Past, Current & Future Studies: Paratestis

Jonathan C. Routh, MD, MPH

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Disclosures

- **The views expressed herein are my own, not necessarily those of the pediatric cancer groups I work with**
  - COG soft tissue sarcoma committee
  - Children's Oncology Group surgery committee
  - COG long-term follow-up kidney & testis task forces
  - INSTRuCT PT & BP-RMS committees
  - Societe Internationale d'Oncologie Pediatrique
  - IGHG nephrotoxicity panel

- **I have no financial (or other) conflicts of interest**

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Overview

- **Current / Recent STS Trials**
  - Intermediate Risk
  - Low Risk
- **Upcoming Trials**
  - Low Risk
  - Intermediate Risk?
- **Ongoing/Upcoming Analyses**

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Prospective COG Studies

- **Recently Completed**
  - ARST0331 – Low Risk RMS
  - ARST0531 – Intermediate Risk RMS
- **Ongoing**
  - ARST1431 – Intermediate Risk RMS
  - ARST2032 – Low Risk RMS
- **Future**
  - ARST22P1 – Intermediate Risk RMS

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ARST0331 – low risk RMS

Reduction of Cyclophosphamide Dose for Patients With Subset 2 Low-Risk Rhabdomyosarcoma Is Associated With an Increased Risk of Recurrence: A Report From the Soft Tissue Sarcoma Committee of the Children's Oncology Group

David O. Walterhouse, MD[1]; Alberto S. Pappo, MD[2]; Jane L. Meza, PhD[3]; John C. Breneman, MD[4]; Andrea Hayes-Jordan, MD[5]; David M. Parham, MD[6]; Timothy P. Cripe, MD, PhD[7]; James R. Anderson, PhD[8]; William H. Meyer, MD[9]; and Douglas S. Hawkins, MD[10]

- **92% OS, 70% EFS**
- **Defined need & duration for RT, cyclophosphamide in low risk RMS**

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ARST0531 – intermediate risk RMS

Increased Local Failure for Patients With Intermediate-Risk Rhabdomyosarcoma on ARST0531: A Report From the Children's Oncology Group

Dana L. Casey, MD [1]; Yueh-Yun Chi, PhD[2]; Sarah S. Donaldson, MD[3]; Douglas S. Hawkins, MD [4]; Jing Tian, MS[2]; Carola A. Arndt, MD[5]; David A. Rodeberg, MD[6]; Jonathan C. Routh, MD, MPH[7]; Timothy B. Lautz, MD[8]; Abha A. Gupta, MD, MSc [9]; Torunn I. Yock, MD[10]; and Suzanne L. Wolden, MD[1]

Addition of Vincristine and Irinotecan to Vincristine, Dactinomycin, and Cyclophosphamide Does Not Improve Outcome for Intermediate-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group

Douglas S. Hawkins, Yueh-Yun Chi, James R. Anderson, Jing Tian, Carola A.S. Arndt, Lisa Bomgaars, Sarah S. Donaldson, Andrea Hayes-Jordan, Leo Mascarenhas, Mary Beth McCarville, Jeannine S. McCune, Geoff McCowage, Lynn Million, Carol D. Morris, David M. Parham, David A. Rodeberg, Erin R. Rudzinski, Margarett Shnorhavorian, Sheri L. Spunt, Stephen X. Skapek, Lisa A. Teot, Suzanne Wolden, Torunn I. Yock, and William H. Meyer

- **OS 82% for CR, 76% for PR**
- **Local failure 27.9%**
- **Local failure, EFS, and OS all worse on ARST0531 than D9803**
- **Perhaps due to reduced cyclophosphamide dose?**

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ARST1431 - Intermediate RMS

- **8-12 weeks chemo (VAC/VI +/- mTORi)**
- **Local Control: Surgery, RT, or both**
- **Emphasis on DPE and RT boost**
  - DPE if “easily resectable”
  - RT boost to 59.4 cGy if tumor size > 5 cm
- **Study redesigned, relaunched to include longer cyclophosphamide ‘tail’ following ARST0531/D9803 comparison**

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ARST2032 – low & very low risk RMS

- Prospective Phase 3 Study of Low-Risk, Fusion-Negative RMS
- Primary Objectives:
  - FFS of patients with VLR RMS with 24 weeks VA
  - FFS of patients with LR RMS with 12 weeks VAC then 12 weeks VA
- Secondary Objectives:
  - OS of patients with VLR RMS with 24 weeks VA
  - OS of patients with LR RMS with 12 weeks VAC then 12 weeks VA
  - Feasibility of central molecular risk stratification of patients with newly diagnosed RMS in the context of a prospective clinical trial

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COG low risk data

Protocol	Population	Treatment Regimen	Long Terms FFS	Long Term OS
D9602	Subgroup A: ERMS Stage 1 CG I, IIA, III (orbit only) ERMS Stage 2 CG I	48w VA	89%	97%
ARST0331	Subset 1: ERMS Stage 1 or 2, CG I, II, or III (orbit only)	12w VAC then 12w VA	89%	98%

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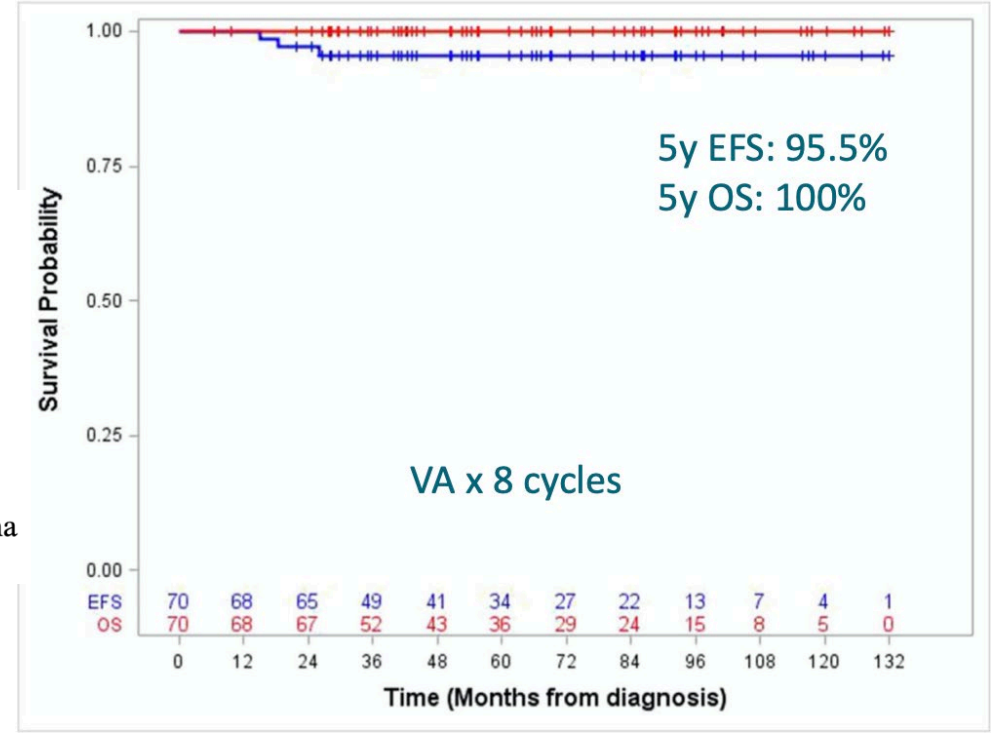
Crist et al., JCO, 2001
Raney et al., JCO, 2011
Walterhouse et al., JCO, 2014

EpSSG low risk data

Embryonal rhabdomyosarcoma completely resected at diagnosis: The European paediatric Soft tissue sarcoma Study Group RMS2005 experience

Christophe Bergeron [a,*], Meriel Jenney [b], Federica De Corti [c], Soledad Gallego [d], Hans Merks [e], Heidi Glosli [f], Andrea Ferrari [g], Dominique Ranchère-Vince [h], Gian Luca De Salvo [i], Ilaria Zanetti [j], Julia Chisholm [k], Véronique Minard-Colin [l], Timothy Rogers [m], Gianni Bisogno [j], on behalf of the European paediatric Soft tissue sarcoma Study Group (EpSSG)[1]



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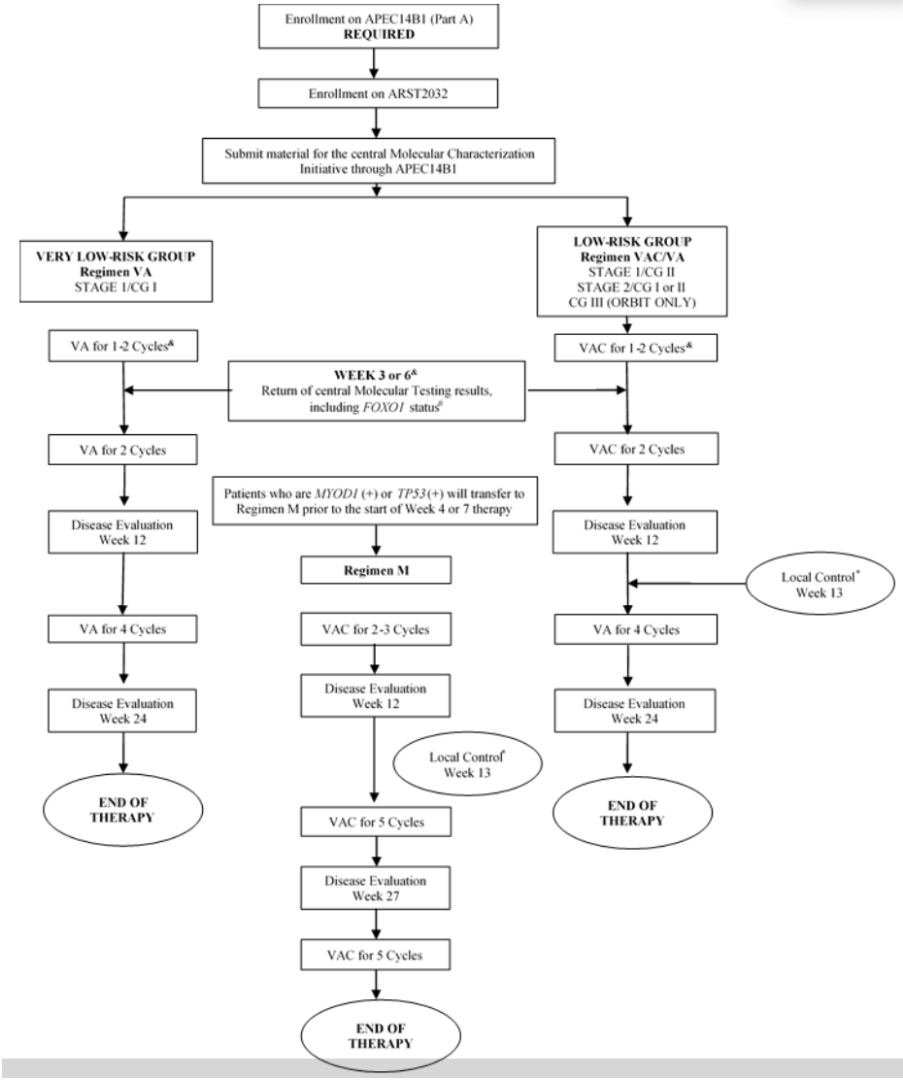
ARST2032

- Age ≤ 21 yo
- Stage 1, CG I/II/III (orbit only)
- Stage 2, CG I/II
- Target accrual is ~180 patients over 5 years
- Launch date 6/28/2022



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Ongoing/future COG analyses

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Late Effects: Background

- Prior IRSG study (Sung et al, 2004) estimated 5% late event rate >5 years after treatment
  - 22 events were recurrent RMS, 17 were SMNs, and 9 were deaths due to other causes
  - Most recurrences were local
  - Most SMNs were solid and occurred within original radiation field
- Patients with both advanced disease (Group III/IV) and large primary tumors (>5 cm) at diagnosis were more likely to have late events

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Late Effects: Recent Data

- Retrospective review of RMS treated on IRSG and COG trials:
  - D9602 (1997-2004) (Raney et al, 2011)
  - D9803 (1999-2005) (Arndt et al, 2009)
  - D9802 (1999-2004) (Pappo et al, 2007)
  - ARST0331 (2004-2011) (Walterhouse et al, 2014 & 2017)
  - ARST0531 (2006-2012) (Hawkins et al, 2018) (Casey et al, 2019)
  - ARST0431 (2006-2008) (Weigel et al, 2015) (Gupta et al, 2017)
  - ARST08P1 (2010-2013) (Malempati et al, 2019)
- All patients who were alive and event-free at 5 years from study entry were eligible for the analysis
  - First late event was defined as recurrence, SMN, or death from any cause

Characteristic	Recurrence (n=15)	SMN (n=13)	Death (n=3)
Time To Event (Median years; range)	5.8 (5-11.3)	6.7 (5-11)	7.9 (7.6-11)
Age at Diagnosis (yrs) 1-9 ≥10	 13 (86.7%) 2 (13.3%)	 12 (92.3%) 1 (7.7%)	 3 (100%) 0
Primary Site Favorable Unfavorable	 6 (40%) 9 (60%)	 7 (53.9%) 6 (46.1%)	 0 3 (100%)
Size ≤5 cm >5 cm	 9 (60%) 6 (40%)	 5 (38.5%) 8 (61.5%)	 1 (33.3%) 2 (66.7%)
Group I II III IV Unknown	 3 (20%) 2 (13.3%) 6 (40%) 4 (26.7%)	 0 2 (15.4%) 9 (69.2%) 2 (15.4%)	 0 1 (33.3%) 0 1 (33.3%) 1 (33.3%)
Stage 1 2 3 4 Unknown	 7 (46.7%) 2 (13.3%) 2 (13.3%) 4 (26.7%)	 5 (38.5%) 1 (7.7%) 5 (38.5%) 2 (15.4%)	 0 1 (33.3%) 0 1 (33.3%) 1 (33.3%)

Study	Primary Site	Radiation	SMN	SMN in Radiation Field	Germline Mutation
D9602	Orbit				
D9602	Orbit	Yes	Osteosarcoma (maxilla) Anaplastic Astrocytoma	Yes No	
D9602	Head and Neck (Parameningeal; parapharyngeal)	Yes	Osteosarcoma (maxilla)	Yes	
D9803	Head and Neck (Non-Parameningeal)	Yes	Myelodysplastic	N/A	
D9803	Head and Neck (Parameningeal)	Yes	Pontine Glioma	Yes	
D9803	Head and Neck (Parameningeal)	Yes	Osteosarcoma	Unknown	
D9803	Extremity	Yes	Osteosarcoma AML	Yes	Li-Fraumeni
D9803	Head and Neck (Parameningeal)	Yes	Undifferentiated Sarcoma Osteosarcoma	No Yes	
D9803	Extremity		AML	N/A	Li-Fraumeni
ARST0331	Head and Neck	No	Basal Cell Carcinoma	N/A	Gorlin
ARST0331	GU (Cervix)	No	Sertoli-Leydig	N/A	DICER1
ARST0431	GU (Paratesticular)	Yes	AML	N/A	
ARST0431	Head and Neck (Non-Parameningeal)	Yes	Thyroid Carcinoma	Unknown	

Late Effects: Conclusions

- Estimated 5-year event rate for patients alive and failure-free at 5 years was **3%**
  - Compared to 5% in prior RMS cohorts

- This late event analysis justifies **discontinuation of surveillance for recurrence after 5 years from diagnosis**

- For patients who develop late SMN, **germline evaluation** should be considered if not already performed

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Collaborative Groups

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INSTRuCT Overview

- **Overall goal: international risk stratification for RMS**
- **Use clinical trial data from mid-1990s onward**
- **Resolve areas of uncertainty:**
  - Favorable vs. unfavorable sites
  - Tumor size cut-point
  - PAX3 vs. PAX7 fusion
- **Challenges:**
  - Missing data (especially FOXO1)
  - Evolving histology classification
  - Different treatment philosophies

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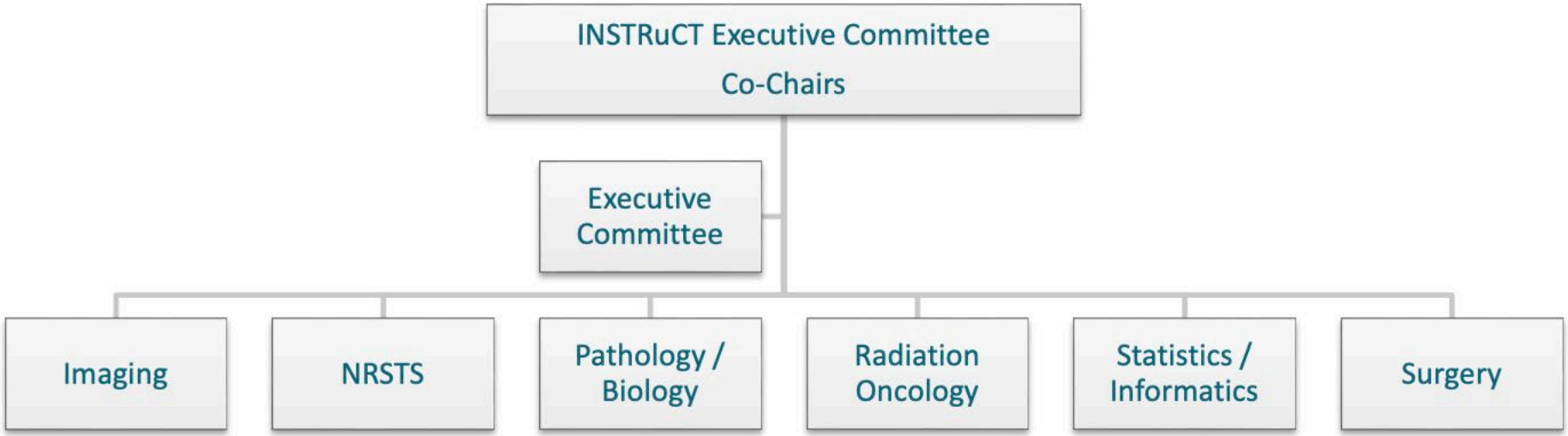
INSTRuCT structure



- **Chairs:**
  - Gianni Bisogno (EpSSG), Doug Hawkins (COG), Ewa Koscielniak (CWS)

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Recent PT-RMS publications

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Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

CLINICAL PRACTICE GUIDELINES

Surgical management of paratesticular rhabdomyosarcoma: A consensus opinion from the Children's Oncology Group, European paediatric Soft tissue sarcoma Study Group, and the Cooperative Weichteilsarkom Studiengruppe

Timothy N. Rogers[1] | Guido Seitz[2] | Jörg Fuchs[3] | Helene Martelli[4] | Roshni Dasgupta[5] | Jonathan C. Routh[6] | Douglas S. Hawkins[7] | Ewa Koscielniak[8] | Gianni Bisogno[9] | David A. Rodeberg[10]

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