ARST1431

A Randomized Phase III Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) vs. VAC/VI Plus Temsirolimus (TORI, Torisel, NSC #683864) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)

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FOR KIDS WITH CANCER
FOR NOW, FOR LIFE.

Background

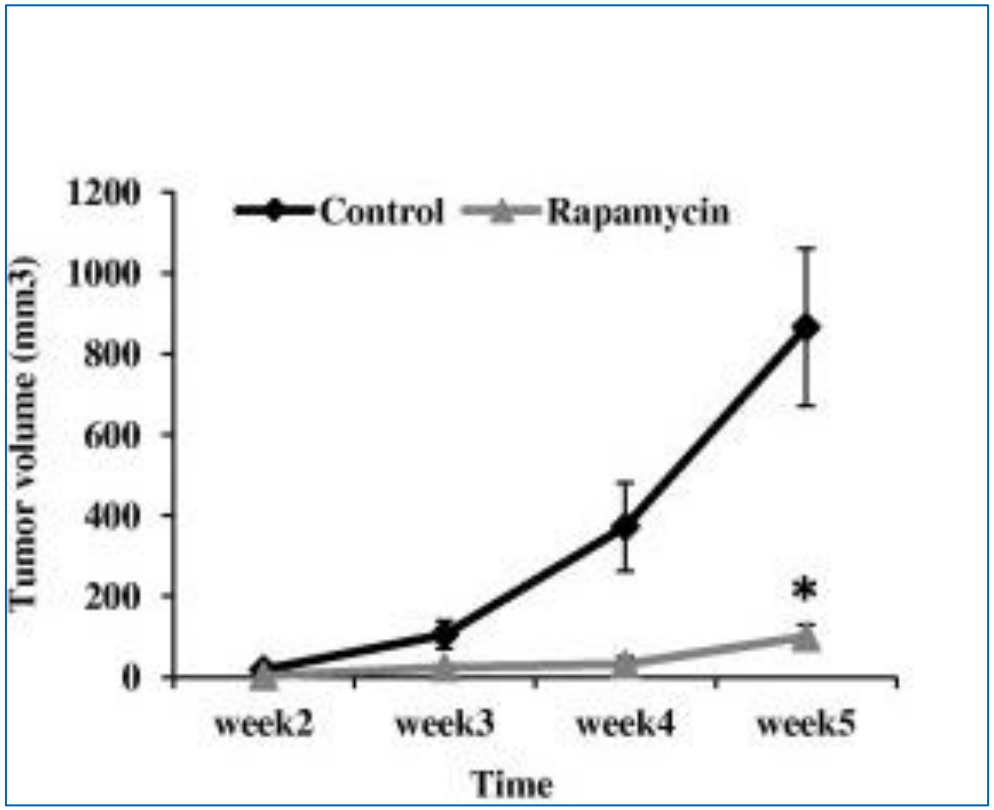
Five-year survival rates for children with cancer is close to 83%. Rates have been improving, some drastically like those for acute lymphoblastic leukemia. By contrast, survival rates remain much lower in some cancer types, one being Rhabdomyosarcoma (RMS).

There is a 25-50% chance of disease recurrence with a resulting long-term event-free survival (EFS) of only 65%.

This clinical trial is comparing 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.

Background

- The mTOR pathway is important in RMS biology.
- mTOR inhibition by rapamycin has shown significant inhibition of RMS.
- Temsirolimus, an mTOR inhibitor, has demonstrated significant clinical activity in relapsed patients with RMS.



Kaylani SZ, Xu J., Srivastava RK, Kopelovich L., Pressey JG, Athar M. Rapamycin targeting mTOR and hedgehog signaling pathways blocks human rhabdomyosarcoma growth in xenograft murine model. Biochemical and biophysical research communications. 2013 Jun 14; 435 (4): 557-61.

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Background: Temsirolimus

Temsirolimus is an ester of sirolimus (rapamycin) and a specific inhibitor of mammalian target of rapamycin (mTOR), a signaling protein that regulates cell growth, proliferation, angiogenesis, and cellular survival pathways.

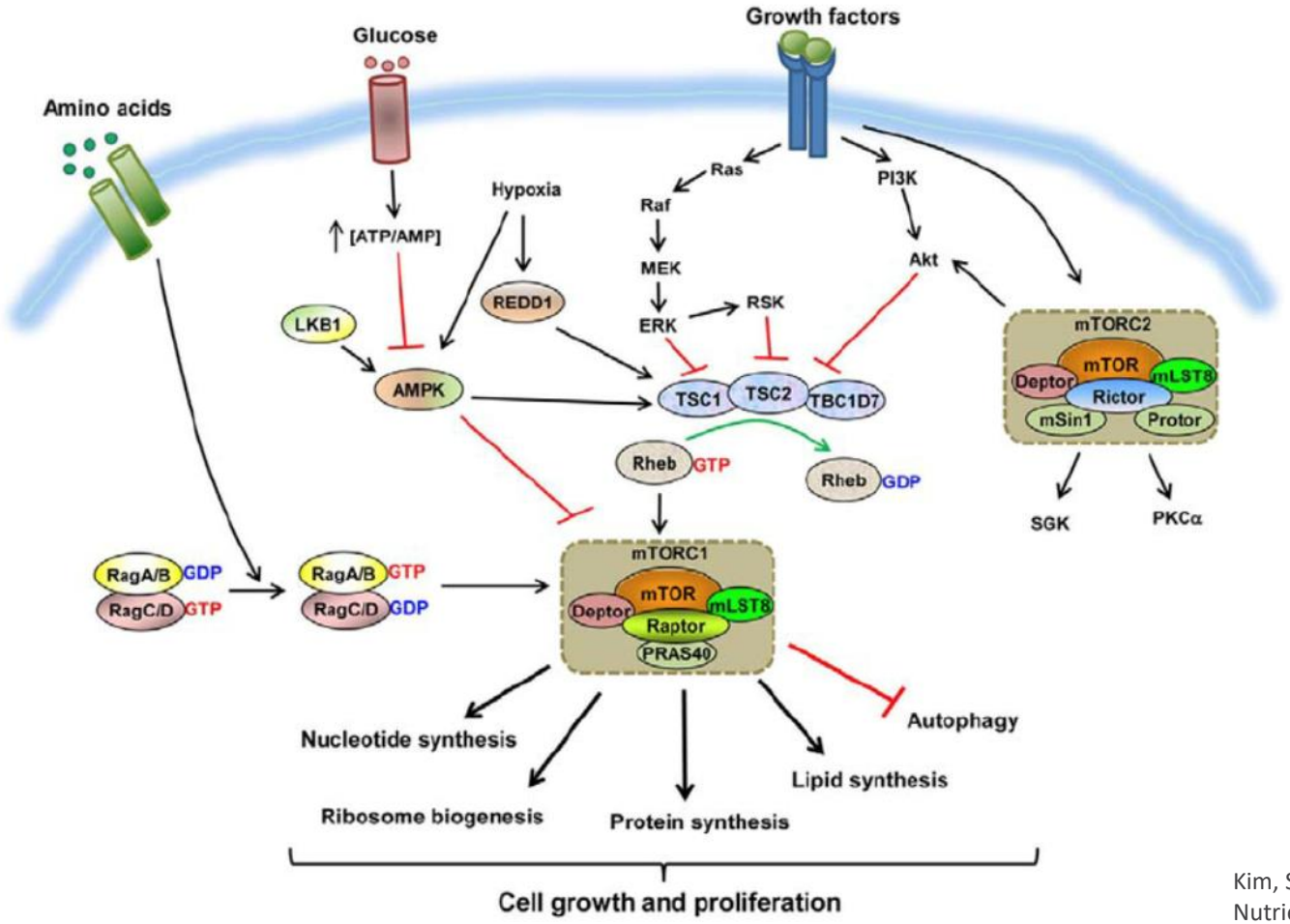
Inhibition of mTOR leads to reduced synthesis of cell cycle regulatory proteins and, via inhibition of hypoxia-inducible factor alpha-1 (HIF-1$^{\alpha}$), reduces expression of vascular endothelial growth factor (VEGF), an important pro-angiogenic factor.

Temsirolimus is a targeted therapy drug.

Background: mTOR Pathway

The mammalian target of rapamycin (mTOR) exists in two distinct structural and functional complexes:

mTOR complex 1 (mTORC1
and
mTOR complex 2 (mTORC2



mTORC1 couples nutrient abundance to cell growth and proliferation by sensing and integrating a variety of inputs arising from amino acids, cellular stresses, energy status, and growth factors.

Defects in mTORC1 regulation are implicated in the development of many metabolic diseases, including cancer.

Kim, Sang-Gyun & Buel, Gwen & Blenis, John. (2013). Nutrient Regulation of the mTOR Complex 1 Signaling Pathway. Molecules and Cells. 35. 10.1007/s10059-013-0138-2.

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Background: Temsirolimus

The most frequent side effects are:

Maculopapular rash (76%)
Mucositis (70%)
Asthenia (50%)
Nausea (43%)

Severe adverse events are uncommon. The most frequent Grade 3 or 4 adverse events include:

Hyperglycemia (17%)
Hypophosphatemia (13%)
Anemia (9%)
Hypertriglyceridemia (6%)

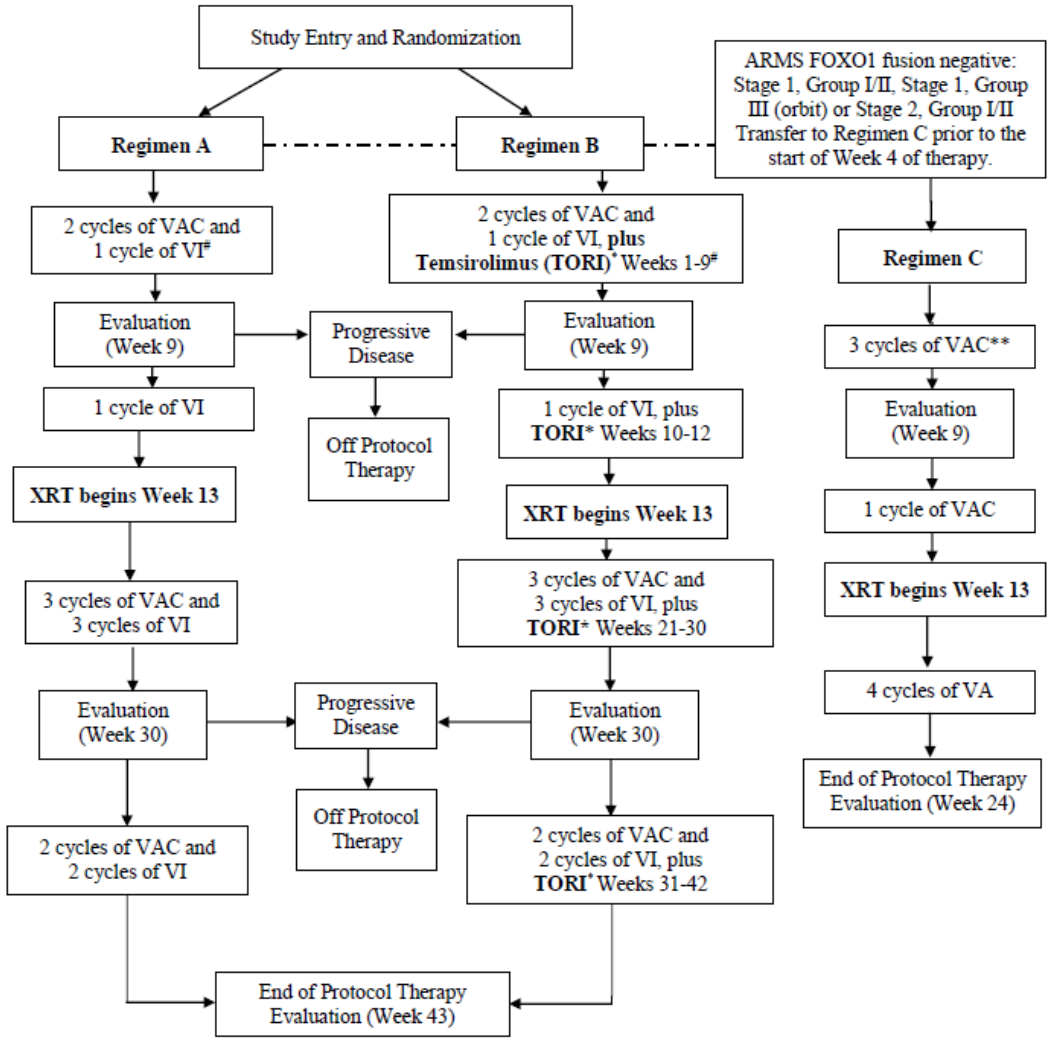
Hypersensitivity reactions and dyspnea have also been reported and may be life-threatening.

ARST1431: Study Aim

To compare the event-free survival (EFS) and overall survival (OS) of patients with IR RMS treated with surgery, radiotherapy, and VAC alternating with VI (VAC/VI) to that of patients treated with surgery, radiotherapy, and VAC/VI plus temsirolimus.

Study Schema

There are three arms: Regimen A, B, and C



Correlative biology studies will be performed including a determination of the FOXO1 gene fusion status in the tumour and measurement of cell-free tumour DNA.

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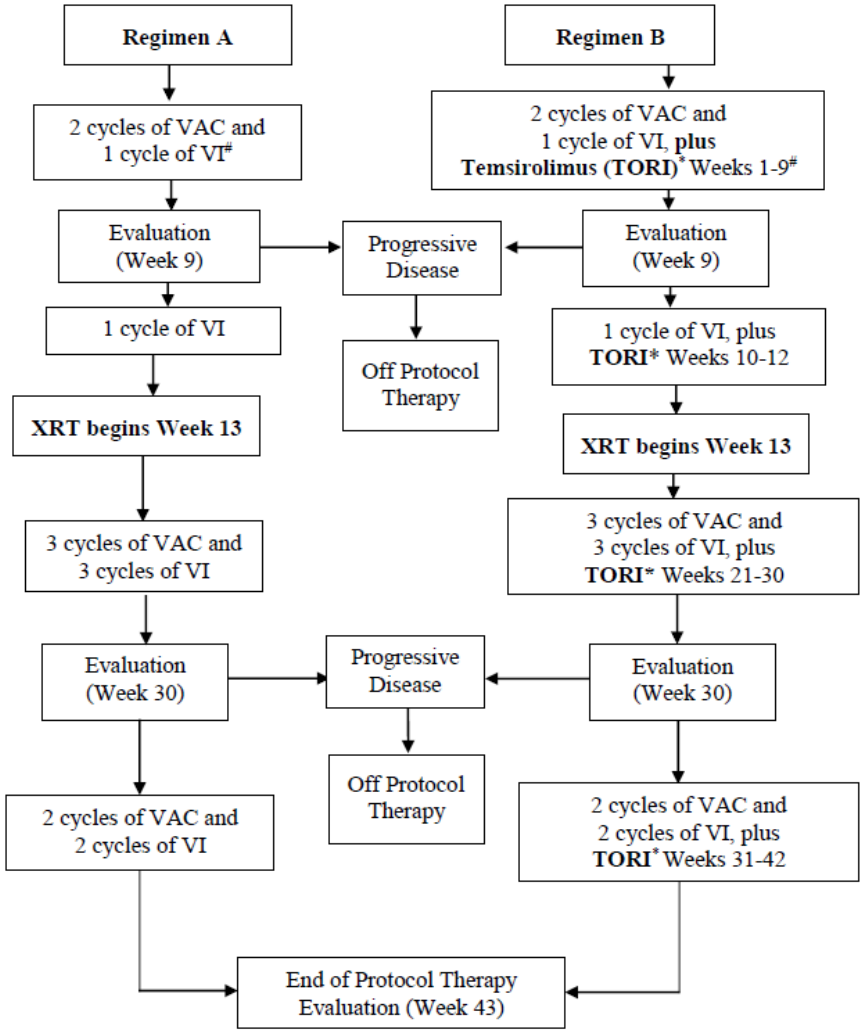
Regimen A and B

Regimen A:
These patients receive VAC + VI

These are Satellite-friendly agents and can be given at the Satellite Clinic.



Regimen B:
These study patients are randomized to receive Temsirolimus.

These patients were receive their treatment in the tertiary hospitals.

However, they can still be seen for supportive care, making sure to notify the tertiary hospital of any toxicity noted.

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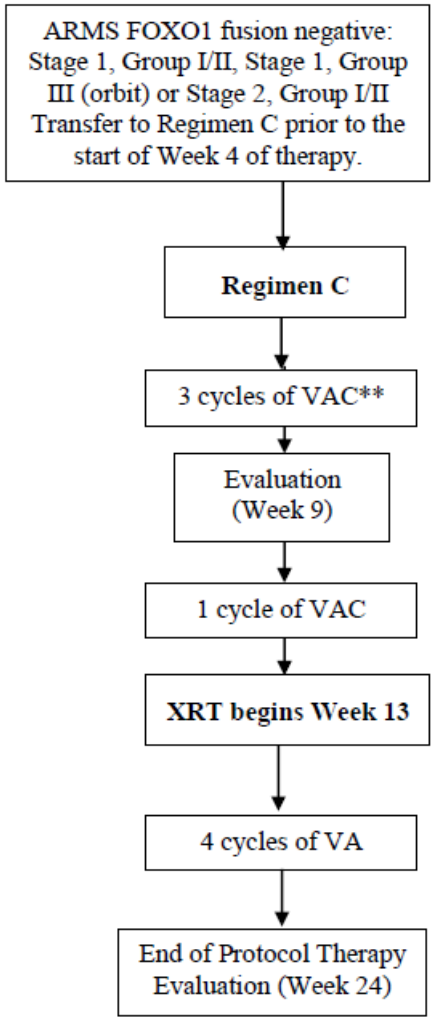
Regimen C



Regimen C:

This is the “low-risk” arm. These patients are negative for FOXO1 fusion and will receive 24 weeks of VAC/VA (as per ARST0331).

The goal being to estimate the success of reduced intensity therapy for low-risk patients that are negative for FOXO1 fusion.

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Regimen C

Cycles 1-4

Date Due	Date Given	Cycle	Week	Day	VCR ____mg	DACT ____mg	CPM ____mg	MESNA ____mg	Myeloid growth factor used: Calc. dose____mcg		Studies
					Enter calculated dose above and actual dose administered below				Start date	Stop date	
		1	1	1	___mg	___mg	___mg	___mg ___mg ___mg			a-p
			2	1	___mg						b
			3	1	___mg						b
		2	4	1	___mg	___mg	___mg	___mg ___mg ___mg			a-c, p
			5	1	___mg						b
			6	1	___mg						b
		3	7	1	___mg	___mg	___mg	___mg ___mg ___mg			a-c, p
			8	1	___mg						b
			9	1	___mg						a, b, f-j
		4	10	1	___mg	___mg	___mg	___mg ___mg ___mg			a-c
			11								b
			12								b
					Continue to Cycle 5 (Week 13) therapy if all criteria to start the next cycle have been met.						

Many chemotherapy and bloodwork visits available to Satellite Clinics, see highlighted weeks.

Date Due	Date Given	Cycle	Week	Day	VCR ____mg	DACT ____mg	Studies
					Enter calculated dose above and actual dose administered below		
		5	13	1	___mg	___mg	a-c
			14	1	___mg		b
			15	1	___mg		b
		6	16	1	___mg	___mg	a-c
			17	1	___mg		b
			18	1	___mg		b
		7	19	1	___mg	___mg	a-c, g
			20	1	___mg		a, b
			21	1	___mg		b
		8	22	1	___mg	___mg	a-c
			24				a, b, d-f
Note: Protocol therapy on Regimen C ends with Week 24 evaluations; however, there are ctDNA timepoints at Week 43.							

Cycles 5-8

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Summary

In comparison to other pediatric cancers, survival rates remain very low for RMS.

Temsirolimus has demonstrated impressive clinical activity in patients with RMS. This study will compare EFS and OS of patients with IR RMS treated with VAC/VI versus patients treated with VAC/VI plus temsirolimus.

Three arms:

- **A arm** – VAC/VI: Satellite Clinics can provide therapy and supportive care
- **B arm** – VAC/VI plus temsirolimus: Therapy in tertiary hospitals, Satellite Clinics can provide supportive care.
- **C arm** – VAC/VA: “Low-risk” decreased therapy intensity, Satellite-friendly therapy

** Temsirolimus Toxicities **

The most frequent side effects are:

Maculopapular rash (76%)
Mucositis (70%)
Asthenia (50%)
Nausea (43%)

Severe adverse events are uncommon. The most frequent Grade 3 or 4 adverse events include:

Hyperglycemia (17%)
Hypophosphatemia (13%)
Anemia (9%)
Hypertriglyceridemia (6%)

Remember to discuss any toxicity concerns or suspicions with the tertiary hospitals!

References

Kaylani SZ, Xu J, Srivastava RK, Kopelovich L, Pressey JG, Athar M. Rapamycin targeting mTOR and hedgehog signaling pathways blocks human rhabdomyosarcoma growth in xenograft murine model. Biochemical and biophysical research communications. 2013 Jun 14;435(4):557-61

Réguerre Y, Martelli H, Rey A, Rogers T, Gaze M, Arush MW, Devalck C, Oberlin O, Stevens M, Orbach D. Local therapy is critical in localised pelvic rhabdomyosarcoma: experience of the International Society of Pediatric Oncology Malignant Mesenchymal Tumor (SIOP-MMT) committee. European journal of cancer. 2012 Sep 1;48(13):2020-7.

WW Wong, SJ Buskirk, WW Tan… - Clinical …, 2011 - mayoclinic.pure.elsevier.com
Kidney and Ureteral Carcinoma. / Wong, William W.; Buskirk, Steven J.; Tan, Winston W.; Peterson, Jennifer L.; Haddock, Michael G.; Parker, Alexander S.; Wehle, Michael J … Clinical Radiation Oncology: Third Edition. Elsevier Inc., 2011. p. 1145-1165 … Powered by Pure, Scopus & Elsevier Fingerprint Engine™ © 2017 Elsevier BV.

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