

COG-ARST1431, A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temozolomide (TORI, Torisel, NSC# 683864, IND# 122782) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (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. Prior to obtaining informed consent and enrolling a patient, a reservation must be made.
- ___ 2. 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.
Patients must start protocol therapy within 42 days from the date of collection of the material that establishes the diagnosis of RMS.
- ___ 3. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.
- ___ 4. Emergent RT Therapy
Patients for whom emergency RT (prior to Week 13) is planned should not enroll on ARST1431. The use of steroids in this regard is permissible.
- ___ 5. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are >7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 4 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).**
- ___ 6. Age
Feasibility Phase: Completed 1-2-2018.
Efficacy Phase: Patients must be ≤ 40 years of age at the time of enrollment.
- ___ 7. 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.
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 2013 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). Classification of ARMS in the 2013 WHO Classification is the same as in the ICR and includes classic and solid variants.
 - ERMS
 - Stage 1, Group III (non-orbit)
 - Stage 3, Group I/II
 - Stage 2/3, Group III
 - Stage 4, Group IV, < 10 years old
 - ARMS: Stages 1-3, Groups I-III
- ___ 8. Specimen Submission
Patients must have sufficient tissue available for the **required** biology study (see Section 15.0).

9. Performance Level

Lansky performance status score ≥ 50 for patients ≤ 16 years of age.
 Karnofsky performance status score ≥ 50 for patients >16 years of age.

10. Organ Function Requirements

- Adequate Bone Marrow Function Defined As:
 - Peripheral absolute neutrophil count (ANC) $\geq 750/\mu\text{L}$
 - Platelet count $\geq 75,000/\mu\text{L}$
- Adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR $\geq 70 \text{ mL/min/1.73 m}^2$ 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 GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

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 via diversion (i.e., percutaneous nephrostomies or ureteric stents) of the urinary tract.

- Adequate liver function defined as:
 - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) for age

EXCLUSION CRITERIA:

- ___ 1. Patients who have previously received temsirolimus, another mTOR inhibitor, or any other investigational agent.
- ___ 2. Patients who have received any chemotherapy (excluding steroids) and/or RT prior to this enrollment.
- ___ 3. Patients with uncontrolled hyperglycemia
- ___ 4. Patients with uncontrolled hyperlipidemia.
- ___ 5. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for at least 3 months after treatment is completed.
- ___ 6. Female patients who are pregnant are not eligible since fetal toxicities or teratogenic effects have been noted for several of the study drugs.
 Note: A pregnancy test is required for female patients of childbearing potential prior to study entry.
- ___ 7. Lactating females who plan to breastfeed their infants are not eligible.

REQUIRED OBSERVATIONS:

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 protocol therapy (but remain on study) for failure to comply with protocol requirement. If fusion study is performed but the result is indeterminant, the patient will remain on therapy.

FOXO1 status results must be available by Week 3 (Day 21) of therapy.

Every effort should be made to SUBMIT FOXO1 results as an upload to RAVE soon as they are available.

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)

- FOXO1 fusion negative:
 - Stage 1, Group III (non-orbit)
 - Stage 3, Group I/II
 - Stage 2/3, Group III
 - Stage 4, Group IV, < 10 years old
- FOXO1 fusion positive: Stage 1-3, Group I-III

Note: As of August 24, 2019, 92 evaluable specimens have been analyzed at the Biopathology Center (BPC), of which 91 had concordant *FOXO1* fusion status determined by FISH with local institutions, for an overall concordance rate of 98.9%. We will no longer be evaluating *FOXO1* fusion status at the BPC as of Amendment #4. PAX3 and PAX7 evaluations will continue.

Note: FOXO1 fusion status must be performed at local institutions.

Patients with institutional histologic classification of ARMS but FOXO1 fusion negative with the following Stage and Group can remain on study but will receive VAC/VA therapy on Regimen C instead of the previously assigned treatment regimen. Patient consent is required to transfer to Regimen C. See Section 3.1.8 for callback details:

- Stage 1, Group I/II
- Stage 1, Group III (orbit)
- Stage 2, Group I/II

Required Observations:

- Physical exam/weight /height.
- CBC/diff/platelets
- Total bilirubin, ALT, creatinine.
- Bilateral bone marrow biopsy (not required for patients with ERMS and clinically uninvolved nodes, and no lung or bone metastases). Repeat bone marrow examinations are only required in patients who had positive bone marrow disease at diagnosis
- Cerebrospinal fluid cytology for parameningeal tumors, including orbital site with parameningeal extension and paraspinal tumors with dural involvement.
- MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0. CT may be used for regional nodes. Post-operative imaging is required at Week 12 (prior to RT) only for patients who undergo DPE.
- CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat staging CT chest is required at Week 9 only for those patients who had lung metastases at diagnosis. See Section 16.0.
- FDG-PET with diagnostic quality CT. For patients who consented to the FDG-PET part of the study. See Section 16.0.
- Bone scan. May be omitted if PET-CT is performed. May be omitted for patients with ERMS and clinically uninvolved nodes and no lung metastases. Only needs to be repeated at Week 9 in those patients who had bone metastases at diagnosis. See Section 16.0
- CT or MRI of regional nodal basin. Week 9. May omit if PET-CT is done. Perform in those patients who had clinically involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
- Lymph node biopsy. See Section 13.4.2 for details. **Mandatory** for extremity tumors, paratesticular tumors in patients ≥ 10 years of age regardless of histology; **strongly recommended** in *all* patients with alveolar histology (particularly if FOXO1 fusion positive) and in those with *clinically involved* nodes regardless of histology or fusion status).
- Performance status. Use the Lansky performance score if < 16 years of age and the Karnofsky performance scale if ≥ 16 years of age.
- Tissue submission for biology studies. Identification of fusion partners and variant gene fusions in RMS (Required). See Section 15.0.
- Sperm banking. Recommended for post-pubertal males.
- Fertility consult. Recommended for patients with abdominal/pelvic disease.
- Circulating tumor DNA. Patient Consent required. Samples must be drawn within 7 days prior to starting therapy (day 1); Week 4 and 7 (prior to chemotherapy on that day). See Section 15.2

Please review the Surgical Principles found in Section 13.4 for the protocol required lymph node sampling/dissection details.

Patients randomized to Regimen B also need the following:

- Calcium,phosphorus
- Triglycerides, cholesterol, urinalysis. If triglycerides or cholesterol levels are elevated, repeat with fasting.
- For patients who have consented to the FDG-PET part of the study, PET scans must be performed no sooner than **4 days following temsirolimus infusion**. See Section 16.0.

TREATMENT PLAN:

In an attempt to improve long-term survival for patients with IR RMS, ARST1431 will compare the EFS of patients with newly diagnosed IR RMS randomly assigned to standard vincristine, dactinomycin, and cyclophosphamide (VAC) alternating with vincristine and irinotecan (VI) versus VAC/VI plus temsirolimus. Radiotherapy will start at Week 13 of therapy for all patients. Correlative biology studies will be performed including a determination of the FOXO1 gene fusion status in the tumor and measurement of cell free tumor DNA.

Efficacy Phase

Patients will be randomly assigned to Regimen A or B in which the only difference is the addition of temsirolimus. **With Amendment #3**, following completion of 42 weeks of therapy, all patients in Regimen A or B will receive 24 weeks of maintenance therapy. See Section 4.1 regarding Regimen C.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

Retrospective pathology review of blocks or slides. See Section 14.