COG- ARST2531, A Randomized Phase 3 Study to Compare VAC (Higher Cyclophosphamide Dose and Intensity) versus VAC/VI (Lower Cyclophosphamide Dose and Intensity) Plus Maintenance Therapy in Patients with Newly Diagnosed Intermediate-Risk Rhabdomyosarcoma

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

Timing Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment.

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. Laboratory Studies
All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.

The following laboratory studies must be repeated prior to the start of protocol therapy if > 7 days have elapsed from their most recent prior assessment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment

If the result of a laboratory study that is repeated at any time post-enrollment and prior to the start of protocol therapy is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

____2. Clinical Studies
Clinical studies (eg, cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary).

____3. Disease/Staging Imaging
Disease/staging imaging studies, if applicable, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary).

The CIRB has determined that assent of children age ___ and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix _.

INCLUSION CRITERIA:

- Age
  Patient must be ≤ 50 years of age at the time of enrollment.

- Diagnosis
  Patients with newly diagnosed soft tissue RMS of any subtype, except adult-type pleomorphic, based upon institutional histopathologic classification, are eligible to enroll on the study based upon FOXO1 fusion status,

Stage, IRS Group, and age, as below. FOXO1 fusion status must be determined as outlined in Section 3.2.2.1 prior to enrollment.

- FOXO1 fusion negative (FN)
  - Stage 2/3, Group III
  - Stage 4, Group IV, < 10 years old
- FOXO1 fusion positive (FP)
  - Stages 1-3, Groups I-III

See Appendix III and Appendix IV for Stage and Grouping information.

FOXO1 Fusion Status
FOXO1 status results must be available to enroll.

All patients will undergo institutional pathology review and institutional FOXO1 fusion determination **regardless of histology** prior to enrollment.

FOXO1 status may confirmed by cytogenetic, FISH, or next generation sequencing techniques. FOXO1 fusion results should be SUBMITTED as an upload to RAVE at study enrollment because this information is required for randomization.

Please note the following:
• Institutional PAX3 vs. PAX7 determination is not required but should be submitted if available. Institutional FOXO1 testing may be performed at a contract or commercial lab as long as reports can be submitted and uploaded to RAVE. Additional molecular pathology reports, including the MCI report, are not required but should be submitted if available.

• Patients who are < 10 years old with distant metastatic disease (Stage 4) who have institutional molecular testing indicating FN RMS but are later found to have FP RMS by MCI or other testing will be considered to have metastatic FP disease and will go off study (Section 8.2).

Lymph Node Sampling
Appropriate lymph node sampling based on primary site of disease is required**.** See Section 13.4.3

Performance Level
Patients must have a performance status of Lansky performance status score ≥ 50 for patients ≤ 16 years of age or Karnofsky performance status score ≥ 50 for patients >16 years of age.

See Appendix IX for details.

Organ Function Requirements
Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/µL - Platelet count ≥ 75

Adequate renal function defined as:
• For pediatric patients < 18 years of age:
- A serum creatinine based on age/sex 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[80] utilizing child length and stature data published by the CDC.

OR - a 24-hour urine Creatinine clearance ≥ 50 mL/min/1.73 m2

OR - a GFR ≥ 70 mL/min/1.73 m2. GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard).

Patients with an elevated serum creatinine due to obstructive hydronephrosis secondary to tumor are still eligible. However, patients with urinary tract obstruction by tumor must have unimpeded urinary flow established diversion (ie, percutaneous nephrostomies or ureteric stents) of the urinary tract.

For adult patients (aged 18 years or older):

Creatinine clearance ≥ 50 mL/min, as estimated by the Cockcroft and Gault formula or as a 24-hour urine collection. Estimated creatinine clearance is based on actual body weight.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg}\dagger}{72 \times \text{creatinine (mg/dL)}}$$

Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the ideal body weight (IBW).

An online calculator is available through the National Kidney Foundation at
https://www.kidney.org/professionals/kdoqi/gfr_calculatorcoc

Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- If there is evidence of biliary obstruction by tumor, then total bilirubin must be < 3 x ULN for age
- SGPT (ALT) ≤ 135 U/L*

**Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L.*

HIV Status
Known HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

EXCLUSION CRITERA:

Pre-existing conditions
Patients with evidence of uncontrolled infection are not eligible.

Previous or concurrent cancer(s) that is/was being treated with chemotherapy and/or radiation.

Note: Surgical resection alone of previous or concurrent cancer(s) is allowed.

Patients with central nervous system involvement of RMS as defined below:

- Malignant cells detected in cerebrospinal fluid
- Intra-parenchymal brain metastases separate and distinct from primary tumor (i.e., direct extension from parameningeal primary tumors is allowed)
- Diffuse leptomeningeal disease

Patients with known Charcot-Marie-Tooth disease.

Prior Therapy
Patients who have received any chemotherapy (excluding steroids) and/or radiation therapy for RMS prior to enrollment. Note: the following exception:

• Patients requiring emergency radiation therapy for life threatening complications of tumor burden due to RMS. These patients are eligible, provided they are consented to ARST2531 prior to administration of radiation. (See Section 17.3 for radiation therapy guidelines).

Note: Patients who have received or are receiving chemotherapy or radiation for non-malignant conditions (eg, autoimmune diseases) are eligible. Patients must discontinue chemotherapy for non-malignant conditions prior to starting protocol therapy.

Pregnancy and Breastfeeding

Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential. 3.2.9.2 3.2.9.3

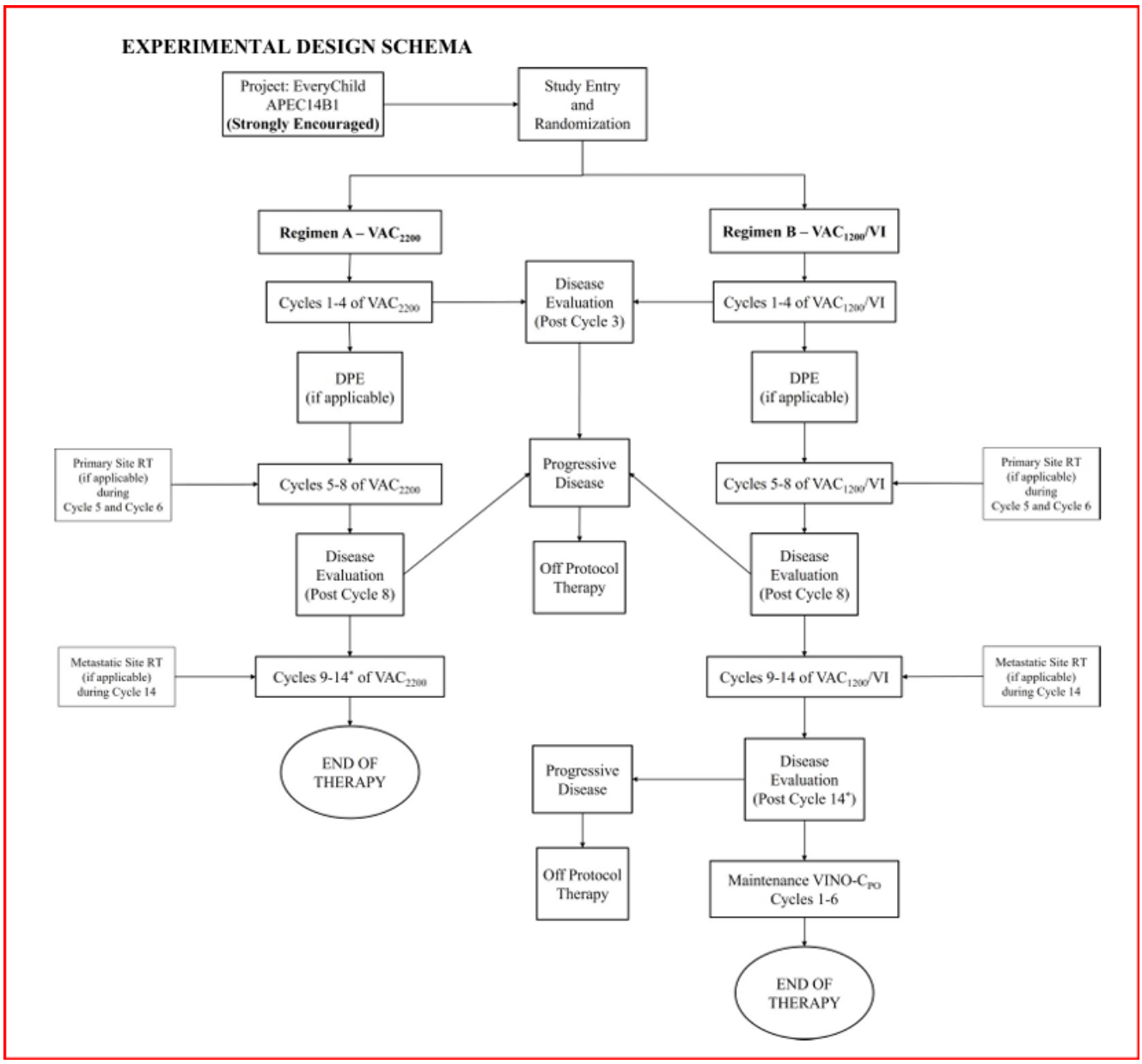
Lactating females who plan to breastfeed their infants.

Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

TREATMENT PLAN:

Overview of Treatment Plan All patients will be stratified by tumor size and fusion status and randomized at study entry to receive Regimen A (VAC, cumulative cycloPHOSphamide dose of 30.8 grams/m2) or Regimen B (VAC/VI Induction, cumulative cycloPHOSphamide dose of 8.4 grams/m2 plus vinorelbine/oral cycloPHOSphamide Maintenance, cumulative dose of 4.2 grams/m2 (total cumulative dose of 12.6 grams/m2 for Regimen B)). Patients randomized to Regimen A will receive 42 weeks of VAC therapy without maintenance therapy. Patients randomized to Regimen B will receive 42 weeks of VAC/VI therapy plus 24 weeks of vinorelbine/oral cycloPHOSphamide maintenance therapy.

See Section 15 for Optional Studies.



Required Observations – Regimen A – VAC, Cycles 1-4

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam with vital signs, height and weight.

b. CBC, differential and platelets. Note: Obtain additional CBCs as needed for good patient care.

c. Electrolytes, BUN, and urinalysis

d. Creatinine, bilirubin, AST, & ALT

e. Bilateral bone marrow aspirate/biopsy. Prior to Cycle 1 and after Cycle 3 only. Not required for patients with FOXO1 fusion negative RMS who have uninvolved lymph nodes clinically or by imaging and do not have distant metastases. Note: Cycle 3 requirement only if previous asp/bx abnormal or if clinically indicated; Cycle 3 asp/bx may be done between Day 15 and prior to the start of the next cycle.

f. MRI or CT of primary site and regional nodal basin. Prior to Cycle 1 and after Cycle 3 only. MRI preferred for head and neck, extremity, paraspinal, abdomen, pelvis and GU sites. CT may be used for regional nodes. Cycle 3 scan may be done between Day 15 and prior to the start of the next cycle. Note: Baseline and Cycle 3 images must be submitted for retrospective central review. See Section 16.2.2 for instructions.

g. CT Chest. Prior to Cycle 1 and after Cycle 3 only. May be omitted if FDG-PET is performed. Note: Cycle 3 requirement only if positive for lung metastasis at baseline; may be done between Day 15 and prior to start of the next cycle. Note: Baseline and Cycle 3 images must be submitted for retrospective central review. See Section 16.2.2 for instructions.

h. FDG-PET scan with diagnostic quality CT. Prior to Cycle 1 and after Cycle 3 only. **Optional** and if available at treating institution. Cycle 3 scan may be done between Day 15 and prior to the start of the next cycle. Note: Baseline and Cycle 3 images must be submitted for retrospective central review. See Section 16.2.2 for instructions.

i. Bone scan. Prior to Cycle 1 and after Cycle 3 only. May be omitted if FDG-PET is performed. Not required for patients with FOXO1 fusion negative RMS who have uninvolved lymph nodes clinically or by imaging and do not have lung metastases. Note: Cycle 3 requirement only if previous bone scan abnormal or if clinically indicated. Cycle 3 scan may be done between Day 15 and prior to start of the next cycle. See Section 16.2.2 for instructions.

j. CSF evaluation. Prior to Cycle 1 only. Cerebrospinal fluid cytology required only for parameningeal tumors, including orbital site with parameningeal extension with intracranial extension or paraspinal tumors with dural involvement.

k. Lymph node biopsy. Prior to Cycle 1 only. Required for extremity tumors and paratesticular tumors in patients ≥ 10 years of age, regardless of FOXO1 fusion status. Strongly recommended in all patients with FOXO1 fusion-positive tumors and in those with involved nodes clinically or by imaging regardless of FOXO1 fusion status. See Section 13.4.3.3.

l. Pregnancy test. Required prior to Cycle 1 for females that show signs of puberty or attained menarche, then per institutional standards.

m. Fertility counseling. (Strongly recommended for all patients.) Cycle 1 only. See Section 4.1.4.

n. Household Material Hardship questionnaire (consent required). Single collection between enrollment and Cycle 3, Day 1. See Section 18.1.

o. Blood for banking in Streck tubes (strongly recommended; consent required). Initial sample must be collected within 7 days before Cycle 1, Day 1. Day 8 collection for Cycle 1 only. Day 1 collection for Cycles 2 and 3. See Section 15.1.3.3.

p. Blood for banking in EDTA (consent required). Cycle 4 only. See Section 15.1.3.2.

q. Blood for gonadal hormone level studies (consent required). Cycle 1 only. See Section 15.1.1.

r. Post-operative imaging of primary site after Cycle 4 is required only for patients who undergo DPE. See Section 16.2.1.

Regimen A - VAC, Cycles 1-4