastases should be imaged by the most appropriate modality.

G 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.

H 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.

I 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.

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

K 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.

L 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.

M 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).

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

Regimen B: CHEMORADIOTHERAPY

Observation

- History, Physical Exam, Ht, Wt, BSA, Vital Signs including Blood Pressure
- CBC with differential and platelets
- Electrolytes including Ca, Mg, PO4
- Creatinine, ALT, Total bilirubin [A]
- Urinalysis
- Pregnancy test (females of childbearing potential)
- Sperm banking (optional)
- Echocardiogram or MUGA
- Pulmonary function tests [B]
- MRI or CT scan of primary site [C]
- CT chest
- FDG PET scan (optional, see Sec 16.4)
- Metastatic site imaging [D]
- Central imaging review [E]
- Operative notes & pathology reports [F]
- Central pathology review [G]
- Central radiotherapy review [H]
- Required biology studies [I]
- Optional biology studies [J]

A Obtain direct bilirubin if total bilirubin is abnormally elevated

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

C 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).

D Metastases should be imaged by the most appropriate modality.

E 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.

F 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.

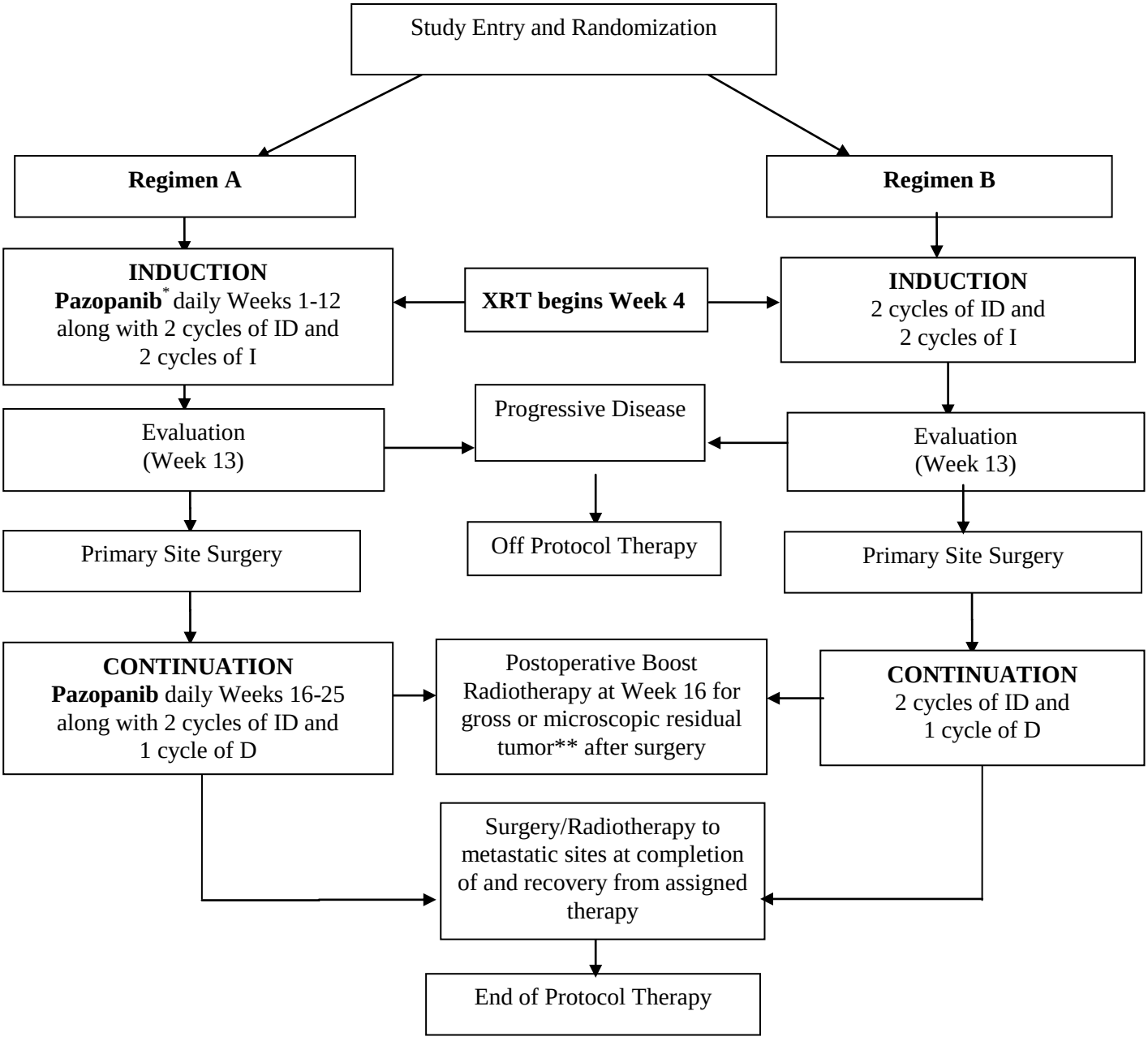
G The pathologic specimen obtained at the time of diagnosis and definitive surgery at Week 13 will be centrally reviewed to assess response to treatment (see Section 14.2).Material is also to be submitted for central review at the time of tumor progression/recurrence and at the development of a second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

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

I 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.

J 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.

EFFICACY PHASE- CHEMOTHERAPY COHORT



* Dose determined in the dose finding phase. 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.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
See Section 15.0

Also see Appendix 13.
Snap Frozen Tissue is requested.
Required:

- Blocks or slides – also see Section 14.2.
- Blood 2.5 ml in a PAXgene RNA tube, 5 ml in EDTA, also see Section 15.1.1