ARST 2031

Satellite Educational Training Module

DECEMBER 10, 2024

Presented to: Satellite Clinic Healthcare Providers
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ARST 2031

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).

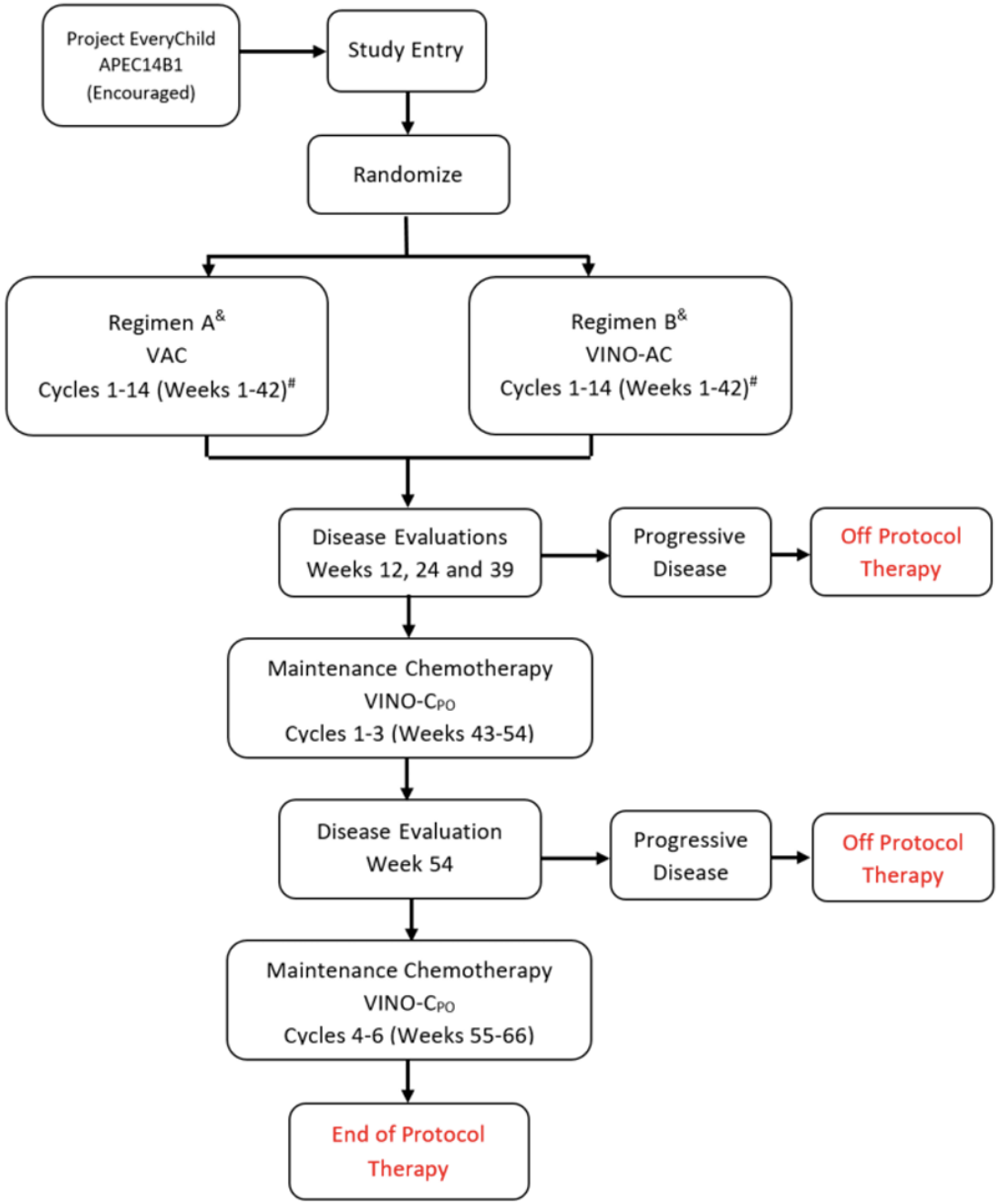
Background

- Patients with high-risk rhabdomyosarcoma (HR-RMS) continue to have poor outcomes with 3-year event free survival (EFS) rates of 30% or les
- Vinorelbine (VINO) has demonstrated clinical activity in RMS patients with relapsed and refractory disease and has been shown to provide a survival benefit when given as maintenance with oral cyclophosphamide for patients who have achieved a complete remission.

Background

- ARST2031 evaluates vinca alkaloid intensification and maintenance therapy
- Patients will be randomly assigned to vincristine, dactinomycin and cyclophosphamide (VAC) followed or vinorelbine, dactinomycin and cyclophosphamide (VINO-AC)
- Both groups will receive maintenance with vinorelbine and oral cyclophosphamide (VINO-C_{PO})

Study Design



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Maintenance Therapy in Rhabdomyosarcoma

- 6 planned cycles total
- Oral Cyclophosphamide:
  - May be administered as tablets, rounded to nearest 12.5mg (half tablet): See Chart
  - May also be prepared as liquid solution from IV cyclophosphamide
  - Moderately emetogenic: ensure prophylaxis available
- IV Vinorelbine: Given 3 or 4 weeks of each cycle

Cycle	M1				M2				M3			
Week	43	44	45	46	47	48	49	50	51	52	53	54
	VINO	VINO	VINO		VINO	VINO	VINO		VINO	VINO	VINO	**Evaluation**
	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO

Body Surface Area (m^2)*	**US sites** **Suggested Daily Dose (d) over 7 days** (1 capsule = 25 mg)	**Canadian sites** **Suggested Daily Dose (d) over 7 days** (1 tablet = 25 mg)	**Cumulative Weekly Dose**
0.32-0.38	use liquid formulation	1/2 tab / d x 5	62.5 mg/wk
0.39-0.46	use liquid formulation	1/2 tab / d x 6	75 mg/wk
0.47-0.53	use liquid formulation	1/2 tab /d x 7	87.5 mg/wk
0.54-0.60	use liquid formulation	1 tab / d x 2; 1/2 tab / d x 4	100 mg/wk
0.61-0.64	use liquid formulation	1 tab / d x 2; 1/2 tab / d x 5	112.5 mg/wk
0.65 - 0.78	1 cap / d x 5	1 tab / d x 3; 1/2 tab / d x 4	125 mg/wk
0.79 - 0.92	1 cap / d x 6	1 tab / d x 6	150 mg/wk
0.93 – 1.07	1 cap / d x 7	1 tab / d x 7	175 mg/wk
1.08 – 1.21	2 cap / d x 1; 1 cap / d x 6	2 tab / d x 1; 1 tab / d x 6	200 mg/wk
1.22 – 1.35	2 cap / d x 2; 1 cap / d x 5	2 tab / d x 2; 1 tab / d x 5	225 mg/wk
1.36 – 1.49	2 cap / d x 3; 1 cap / d x 4	2 tab / d x 3; 1 tab / d x 4	250 mg/wk
1.50 – 1.64	2 cap / d x 4; 1 cap / d x 3	2 tab / d x 4; 1 tab / d x 3	275 mg/wk
1.65 – 1.78	2 cap / d x 5; 1 cap / d x 2	2 tab / d x 5; 1 tab / d x 2	300 mg/wk
1.79 – 1.92	2 cap / d x 6; 1 cap / d x 1	2 tab / d x 6; 1 tab / d x 1	325 mg/wk
1.93 – 2.07	2 cap / d x 7	2 tab / d x 7	350 mg/wk
2.08 – 2.21	3 cap / d x 1; 2 cap / d x 6	3 tab / d x 1; 2 tab / d x 6	375 mg/wk
2.22 - 2.35	3 cap / d x 2; 2 cap / d x 5	3 tab / d x 2; 2 tab / d x 5	400 mg/wk
2.36 – 2.49	3 cap / d x 3; 2 cap / d x 4	3 tab / d x 3; 2 tab / d x 4	425 mg/wk
2.50 – 2.64	3 cap / d x 4; 2 cap / d x 3	3 tab / d x 4; 2 tab / d x 3	450 mg/wk
2.65 – 2.78	3 cap / d x 5; 2 cap / d x 2	3 tab / d x 5; 2 tab / d x 2	475 mg/wk
2.79 – 2.92	3 cap / d x 6; 2 cap / d x 1	3 tab / d x 6; 2 tab / d x 1	500 mg/wk
2.93 – 3.00*	3 cap / d x 7	3 tab / d x 7	525 mg/wk

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Dose Modifications: Maintenance

- CBC checked weekly during the first three weeks of each cycle.
- Cyclophosphamide AND vinorelbine should held if ANC < 750/µL or platelets < 75,000/µL.
- Resume 100% dose if counts recover within 7 days
- If cyclophosphamide is held for > 7 consecutive days during any cycle,
  - reduce oral cyclophosphamide and vinorelbine by 25% once counts have recovered
- Refer to protocol document for more information on dose modications

A review of select protocol agents

- The Drug Reminders of important toxicities
  - **Actinomycin**
    - Highly Emetogenic (ensure adequate CINV prophylaxis)
    - RARELY: associated with sinusoidal obstruction syndrome (aka VOD: Fluid retention, RUQ pain, platelet refractory: Contact referring centre with any concer
  - **Vinorelbine**
    - Flush vinorelbine injection site with 75-125 mL of a compatible IV fluid for 15-60 min after administration to prevent burning at the injection site.
  - **Cyclophosphamide**
    - Requires pre-hydration and MESNA infusions to prevent hemorrhagic cystitis
- Refer to protocol document for full review of Common, Occasional and Rare toxicities

In Summary

- ARST 2031 randomizes the addition of Vinorelbine IN PLACE of the standard Vincristine in High-Risk Rhabdomyosarcoma
- Maintenance therapy is added for ALL patients
- Tertiary centres remain responsible for consenting, disease evaluation and all adverse event reporting

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