

**COG-ARST0332: Risk-Based Treatment for Pediatric Non-Rhabdomyosarcoma
Soft Tissue Sarcomas NRSTS**

FAST FACTS

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG Policy 7.2). 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. Prior to enrollment on ARST0332, all patients must have been registered via the eRDE system and enrolled on D9902 for central pathology review.
2. A Biopathology Center (BPC) number was assigned as part of the registration process for D9902. Please use this number as part of the labeling information on all specimens sent to the Biopathology Center. If you have a question about a patient's BPC Number, please call the Biopathology Center at (800) 347-2486.
3. Patients must be enrolled on the study once all eligibility requirements have been met and BEFORE protocol chemotherapy and/or radiotherapy begins. The first biopsy that obtained tissue adequate to determine the diagnosis must have been performed within 12 weeks (84 days) of study enrollment in all patients. Patients enrolled on Treatment Arms A and C must be enrolled within 42 days of the last tumor resection (regardless of whether tumor was present in the surgical specimen). Patients enrolled on Treatment Arm B must begin radiotherapy within 42 days of the last tumor resection. Patients enrolled on Treatment Arms C and D must start Week 1 chemotherapy within 14 calendar days of enrollment on study. An exception will be made for patients enrolled on Arm C who receive brachytherapy. These patients should begin Week 1 chemotherapy within 2 weeks of completion of brachytherapy.
4. Age < 30 years at the time of the biopsy that established the diagnosis of NRSTS.
5. Patients < 2 years of age with infantile fibrosarcoma are ineligible.
6. Newly diagnosed NRSTS, **confirmed by central pathology review via enrollment on D9902**, of the following histologic types:
 - "Intermediate (rarely metastasizing)" or "malignant" tumors listed below, as defined in the WHO Classification of Soft Tissue Tumours (see Appendices IIA and IIB for the complete WHO classification):
 - Adipocytic tumours – Liposarcoma (dedifferentiated, myxoid, round cell, pleomorphic, mixed-type, not otherwise specified)
 - Fibroblastic/myofibroblastic tumours – Solitary fibrous tumour, hemangiopericytoma, low grade myofibroblastic sarcoma, myxoinflammatory fibroblastic sarcoma, adult fibrosarcoma, myxofibrosarcoma, low grade fibromyxoid sarcoma (or hyalinizing spindle cell tumour), sclerosing epithelioid fibrosarcoma
 - So-called fibrohistiocytic tumours – plexiform fibrohistiocytic tumour, giant cell tumour of soft tissues, pleomorphic 'MFH'/undifferentiated pleomorphic sarcoma, giant cell 'MFH'/undifferentiated pleomorphic sarcoma with giant cells, inflammatory 'MFH'/undifferentiated pleomorphic sarcoma with prominent inflammation
 - Smooth muscle tumours – Leiomyosarcoma
 - Pericytic (perivascular) tumours – Malignant glomus tumour, glomangiosarcoma
 - Vascular tumours – Angiosarcoma of soft tissue
 - Chondro-osseous tumours – Mesenchymal chondrosarcoma, extraskeletal osteosarcoma
 - Tumours of uncertain differentiation – Angiomatoid fibrous histiocytoma, ossifying fibromyxoid tumour, myoepithelioma, parachordoma, synovial sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma of soft tissue, extraskeletal myxoid chondrosarcoma ("chordoid type"), malignant mesenchymoma, neoplasms with perivascular epithelioid cell differentiation (PEComa), clear cell myomelanocytic tumour, intimal sarcoma
 - Malignant peripheral nerve sheath tumor
 - Dermatofibrosarcoma protuberans – Only tumors that are both non-metastatic and grossly resected. Patients with non-metastatic unresected and metastatic dermatofibrosarcoma protuberans are NOT eligible.
 - Embryonal sarcoma of the liver
 - 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")

The diagnosis of NRSTS **must be confirmed by central pathology review via enrollment on the COG study D9902**. Enrollment on D9902 must occur prior to or on the same date as enrollment on ARST0332. Treatment may begin before the central pathology review process is complete as long as the patient has been enrolled on D9902 and ARST0332. Patients found to have an ineligible diagnosis on central pathology review will be declared ineligible for ARST0332. If there is any question of whether the patient meets the pathologic eligibility criteria for ARST0332, delaying enrollment until central pathology review on D9902 is complete should be considered so that the patient will not be declared ineligible. Similarly, if there is uncertainty about the POG grade of the tumor and this factor will influence the treatment assignment, delaying enrollment on ARST0332 until the central pathology review information from D9902 is available should be considered so that the patient does not begin treatment on the incorrect treatment arm.

7. Gross total resection of the primary tumor prior to enrollment on ARST0332 is required *except* in the case of:
 - Non-metastatic high grade tumor > 5cm in maximal diameter and gross or microscopic residual tumor is anticipated following resection
 - Tumor of either high or low grade that cannot be grossly excised without unacceptable morbidity
 - High grade tumor with metastases
8. Patients with metastatic low grade tumors whose disease at all sites is amenable to gross resection must undergo gross excision of all sites of tumor involvement prior to study enrollment. See Section 14.2 for guidelines for surgical therapy prior to study enrollment.
9. Patients who have experienced tumor recurrence after a gross total tumor resection are NOT eligible.
10. Patients with non-metastatic and metastatic disease are eligible.
11. Patients with clinical or radiologic evidence of regional lymph node enlargement and those with epithelioid sarcoma or clear cell sarcoma must undergo sentinel lymph node biopsies or lymph node sampling to confirm the status of regional lymph nodes prior to study enrollment (see Section 14.2.5 for lymph node sampling guidelines). An exception will be made in cases where the study radiologist reviews the imaging and indicates that a biopsy is not needed to confirm that the patient has lymph node involvement. If lymph node biopsies are positive for tumor (or the lymph nodes are classified as positive by the study radiologist), formal lymph node dissection must be done either before study entry or, in Treatment Arm D patients only, at the time of Week 13 definitive surgery. In patients to be enrolled on Treatment Arm C, lymph node dissection **must** be performed prior to study enrollment.
12. Patients who will be categorized as having metastatic disease **must** undergo a biopsy to confirm the presence of metastatic tumor if all metastases are < 1 cm in maximal diameter (see Section 14.2.3). An exception will be made in cases where the study radiologist reviews the imaging and indicates that a biopsy is not needed to confirm that the patient has metastatic disease.
13. Lansky performance status score ≥ 50 for patients ≤ 16 years of age.
Karnofsky performance status score ≥ 50 for patients >16 years of age.
14. No prior anthracycline (e.g., doxorubicin, daunorubicin) or ifosfamide chemotherapy if patient will be enrolled on Treatment Arm C or D. No prior radiotherapy to tumor-involved sites. Prior use of steroids is acceptable. Patients previously treated for cancer are eligible provided they meet the prior therapy requirements.

15. Patients eligible for the observation arm (Treatment A) are not required to meet the organ function requirements listed below.

Patients eligible for the radiotherapy arm (Treatment B) are required to have adequate organ function in the organs that will be within the radiotherapy field. All of these patients must meet the criteria for bone marrow function.

Patients eligible for the chemotherapy treatment arms (Treatments C and D) must meet all organ function requirements.

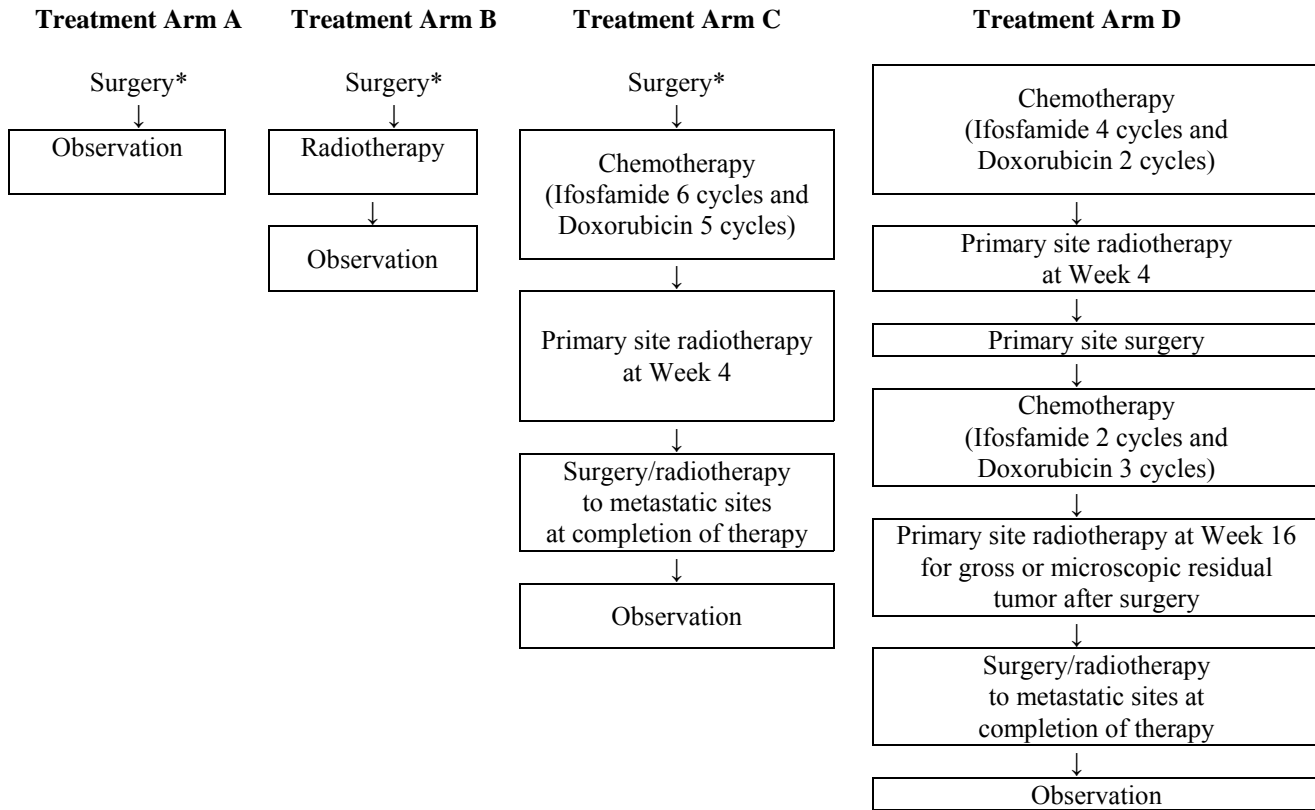
- Patients must have adequate bone marrow function defined as:
 - Hemoglobin \geq 10 g/dL (may be supported by transfusion)
 - Absolute neutrophil count \geq 1000/ μ L
 - Platelet count \geq 100,000/ μ L
- Patients must have adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR \geq 70mL/min/1.73 m² or
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
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
\geq 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Patients with urinary tract obstruction by tumor must meet the renal function criteria listed above AND must have unimpeded urinary flow established via decompression of the obstructed portion of the urinary tract.
 - Patients must have adequate liver function defined as:
 - Total bilirubin \leq 1.5 x upper limit of normal (ULN) for age
 - Patients must have adequate cardiac function defined as:
 - Shortening fraction of \geq 24% by echocardiogram *OR*
 - Ejection fraction of \geq 50% by radionuclide angiogram.
 - Patients must have adequate pulmonary function defined as:
 - No evidence of dyspnea at rest, no exercise intolerance, and in those with respiratory symptoms, a resting pulse oximetry reading $>$ 94% on room air.
16. Patient must have a life expectancy of at least 3 months with appropriate therapy.
17. Female patients of childbearing age must have a negative pregnancy test prior to study enrollment. Sexually active patients of childbearing potential must agree to use effective contraception during and for at least 1 month after treatment is completed.
18. Lactating female patients who are eligible for Treatment Arm C or D must agree not to breastfeed during treatment and for a period of 1 month following completion of treatment.

INDUCTION STRATIFICATION FACTORS:



*Surgery will be done prior to study enrollment

Progressive Disease (PD) at any time during study therapy will take the patient off protocol therapy

REQUIRED OBSERVATIONS:

Varies with arm of study. See Section 7.0.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

Per D9902.

BIOLOGY REQUIREMENTS:

The Diagnostic Tumor Biopsy

Diagnostic material may be obtained via incisional biopsy or multiple core needle biopsies. Fine needle aspiration biopsy is not acceptable to establish the diagnosis. Core needle biopsies are prone to sampling error, which may make histologic subclassification difficult and may result in an underestimate of the tumor grade. Thus, sufficient tissue must be obtained. Incisional biopsy is the preferred approach at all anatomic sites, particularly in the extremities, chest wall, and abdominal wall. Within the thoracic and pelvic cavities, and in the head and neck, multiple core needle biopsies are acceptable. The minimum recommended sampling is 8 core biopsies of 2 cm in length. The surgeon should sample each of the 4 quadrants of the tumor. Care should be taken to prevent penetration of the needle through the tumor into unaffected soft tissues.

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 (via enrollment on the D9902 soft tissue sarcoma biology study).