Past, Current & Future Studies : Bladder/Prostate

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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**
  - High Risk
  - Intermediate Risk
- **Ongoing/Upcoming Projects**

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Current COG Studies

- **Recently Completed**
  - ARST0531 – Intermediate Risk RMS
  - ARST0431 – High Risk RMS
- **Ongoing**
  - ARST1431 – Intermediate Risk RMS
  - ARST2031 – High Risk RMS
- **Future**
  - ARST22P1 – Intermediate Risk RMS

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ARST0431 – High risk RMS

Intensive Multiagent Therapy, Including Dose-Compressed Cycles of Ifosfamide/Etoposide and Vincristine/Doxorubicin/Cyclophosphamide, Irinotecan, and Radiation, in Patients With High-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group

Brenda J. Weigel, Elizabeth Lyden, James R. Anderson, William H. Meyer, David M. Parham, David A. Rodeberg, Jeff M. Michalski, Douglas S. Hawkins, and Carola A.S. Arndt

- **56% OS, 38% EFS**
- **High-dose chemotherapy useful for metastatic tumors, but very-high-risk tumors still challenging**

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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]

- **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

- **Current intermediate risk study**
- **VAC/VI +/- temsirolimus (mTOR inhibitor)**
- **Age < 40 years**
- **FOX01 fusion status, not histology**
- **Primary & secondary aims: OS & EFS**
- **Exploratory aims:**
  - PAX3 vs. PAX7 survival (among fusion positive pts)
  - Correlate FDG-PET response with survival
- **Recently completed accrual – data expected in 2024**

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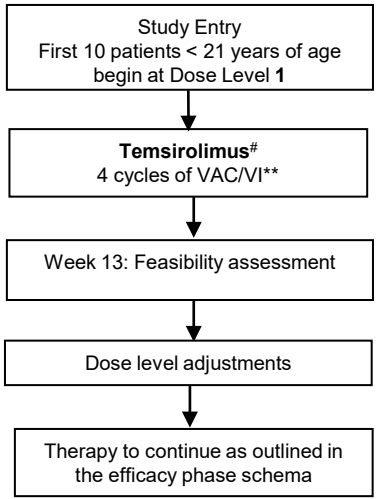
Study Schema: Feasibility Phase

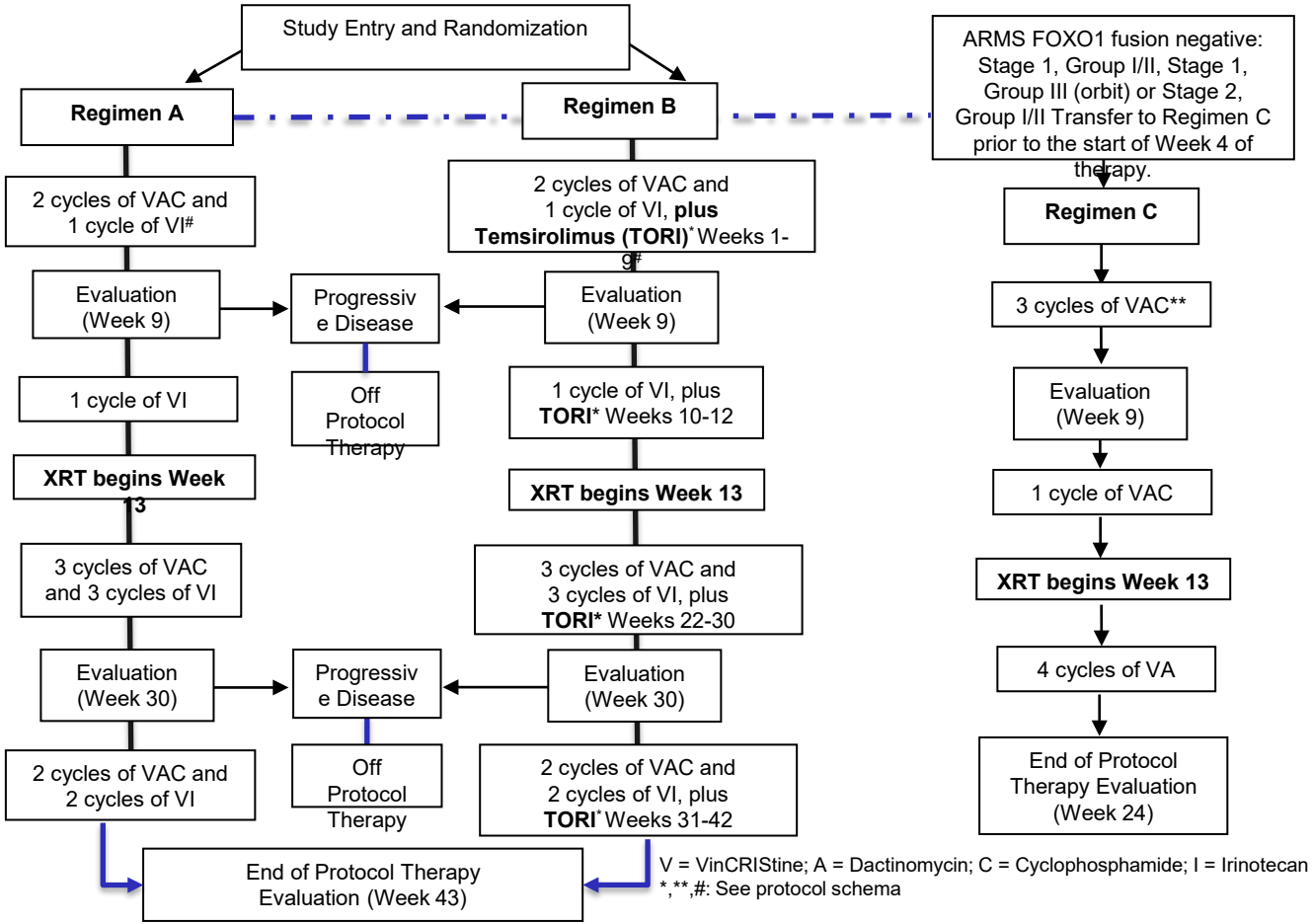
During the feasibility (dose-finding) phase, patients will be non-randomly assigned to treatment with VAC/VI plus temsirolimus.



#Temsirolimus	
Dose Level	Temsirolimus Dose
1	15 mg/m^2 IV, Days 1, 8 and 15 of each cycle
0	10 mg/m^2 IV, Days 1, 8 and 15 of each cycle
-1	10 mg/m^2 IV, Days 1 and 8 of each cycle

V = VinCRIStine; A = Dactinomycin; C = Cyclophosphamide; I = Irinotecan

Study Schema: Efficacy Phase



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 data comparisons**

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ARST22P1 – Intermediate risk RMS

- Planned prospective, Phase 3 trial on temsirolimus and other agents
- Will likely be scrapped due to logistical issues with procurement and payment for temsirolimus or other mTORi

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Recent / ongoing / future COG analyses

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BP-RMS studies

- **Retrospective BP-RMS analysis drawing from recent studies**
  - D9602, D9803, ARST0331, ARST0531
- **Outcomes:**
  - FFS, OS for non-metastatic BP-RMS
  - Adherence to published protocols
- **Currently slated to launch this fall**

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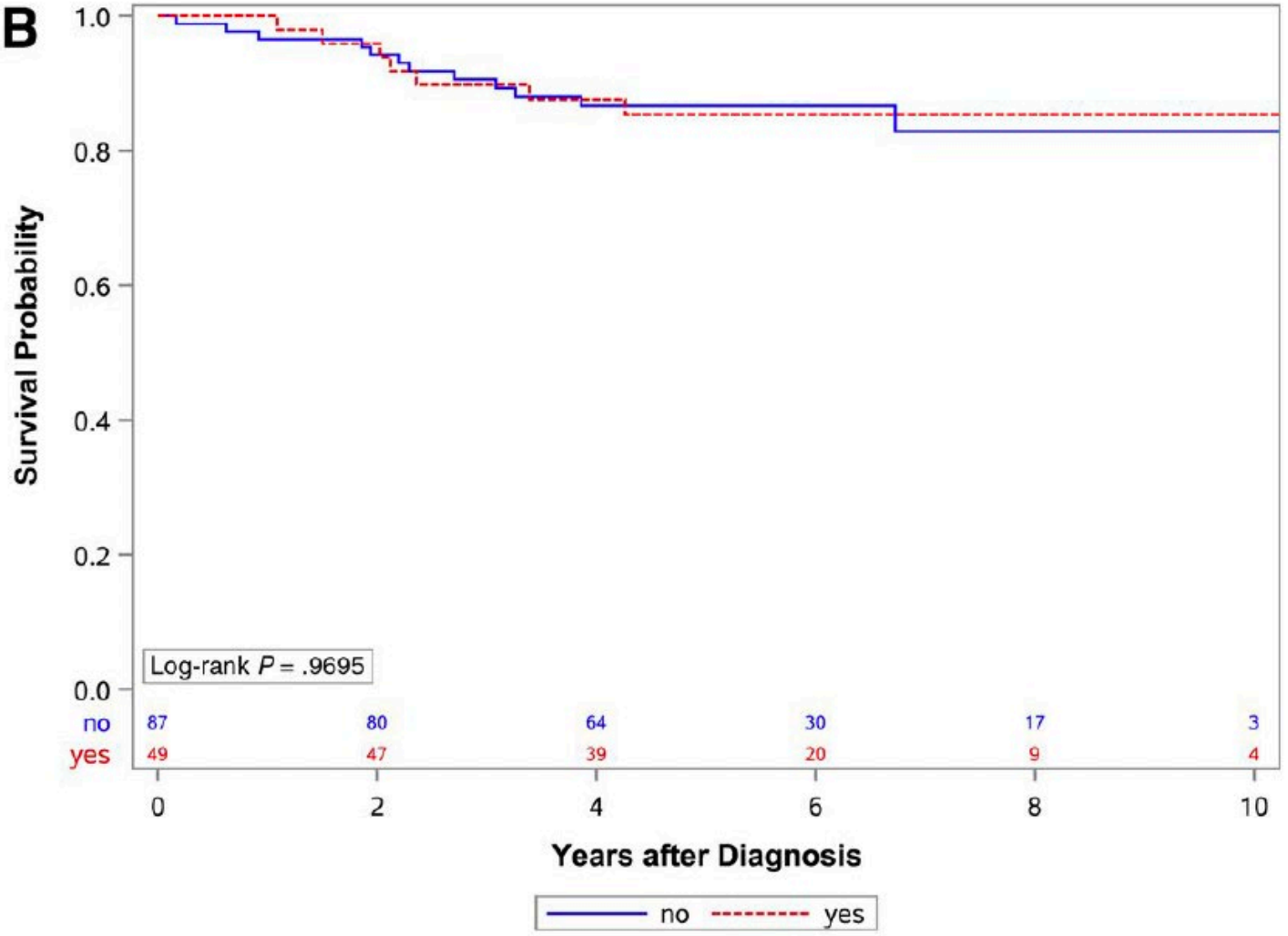
DP|B



- Reti ...ts
- DPE ...).01)
  - P...
  - N...
  - N...

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DPE for BP-RMS

- **Many patients undergoing DPE had an R1 or R2 resection**
- **Patient selection & surgical technique may play a role**
- **These data underline the importance of R0 resection if a DPE is chosen, but also clearly demonstrate the importance of careful discussion with families and shared decision making across disciplines**

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ARST2031: High-Risk RMS

Study	Drugs	Stage 4 ERMS, >10 years	Stage 4 ARMS
D9802 (High Risk)	VAC + V/I Window	23% (5 yr)	12% (5 yr)
ARST 0431 (High Risk)	VI/VDC/IE/VAC	32% (3 yr)*	16% (5 yr)
ARST 08P1 (High Risk)	VI/VDC/IE/VAC +/- Cixutumumab or temozolamide	48% (3 yr)	6% (3 yr)

- **Randomized Phase 3 Trial of Vinorelbine, Dactinomycin, and Cyclophosphamide (VINO-AC) Plus Maintenance Chemotherapy with Vinorelbine and Oral Cyclophosphamide vs Vincristine, Dactinomycin and Cyclophosphamide plus VINO-CPO Maintenance**

ARST2031: High-risk RMS

- **Primary Outcome:**
  - To compare the EFS of patients with HR-RMS treated with VINO-AC followed by 24 weeks of VINO-CPO maintenance therapy to that of patients treated with VAC followed by 24 weeks of VINO-CPO maintenance
- **Secondary Outcomes:**
  - Toxicity, OS, safety & feasibility, objective response

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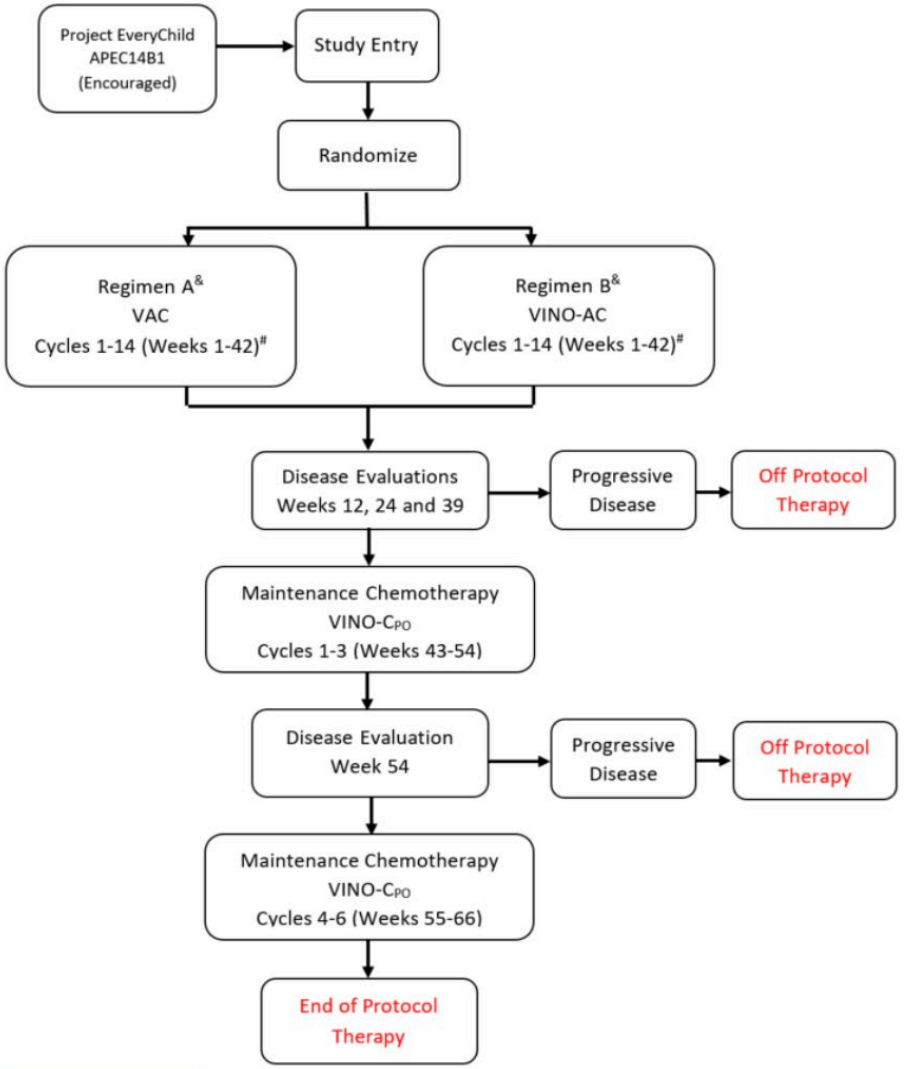
ARST2031: High-risk

- **<50 yo**
- **ERMS: Stage 4, Group IV, ≥ 10 yo**
- **ARMS: Stage 4, Group IV**
- **Max 118 pts (100 randomized)**
- **30 month trial, 2 y follow up**

- **Launched 9/2021**



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Lung Mets in RMS

- Patients with stage 4 disease have dismal prognosis
  - EFS < 20%
  - Exception in ERMS < 10 yrs of age = 3-yr EFS 60-64% • ≥ 10 yrs = 3-yr EFS 32%-48%
- Lung metastases are the most common site of metastatic disease, present at diagnosis in 5.7% of all new RMS
- Retrospective analysis of previous (1999-2013) COG trials
  - D9802, D9803, ARST0431, ARST08P1

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ORIGINAL REPORT

Prognostic Factors in Metastatic Rhabdomyosarcomas: Results of a Pooled Analysis From United States and European Cooperative Groups

Odile Oberlin, Annie Rey, Elizabeth Lyden, Gianni Bisogno, Michael C.G. Stevens, William H. Meyer, Modesto Carli, and James R. Anderson

Table 1. Patient Characteristics

Characteristic	No. of Patients	3-Year EFS (%)	SE	Relative Risk of Event*	Log-Rank Test (*P*)
Lung metastases					
Lung only	145	42	4.2	1	< .0005
Outside the lung	643	24	1.7	1.5	
No. of sites of metastases					
≤ 2	643	30	1.8	1	< .0001
≥ 3	145	14	3.0	1.8	

Pediatr Blood Cancer 2011;56:725–732

Embryonal Rhabdomyosarcoma With Metastases Confined to the Lungs: Report From the CWS Study Group

Tobias M. Dantonello, MD,[1]* Peter Winkler, MD,[2] Tobias Boelling, MD,[3] Godehard Friedel, MD,[4] Irene Schmid, MD,[5] Adrian C. Mattke, MD,[6] Gustaf Ljungman, MD,[7] Stefan S. Bielack, MD,[1,8] Thomas Klingebiel, MD,[9] and Ewa Koscielniak, MD[1,10] on behalf of the CWS Study Group

- 29 patients with ERMS and isolated lung metastases
- (EFS, dotted line) and (OS, solid line)

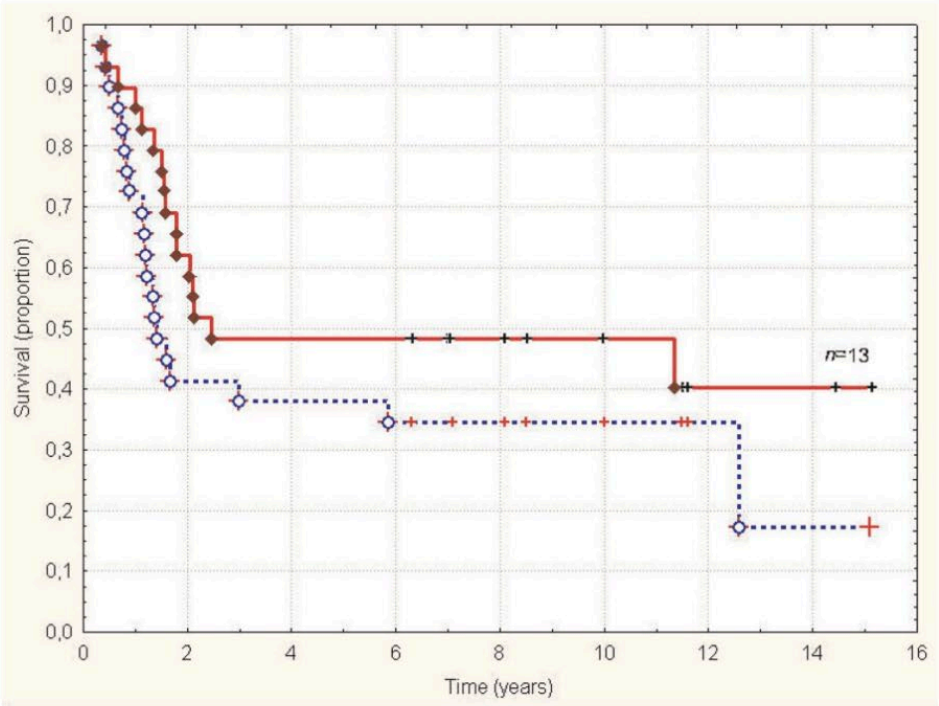
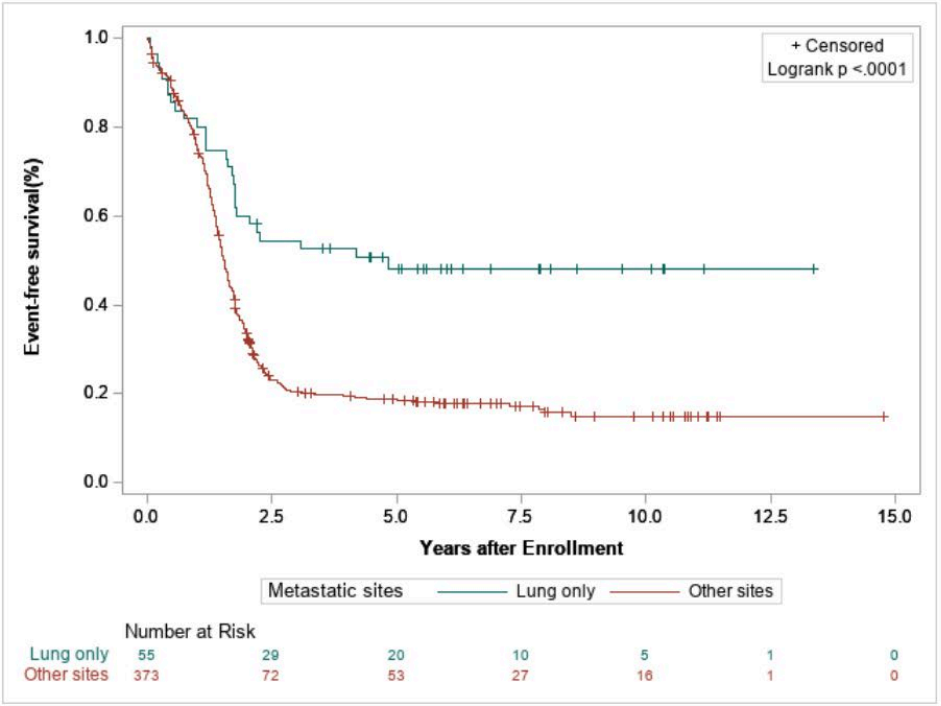
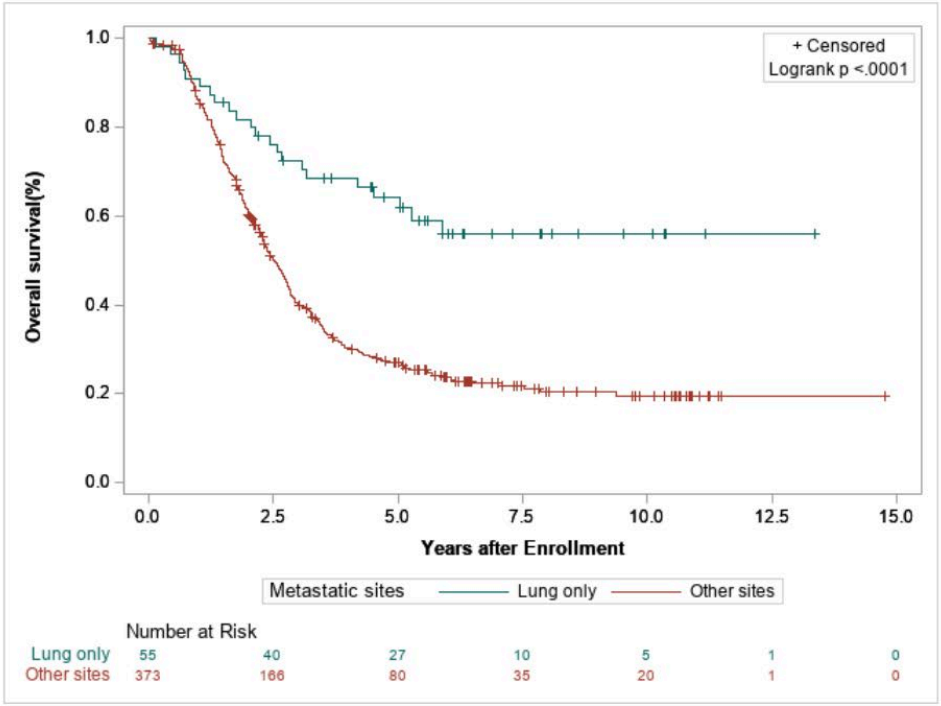


Table 1. Characteristics of patients with rhabdomyosarcoma metastatic to lung only and to other sites

	Lung only		Other sites -/+ lung		p-value*
Variable	Number	(%)	Number	(%)	
Histology Subtype					<.0001
Alveolar	7	12.73	247	66.22	
Embryonal	41	74.55	96	25.74	
Botryoid	1	1.82	0	0	
Spindle cell	3	5.45	3	0.80	
Other	3	5.45	27	7.24	
Primary Site					<.0001
Extremity	4	7.27	101	27.08	
GU Bladder/Prostate	9	16.36	30	8.04	
GU non-Bladder/Prostate#	5	9.09	35	9.38	
Head and Neck, nonparameningeal#	4	7.27	13	3.49	
Orbit#	0	0	1	0.27	
Parameningeal	13	23.64	35	9.38	
Perineum	1	1.82	24	6.43	
Retroperitoneal	9	16.36	60	16.09	
Trunk/paravertebral	3	5.45	36	9.65	
Intrathoracic	0	0	13	3.49	
Other	7	12.73	18	4.83	
Unknown	0	0	7	1.88	
Tumor Invasiveness					0.0014
T1	12	21.82	28	7.51	
T2	43	78.18	344	92.23	
Tx	0	0	1	0.27	

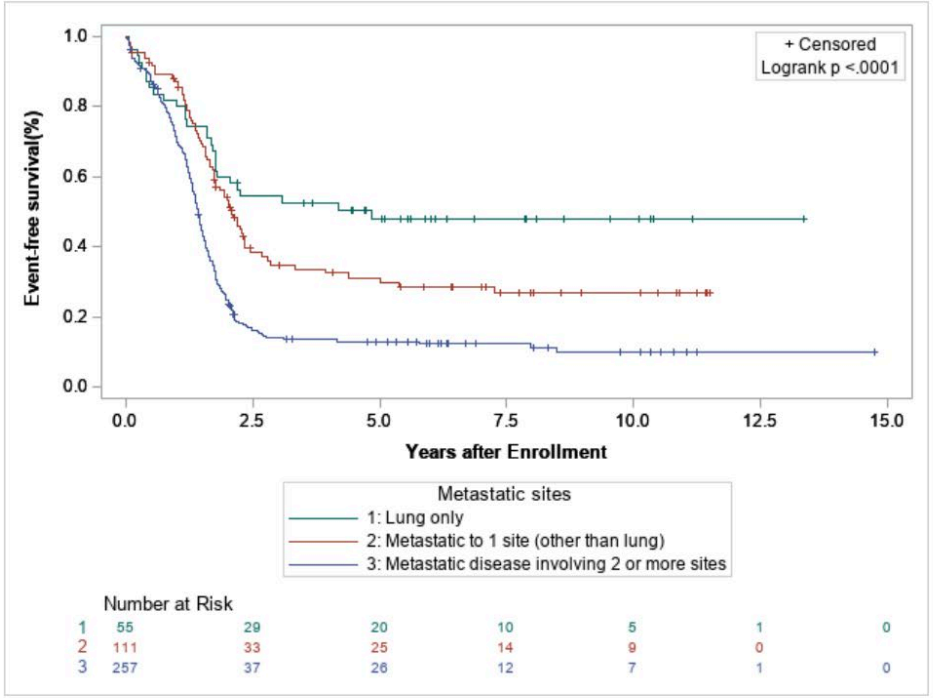
Figure 1. EFS and OS and comparing patients with RMS metastatic disease in lung only vs. all other metastatic sites -/+ lungs

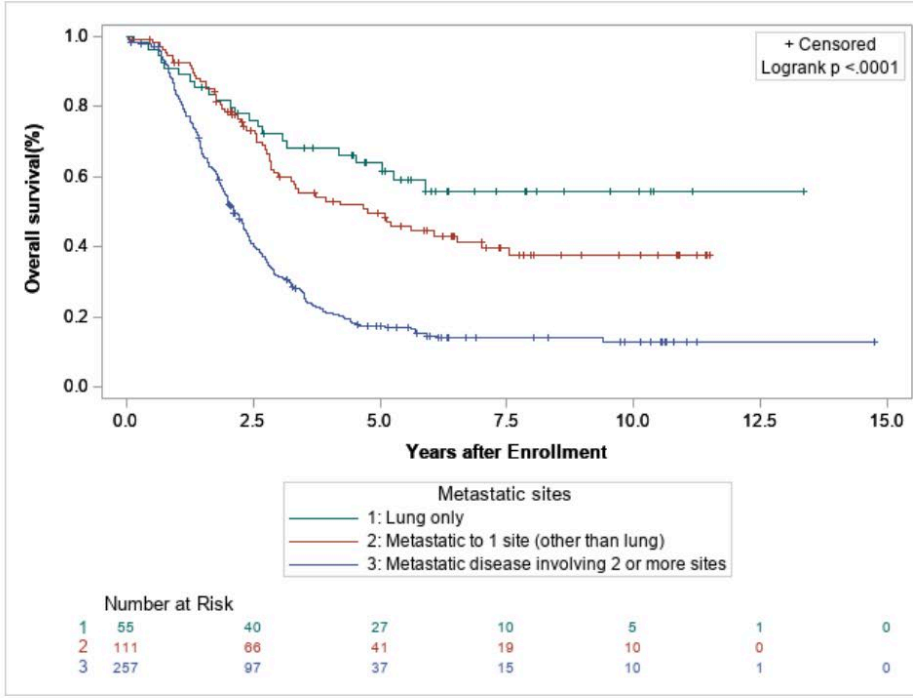




	5-year EFS (%)	p-value	5-year OS (%)	p-value
Metastatic sites		<0.0001		<0.0001
Lung only	48.12 (32.93, 63.31)		64.12 (49.63, 78.61)	
Other sites	18.82 (14.26, 23.39)		26.89 (21.85, 31.93)	

Figure 2. EFS and OS comparing patients with RMS metastatic disease divided into 3 groups: lung only, metastatic disease limited to 1 site (other than lung), and metastatic disease involving 2 or more sites (with or without lung).





	5-year EFS (%)	p-value	5-year OS (%)	p-value
Metastatic sites				
Lung only	48.12 (32.93, 63.31)	<0.0001	64.12 (49.63, 78.61)	<0.0001
Metastatic to 1 site (other than lung)	31.29 (21.12, 41.46)		49.60 (38.82, 60.38)	
Metastatic disease involving 2 or more sites	13.13 (8.43, 17.83)		17.56 (12.43, 22.70)	

Lung metastases in RMS

- Patients with lung-only metasteses:
  - Have a greater proportion of tumors with embryonal histology
  - More likely to be under 10 yrs of age
  - Less likely to have regional nodal involvement
- Patients with ERMS and lung-only mets have superior EFS and OS even when ≧ 10 yrs of age at presentation
- **Patients with lung-only mets that receive lung XRT have lower rates of relapse/progression and trend toward improved EFS**

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Collaborative Groups

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INSTRuCT

- **Upcoming BP RMS study, to follow the COG analysis**

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