

**COG ARST0531: Randomized Study of Vincristine, Dactinomycin and Cyclophosphamide (VAC)  
versus VAC Alternating with Vincristine and Irinotecan (VI)  
for Patients with Intermediate-Risk Rhabdomyosarcoma (RMS).**

***FAST FACTS***

**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. **Prior to enrollment on ARST0531 all patients must have been registered via the eRDE system AND enrolled on D9902 for central pathology review.**
2. Patients must be enrolled on ARST0531 BEFORE treatment begins. The date protocol therapy is projected to start must be no later than 5 calendar days after the date of study enrollment.
3. Patients must start protocol therapy within 42 days of initial surgical procedure (including biopsy) that provided the definitive diagnosis.
4. Patients must be age < 50 years at the time of enrollment.
5. Patients with newly diagnosed embryonal RMS, botryoid or spindle cell variants of embryonal RMS, ectomesenchymoma, or alveolar RMS are eligible for this study. Enrollment on D9902 to confirm local histologic diagnosis with central pathology review is required for all patients. Every effort should be made to enroll patients on D9902 as soon as possible after the diagnostic procedure. Tissue must be submitted for pathologic review within 2 days of patient enrollment on D9902, in order to confirm patient eligibility. Rapid central review of the diagnostic material as part of D9902 will be completed and reported back to the treating institution within 14 days of study enrollment on D9902. Patients may be enrolled on ARST0531 and start protocol treatment prior to receipt of central pathology review results.

All patients will be evaluated at enrollment for Stage and a Clinical Group (See Appendix II, Staging classification; Appendix III, Grouping classification; Appendix IV, Anatomic definitions of parameningeal, orbit and other head and neck sites for use in pre-treatment staging; and Appendix V, Designation of the primary site for use in pre-treatment staging). Note that Stage and Clinical Group designation assigned at the time of enrollment on study remains unchanged regardless of subsequent treatment.

Patient must have Intermediate-risk RMS defined as:

- a. Embryonal, botryoid, or spindle cell RMS, or ectomesenchymoma: Stage 2 or 3 and Group III  
OR
- b. Alveolar RMS: Stage 1-3 and Group I-III

Change in histologic diagnosis by central pathology review will require protocol reassignment and patient re-consent. A patient previously enrolled on ARST0331 (low-risk study) based on institutional pathology diagnosis of embryonal RMS and found on Rapid Central Review of pathology to have alveolar histology fit the above criteria. Such a patient must be reassigned to ARST0531 by Week 3 of therapy. Similarly, a patient enrolled on ARST0531, based on institutional diagnosis of alveolar RMS, must be reassigned and re-consented to ARST0331 if Central Review changes the diagnosis to embryonal RMS (or variant) and the patient Stage and Group qualifies for the low risk study. If the results of the Rapid Review are not available prior to the scheduled start of Week 3 therapy, institutions should contact the STS Pathology Center (Phone: 614 722-2810 or FAX: 614 722-2897) to confirm histologic type.

- Para testicular tumors  
Staging ipsilateral retroperitoneal lymph node dissection (SIRLND) is required for all patients  $\geq 10$  years of age with paratesticular tumors and for patients < 10 years with clinically or radiographically involved lymph nodes (except when extensive lymph node involvement, defined as two or more lymph nodes > 2 cm in dimension, is identified by imaging studies).
- Extremity tumors  
Regional lymph node sampling or sentinel lymph node procedure is required for histologic evaluation in patients with extremity tumors (See Sections 14.4.2 and 14.5.4).
- Clinically or radiographically enlarged nodes  
Clinically or radiographically enlarged nodes should be sampled for histologic evaluation (See Section 14.4.2).
- Detection of metastasis by optional FDG PET (not required for study enrollment)  
FDG PET may detect abnormalities suggestive of metastasis not identified by bone scan, CT, or bone marrow aspiration/biopsy. The prognostic significance of FDG PET-detected abnormalities is not clear. FDG PET-detected

abnormalities MUST be confirmed to be metastases by an additional imaging modality (such as MRI or CT) OR pathologic confirmation. Unless FDG PET abnormalities are confirmed by another imaging modality or biopsy, FDG PET abnormalities will NOT be considered evidence of metastasis.

6. Patients must have a performance status of 0, 1, or 2. The Lansky performance score should be used for patients < 10 years and the Karnofsky performance score for patients ≥ 10 years.
7. Patients who have received prior chemotherapy (excluding steroids) or radiation therapy, except for patients transferring from ARST0331 (low-risk study), are not eligible.
8. Concomitant Medications Restrictions  
Strong inhibitors of cytochrome P450 3A4 are known to alter vincristine metabolism, leading to increased vincristine neurotoxicity. Strong stimulators of cytochrome P450 3A4 alter irinotecan metabolism (leading to lower systemic exposure and reduced efficacy of irinotecan). Strong inhibitors or stimulators of cytochrome P450 3A4, including azole antifungals (such as fluconazole, voriconazole, itraconazole, ketoconazole) rifampin, phenytoin, phenobarbital, carbamazepine, and St. John’s wort, should all be avoided or used with great caution. Aprepitant is known to interact with CYP3A4 and is not permitted during cyclophosphamide chemotherapy.
9. Organ Function Requirements

a. Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m<sup>2</sup> 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
≥ 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.

b. Adequate liver function defined as:

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

c. Adequate bone marrow function defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 750/μL
- Platelet count ≥ 75,000/μL (transfusion independent)

d. No evidence of uncontrolled infection

9. Other criteria

- a. Patients must be able to undergo Radiation Therapy, if necessary, as specified in the protocol.
- b. Female patients of childbearing potential must have a negative pregnancy test.
- c. Female patients who are breast feeding must agree to stop breast feeding.
- d. Sexually active patients of childbearing potential must be willing to use effective contraception during therapy and for at least 1 month after treatment is completed

**INDUCTION STRATIFICATION FACTORS:**

Randomization will take place at the time a patient is enrolled On Study via eRDE. Patients will be assigned to either VAC, or VAC/VI. Randomization will be stratified by 1) embryonal histology, Stage 2 or Stage 3, Clinical Group III; 2) alveolar histology, Stage 1 or Group 1; 3) alveolar histology, Stage 2/3, Group II/III.

**REQUIRED OBSERVATIONS:****Pre-Study and On Therapy Evaluations**

- History, Physical Exam
- CBC/Differential/Platelets
- Urinalysis (pre CPM only)
- Bun, creatinine, SGPT, bili, alk phos
- Lytes, Ca, phosphorus
- LP with cytology <sup>1,2</sup>
- Bilateral bone marrow aspiration/biopsy <sup>1</sup>
- MRI or CT primary site
- CT chest <sup>1</sup>
- CT retroperitoneum, liver <sup>1,3</sup>
- Lymph node biopsy <sup>4</sup>
- Pregnancy test <sup>5</sup>
- Bone Scan <sup>1</sup>
- Performance status <sup>6</sup>
- FDG PET (optional)
- Radiation therapy consult
- Blood for pharmacogenomics (optional, Section 16.1)

1. If marrow, lung, bone, or distant nodal/soft tissue metastases are found, or if CSF cytology is positive, enter patient on protocol for Stage 4 disease
2. For parameningeal tumors, including orbital site with parameningeal extension and paraspinal tumors
3. For GU tumors and tumors below the diaphragm. If omental implants are present or if malignant cells are present in pleural or peritoneal fluid, the patient has Stage 4 disease.
4. Required only for paratesticular ( $\geq 10$  years of age), extremity, or if enlarged nodes on clinical exam or imaging
5. For females of childbearing age
6. The Lansky performance score should be used for patients  $< 10$  year and the Karnofsky performance scale for patients  $\geq 10$  years.

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.

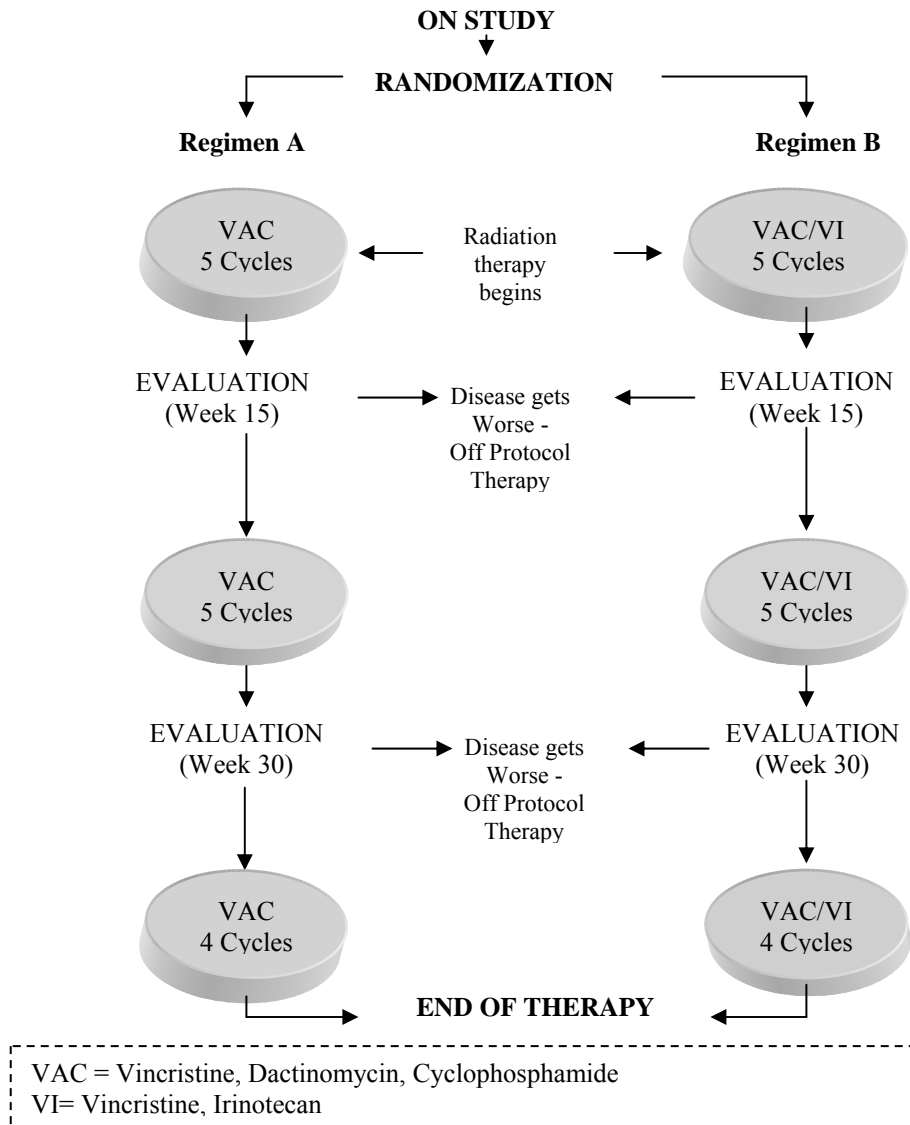
**SPECIMEN REQUIREMENTS:**

Prior enrollment on D9902 is required.

**RAPID CENTRAL REVIEW:**

All patients enrolling on this protocol require Rapid Central Review as part of prior enrollment on D9902.

**TREATMENT PLAN:**  
**(One cycle is three weeks long)**



For more information, contact GRCOP at 616.391.1230.