

COG-ARST2031: A Randomized Phase 3 Trial of Vinorelbine, Dactinomycin, and Cyclophosphamide (VINO-AC) Plus Maintenance Chemotherapy with Vinorelbine and Oral Cyclophosphamide (VINO-CPO) vs Vincristine, Dactinomycin and Cyclophosphamide (VAC) plus VINO-CPO Maintenance in Patients with High Risk Rhabdomyosarcoma (HR-RMS)

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. Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

___ 2. 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.

___ 3. All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

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.

___ 4. 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.

___ 5. 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).

___ 6. 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).

Inclusion Criteria

___ 7. Age

Patients must be ≤ 50 years of age at the time of enrollment.

___ 8. Diagnosis

Patients with newly diagnosed RMS of any subtype, except adult-type pleomorphic, based upon institutional

histopathologic classification are eligible to enroll on the study based upon Stage, Group, and age, as below. FOXO1 fusion status must be determined as outlined in [Section 3.3](#) by Week 4 (Day 28) of therapy.

9. RMS types included under ERMS include those classified in the 1995 International Classification of Rhabdomyosarcoma (ICR) as ERMS (classic, spindle cell, and botryoid variants), which are reclassified in the 2020 WHO Classification as ERMS (classic, dense and botryoid variants) and spindle cell/sclerosing RMS (encompassing the historical spindle cell ERMS variant and the newly recognized sclerosing RMS variant).³⁸ Classification of ARMS in the 2020 WHO Classification is the same as in the ICR and includes classic and solid variants.
- ERMS
 - (a) Stage 4, Group IV, ≥ 10 years of age
 - ARMS
 - (a) Stage 4, Group IV

Patients will be eligible to remain on protocol therapy based upon Stage, Group, and age. See [Appendix III](#) and [Appendix IV](#) for Stage and Grouping information.

10. Bone marrow metastatic disease is based on morphologic evidence of RMS based on H&E stains. In the absence of morphologic evidence of marrow involvement on H&E, patients with bone marrow involvement detected ONLY by flow cytometry, RT-PCR, FISH, or immunohistochemistry will NOT be considered to have clinical bone marrow involvement for the purposes of this study.

11. Organ Function Requirements

- Adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR ≥ 70 mL/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
≥ 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
 - If there is evidence of biliary obstruction by tumor, then total bilirubin must be < 3 x ULN for age.

Assent: The required age of assent is 14.

EXCLUSION CRITERIA:

- ___ 1. Pre-existing conditions
 - Patients with evidence of uncontrolled infection are not eligible.
 - RMS that is considered a second malignancy and previous cancer(s) that were treated with chemotherapy and/or radiation. Surgical resection alone of previous cancer(s) is allowed.
 - Patients with central nervous system involvement of RMS as defined below:
 - Malignant cells detected in cerebrospinal fluid
 - Intra-parenchymal brain metastasis separate and distinct from primary tumor (i.e., direct extension from parameningeal primary tumors is allowed).
 - Diffuse leptomeningeal disease
- ___ 2. 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 RMS. These patients are eligible, provided they are consented to ARST2031 prior to administration of radiation. (See [Section 17.0](#) for radiation therapy guidelines.)
 - Note: Patients who have received or are receiving chemotherapy or radiation for non-malignant conditions (e.g. autoimmune diseases) are eligible. Patients must discontinue chemotherapy for non-malignant conditions prior to starting protocol therapy.
 - Vincristine and vinorelbine are sensitive substrates of CYP450 3A4 isozyme. Patients must not have received drugs that are moderate to strong CYP3A4 inhibitors and inducers within 7 days prior to study enrollment. Please see [Section 4.1.3](#) for the concomitant therapy restrictions for patients during treatment.
- ___ 3. 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.
 - 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.
- ___ 4. **FOXO1 Fusion Status**

All patients will undergo institutional pathology review and FOXO1 fusion determination regardless of histology. If institutions are not able to comply with local fusion testing, the patient will be removed from study for failure to comply with protocol requirement.

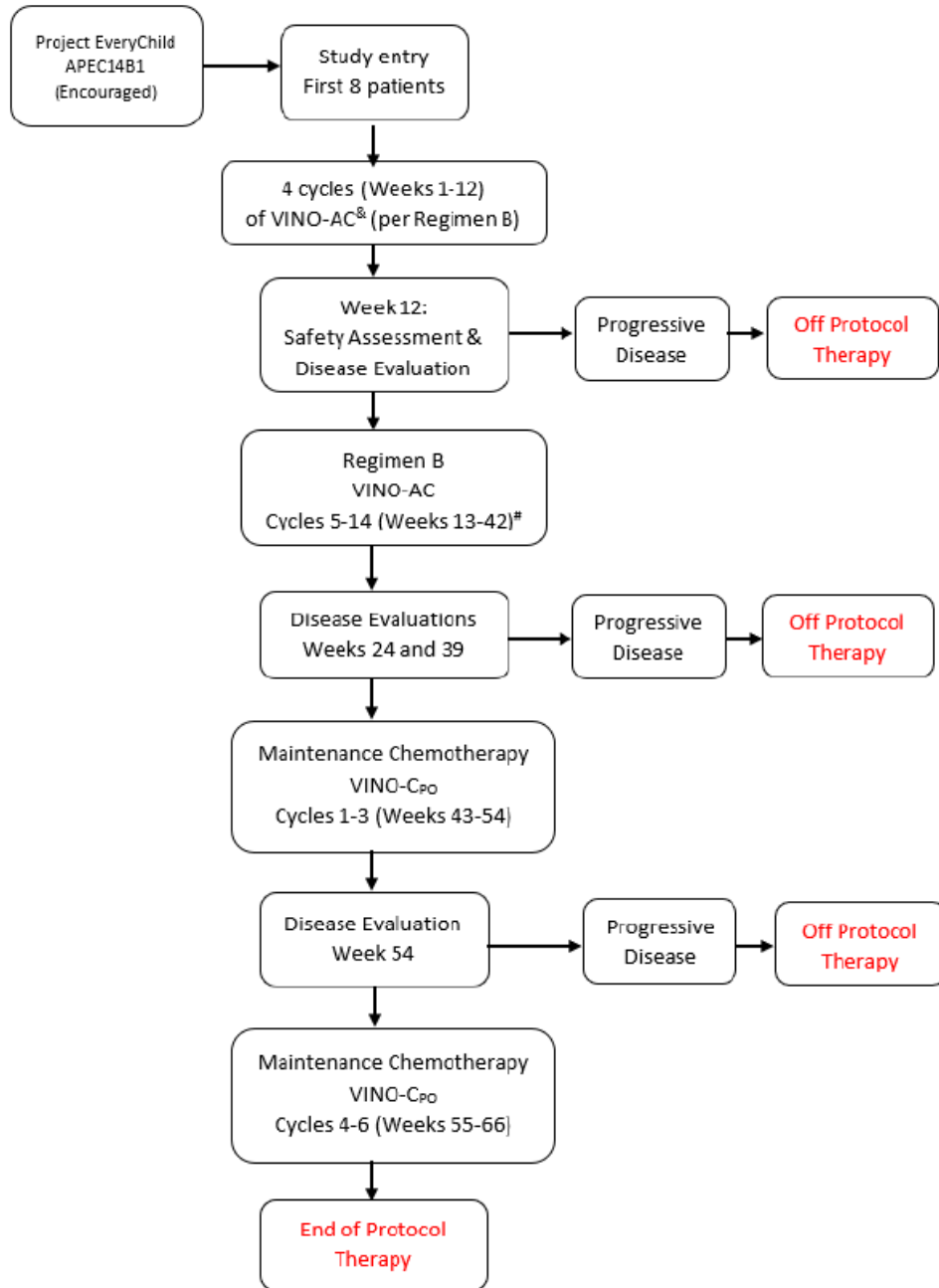
REQUIRED OBSERVATIONS:

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

NOTE: All patients will undergo institutional pathology review and FOXO1 fusion determination. **FOXO1 status results must be available by Week 4 (Day 28) of therapy and submitted as an upload to RAVE as soon as possible.** Patients who are FOXO1 fusion negative and < 10 years old will be removed from study. See [Section 3.3](#).

- a. Physical exam with vital signs, height and weight.
- b. CBC, differential and platelets. Required at beginning of each cycle. Recommended weekly for good patient care.
- c. Electrolytes, BUN, Creatinine, Ca²⁺
- d. AST, ALT, Bilirubin, Total Protein, Albumin, Urinalysis
- e. Bilateral BM Asp/Bx. Prior to Cycle 1 and then Day 15 of Cycle 4 only. Note: Cycle 4 requirement is only if previous asp/bx is abnormal or if clinically indicated, and may be done between Day 15 and prior to the start of the next cycle.
- f. Bone Scan. May be omitted if FDG-PET is performed. Prior to Cycle 1 and then Day 15 of Cycle 4 only. Note: Cycle 4 requirement is only if previous scan is abnormal or if clinically indicated, and may be done between Day 15 and prior to the start of the next cycle.
- g. FDG-PET Scan. Optional and if available at treating institution. May be omitted if bone scan is performed. Prior to Cycle 1 and then Day 15 of Cycle 4 only. Note: Cycle 4 requirement is only if previous scan is abnormal or if clinically indicated, and may be done between Day 15 and prior to the start of the next cycle.
- h. MRI or CT of primary site. MRI preferred for head and neck, extremity, paraspinal, abdomen, pelvis and GU (excludes paratesticular where ultrasound is sufficient). Prior to Cycle 1 and then Day 15 of Cycle 4 only. Cycle 4 scan may be done between Day 15 and prior to the start of the next cycle.
- i. CT chest. Prior to Cycle 1 and then Day 15 of Cycle 4 only. Cycle 4 scan may be done between Day 15 and prior to the start of the next cycle.
- j. Pregnancy test. Required for females that show signs of puberty or attained menarche, and then per institutional standard thereafter. Cycle 1 only.
- k. Radiation consult. Recommended as soon as possible after diagnosis for appropriate planning. Cycle 1 only.
- l. Fertility counseling (recommended). Cycle 1 only. See [Section 4.1.6](#).
- m. Neurosensory exam (use Balis Score). See [Section 5.2.2.1](#).
- n. Blood for banking (optional). Cycle 1 (within 7 days prior to start of treatment), Cycle 3 (Day 1) and Cycle 4 (Day 15). See [Section 15.1.1](#).
- o. Tissue (Day 1 if available). See [Section 15.1.2](#) for other collection time points.

**TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA – SAFETY RUN-IN PHASE**



VINO-AC: vinorelbine, dactinomycin and cyclophosphamide. **Note:** Patients will receive vincristine on the third week (Day 15) of each cycle.

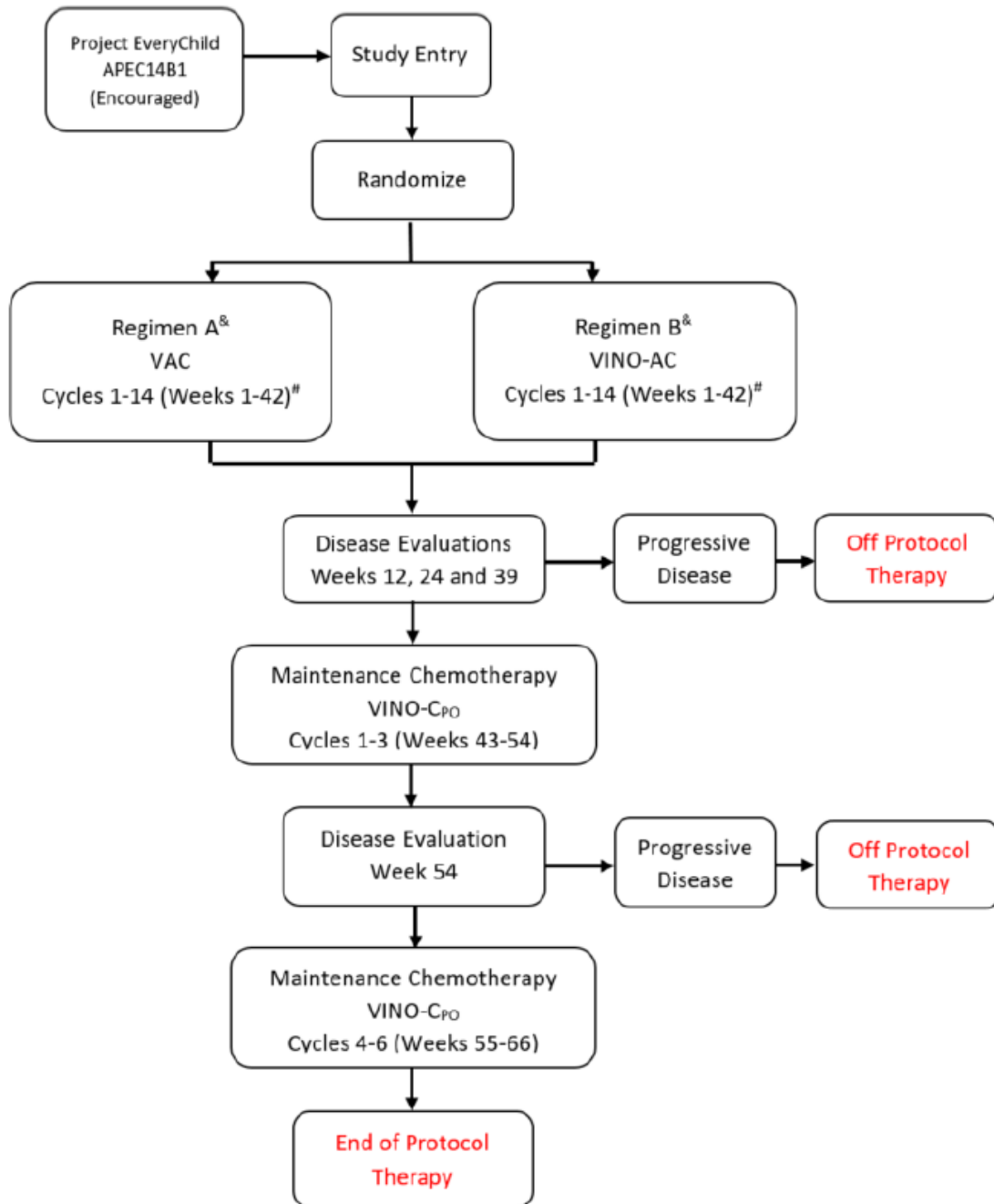
VINO-CPO: vinorelbine and oral cyclophosphamide

&All patients must undergo FOXO1 fusion status determination following diagnosis or study entry. FOXO1 status results must be available by Week 4 (Day 28) of therapy. Patients who are FOXO1 fusion negative and < 10 years old will be removed from study. Patients in whom institutional FOXO1 status cannot be determined within 4 weeks of study entry will also be removed from study.

#Radiotherapy to primary tumor will begin at Cycle 5 (Week 13) and radiotherapy to metastatic sites will start at Cycle 14 (Week 40).

Note: Patients may continue on treatment in the absence of progressive disease or unacceptable toxicity.

EXPERIMENTAL DESIGN SCHEMA – EFFICACY PHASE



VAC: vincristine, dactinomycin and cyclophosphamide

VINO-AC: vinorelbine, dactinomycin and cyclophosphamide. **Note:** Patients will receive vincristine on the third week (Day 15) of each cycle.

VINO-CPO: vinorelbine and oral cyclophosphamide

[&]All patients must undergo FOXO1 fusion status determination following diagnosis or study entry. FOXO1 status results must be available by Week 4 (Day 28) of therapy. Patients who are FOXO1 fusion negative and < 10 years old will be removed from study. Patients in whom institutional FOXO1 status cannot be determined within 4 weeks of study entry will also be removed from study.

[#]Radiotherapy to primary tumor will begin at Cycle 5 (Week 13) and radiotherapy to metastatic sites will start at Cycle 14 (Week 40).

Note: Patients may continue on treatment in the absence of progressive disease or unacceptable toxicity.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.

SPECIMEN REQUIREMENTS:

Pretreatment Blood collection: Peripheral blood samples should be obtained in Streck Cell-Free DNA BCT tubes as follows:

- For patients ≥ 10 kg: Collect 20 mL (10 mL per tube x 2 tubes)
- For patients ≥ 5 kg but < 10 kg: Collect 10 mL (one tube)
- For patients < 5 kg: Research samples will not be collected

Tissue

Tissue submission: At study entry, DPE, relapse, and/or autopsy, submit the following:

- H&E section of all available blocks **and**
- 1-2 representative FFPE block(s)

If blocks absolutely cannot be sent, then submit an additional 20 plus-charged (polarized) unstained sections (4 micron section thickness) from 1-2 representative blocks in addition to the H&E stained slides listed above. The unstained slides from each block must be cut sequentially.

Sample Processing

Unstained slides should be stored in a refrigerator (4°C), until shipped.

Labeling

Blocks and slides must be labeled with the following:

- COG patient ID number
- SPID
- Block number