COG-ARST2032: A Prospective Phase 3 Study of Patients with Newly Diagnosed Very Low-risk and Low-risk Fusion Negative Rhabdomyosarcoma

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. Timing
ALL PATIENTS MUST CONSENT TO AND BE ENROLLED ON PROJECT:EVERYCHILD (APEC14B1) Part A MOLECULAR CHARACTERIZATION, BEFORE ENROLLING ON ARST2032. PATIENTS THAT ENROLL ON ARST2032 PRIOR TO ENROLLING ON APEC14B1 MOLECULAR CHARACTERIZATION ARE INELIGIBLE FOR ARST2032.

___2. Required Enrollment on APEC14B1 and Sample Submissions for Molecular Testing
Patients must be consented and enrolled on APEC14B1, The Project:EveryChild Protocol: A Registry, Eligibility Screening, Biology, and Outcome Study to complete the central molecular testing studies needed to determine *MYOD1* and *TP53* mutation status and *FOXO1* fusion status. The APEC14B1 Part A consent for Molecular Characterization will cover these central molecular testing studies for ARST2032. Confirmation of adequate sample availability for APEC14B1 is required to enroll on ARST2032.

Adequate samples must be provided to the CCDI Molecular Characterization Initiative (MCI) via APEC14B1 to allow for the completion of central molecular testing. Molecular Characterization on APEC14B1 includes enhanced whole exome sequencing (WES) and the RNA Archer Fusion-Plex assay which are needed to determine *MYOD1* and *TP53* mutation status and *FOXO1* fusion status for this study.

Sites must submit specimens via APEC14B1 within one week after patient enrollment on ARST2032. Please see the APEC14B1 Manual of Procedures for details of required sample submission. **NOTE: This submission timeline is necessary to ensure that molecular testing results can be made available by Week 6 of protocol therapy.**

Results from APEC14B1 Molecular Characterization testing must be uploaded to the ARST2032 Rave CRF as soon as they are available, and no later than Week 6 of therapy. The Molecular Characterization results will be accessed by sites via a secure web portal. Please refer to the APEC14B1 Manual of Procedures for complete details. See Section 3.3 for details of how the central molecular testing results may impact subsequent protocol therapy.

___3. Callbacks
Following receipt of Molecular Characterization results, if a patient is found to be eligible for Regimen M (see Section 3.3.2) they will require a separate consent and callback. Callback, performed in OPEN as a Step 2 Registration, should be submitted for eligible subjects who consent to Regimen M.

___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.

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).

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).

___5. Enrollment on APEC14B1 and Consent to Molecular Characterization
All patients must be enrolled on APEC14B1 and consented to the Molecular Characterization Initiative (Part A) prior to enrollment and treatment on ARST2032. See Section 3.1.4 for timing details.

___6. Age
Patients must be ≤ 21 years at the time of enrollment.

___7. Diagnosis
Patients must have newly diagnosed embryonal rhabdomyosarcoma (ERMS), spindle cell/sclerosing RMS, or *FOXO1* fusion negative alveolar rhabdomyosarcoma (ARMS) (institutional *FOXO1* fusion results are acceptable).

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).23 Enrollment in APEC14B1 is required for all patients.

- All patients will be evaluated for Stage and Clinical Group (see Appendices III and IV for Stage and Grouping information). Note that Clinical Group designation assigned at the time of enrollment on study remains unchanged regardless of any second-look operation that may be performed.
  a. Patients will be eligible for the very low-risk stratum (Regimen VA) if they have Stage 1, CG I disease.
  b. Patients will be eligible for the low-risk stratum (Regimen VAC/VA) if they have Stage 1, CG II disease, Stage 2, CG I or II disease, or Stage 1, CG III (orbit only) disease.
- Paratesticular Tumors: Staging ipsilateral retroperitoneal lymph node sampling (SIRLNS) is required for all patients ≥ 10 years of age with paratesticular tumors who do not have gross nodal involvement on imaging.
- Extremity Tumors: Regional lymph node sampling is required for histologic evaluation in patients with extremity tumors (see Appendix III and Appendix IV).
- Clinically or radiographically enlarged nodes must be sampled for histologic evaluation (see Appendix III and Appendix IV).

___8. Performance Level
Patients must have a Lansky (for patients ≤ 16 years of age) or Karnofsky (for patients > 16 years of age) performance status score of ≥ 50. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing performance score. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

___9. Organ Function Requirements

- Adequate bone marrow function defined as:
  - Peripheral absolute neutrophil count (ANC) ≥ 750/µL
  - Platelet count ≥ 75,000/µL (transfusion independent)
- Adequate renal function defined as:
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 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 GFR24 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, and
  - SGPT (ALT) ≤ 135 U/L*
  - If there is evidence of biliary obstruction by the tumor, then the total bilirubin must be < 3 x ULN for age.

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

___10. **Molecular Testing**

All patients on ARST2032 must consent to and complete Molecular Characterization Initiative testing on APEC14B1. These results must be uploaded to the ARST2032 CRF as soon as they are available. This testing is used to determine *FOXO1* fusion status and *MYOD1* and *TP53* mutation status through the CCDI Molecular Characterization Initiative via APEC14B1.

Central molecular testing results should be made available by Week 6* of protocol therapy when tissue is submitted in a timely manner (see Section 3.1.5). See below for details of how the central molecular testing results may impact subsequent protocol therapy. Note: If central molecular testing results are returned after Week 6, patients should remain on the originally assigned regimen.

*If mutation status is determined to be positive by Week 3, patients will transition to Regimen M starting at Week 4 (Cycle 2).

- *FOXO1* Fusion Status
  - Patients who are *FOXO1* positive will be removed from study.
  - If molecular testing yields indeterminate *FOXO1* fusion status results, patient will remain on protocol therapy on the originally assigned regimen.
- *MYOD1* and *TP53* Mutation Status
  - Patients who are *MYOD1*(+) or *TP53*(+) will transfer to Regimen M prior to the start of Week 7 (Cycle 3) therapy. See Section 3.1.5 for callback details. The following findings will be considered mutation positive:
    - Any somatic mutation of *MYOD1* L122R
    - Any Tier I or Tier II somatic alteration of *TP53*
    - Pathogenic germline *TP53*
  - If molecular testing yields indeterminate mutation status results, patient will remain on protocol therapy on the originally assigned regimen.

Assent: The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA

___1. Prior Therapy

- Patients who have received prior chemotherapy and/or radiation therapy for cancer prior to enrollment. Surgical resection alone of previous cancer(s) is permitted.
- Patients who have received 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 is sensitive substrate of the 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.

___2. Patients unable to undergo radiation therapy, if necessary, as specified in the protocol.

___3. Evidence of uncontrolled infection

___4. 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.

REQUIRED OBSERVATIONS:

Required Observations - Regimen VA, Cycles 1-8
All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. APEC14B1 (for molecular characterization). See Sections 3.3 15.1.1and .
b. Physical exam with vital signs, height and weight.
c. Performance status. See Section 3.2.4.
d. Pregnancy test for females of childbearing age.
e. CBC, differential and platelets.
f. Creatinine, bilirubin, AST, & ALT
g. Bilateral BM Asp/Bx. Only for patients with N1 nodal disease.
h. MRI or CT of primary site. Scan may be done between Day 15 and prior to the start of the next cycle.
i. CT chest. Scan may be done between Day 15 and prior to the start of the next cycle.
j. CT of abdomen/pelvis. For GU tumors and tumors below the diaphragm. Scan may be done between Day 15 and prior to the start of the next cycle.
k. Bone scan. Only for patients with N1 nodal disease if FDG PET was not performed.
l. FDG PET (optional). Prior to Cycle 1. For Cycle 4, scan may be done between Day 15 and prior to the start of the next cycle. Note: Only if performed at baseline and FDG PET avid disease.
m. Lymph node sampling. For paratesticular (≥ 10 years of age), extremity, or if enlarged nodes on clinical exam or imaging.
n. Blood for banking (optional). See Section 15.2.1.

Required Observations - Regimen VAC/VA, Cycles 1-4
All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. APEC14B1 (for molecular characterization). See Section 3.1.53.315.1.1, , and .
b. Physical exam with vital signs, height and weight.
c. Performance status. See Section 3.2.4.
d. Pregnancy test for females of childbearing age.
e. CBC, differential and platelets.
f. Creatinine, bilirubin, AST, & ALT
g. Urinalysis.
h. Electrolytes, include a basic metabolic panel (sodium, potassium, chloride, bicarbonate levels) as well as calcium levels.
i. Bilateral BM Asp/Bx. Only for patients with N1 nodal disease.
j. MRI or CT of primary site. Scan may be done between Day 15 and prior to the start of the next cycle.
k. CT chest. Scan may be done between Day 15 and prior to the start of the next cycle.
l. CT of abdomen/pelvis. For GU tumors and tumors below the diaphragm. Scan may be done between Day 15 and prior to the start of the next cycle.
m. Bone scan. Only for patients with N1 nodal disease if FDG PET was not performed.
n. FDG PET (optional). Prior to Cycle 1. For Cycle 4, scan may be done between Day 15 and prior to the start of the next cycle. Note: Only if performed at baseline and FDG PET avid disease.
o. Lymph node sampling. For paratesticular (≥ 10 years of age), extremity, or if enlarged nodes on clinical exam or imaging.
p. Radiation therapy consultation. Only for patients with CG II or III disease.
q. Blood for banking (optional). See Section 15.2.1.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
- 5cc blood in EDTA, Snap Frozen Tumor Tissue.
- 1 H&E slide from all available blocks (only one set of H&E slides needs to be submitted)
- 5 unstained slides from a representative block
- Also see APEC14B1 MOP

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA