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CANCER AND BLOOD DISEASE INSTITUTE

PEDIATRIC SOFT TISSUE SARCOMA

SARCOMA EXCHANGE, SEPTEMBER 12, 2021

LEO MASCARENHAS, MD MS

Pediatric Soft Tissue Sarcomas

- Rhabdomyosarcoma (RMS)
  - Clinical approach and standard treatments
  - Ongoing frontline and upcoming frontline trials
- Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS)
  - Recently completed frontline clinical trials
  - Molecularly targeted treatment

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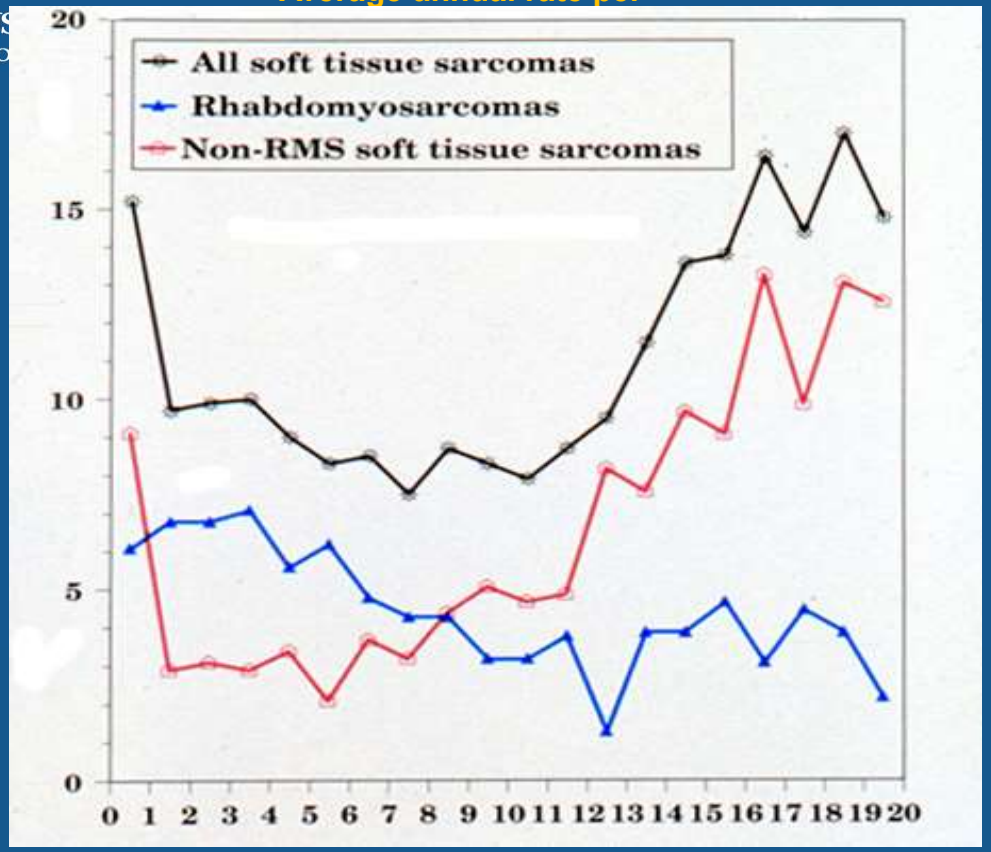

Soft tissue sarcoma age-specific incidence rates by histology (SEER 1976-94 combined)
(SEER Pediatric Monograph, NIH Pub. No.99-4649, 1999)

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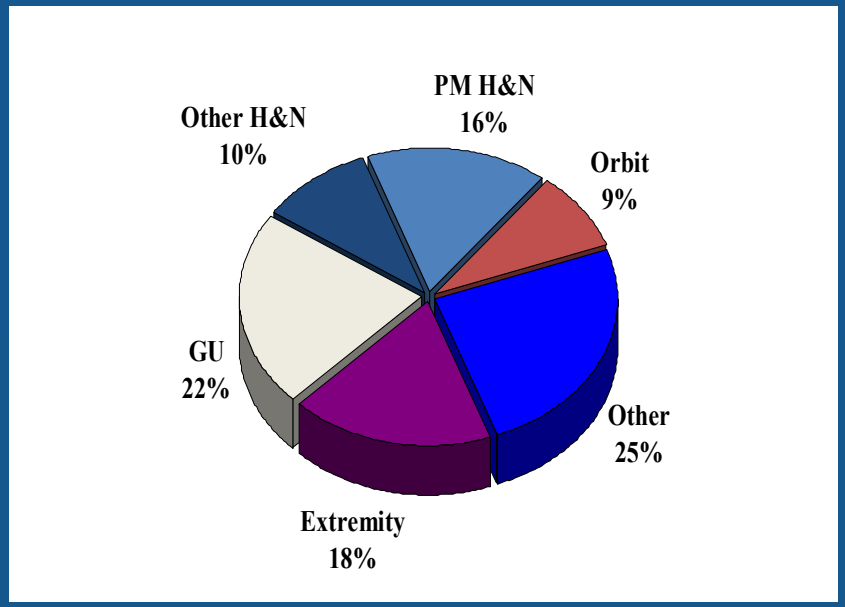
RHABDOMYOSARCOMA

Clinical Presentation

Mass, +/- pain, +/- disturbance in function

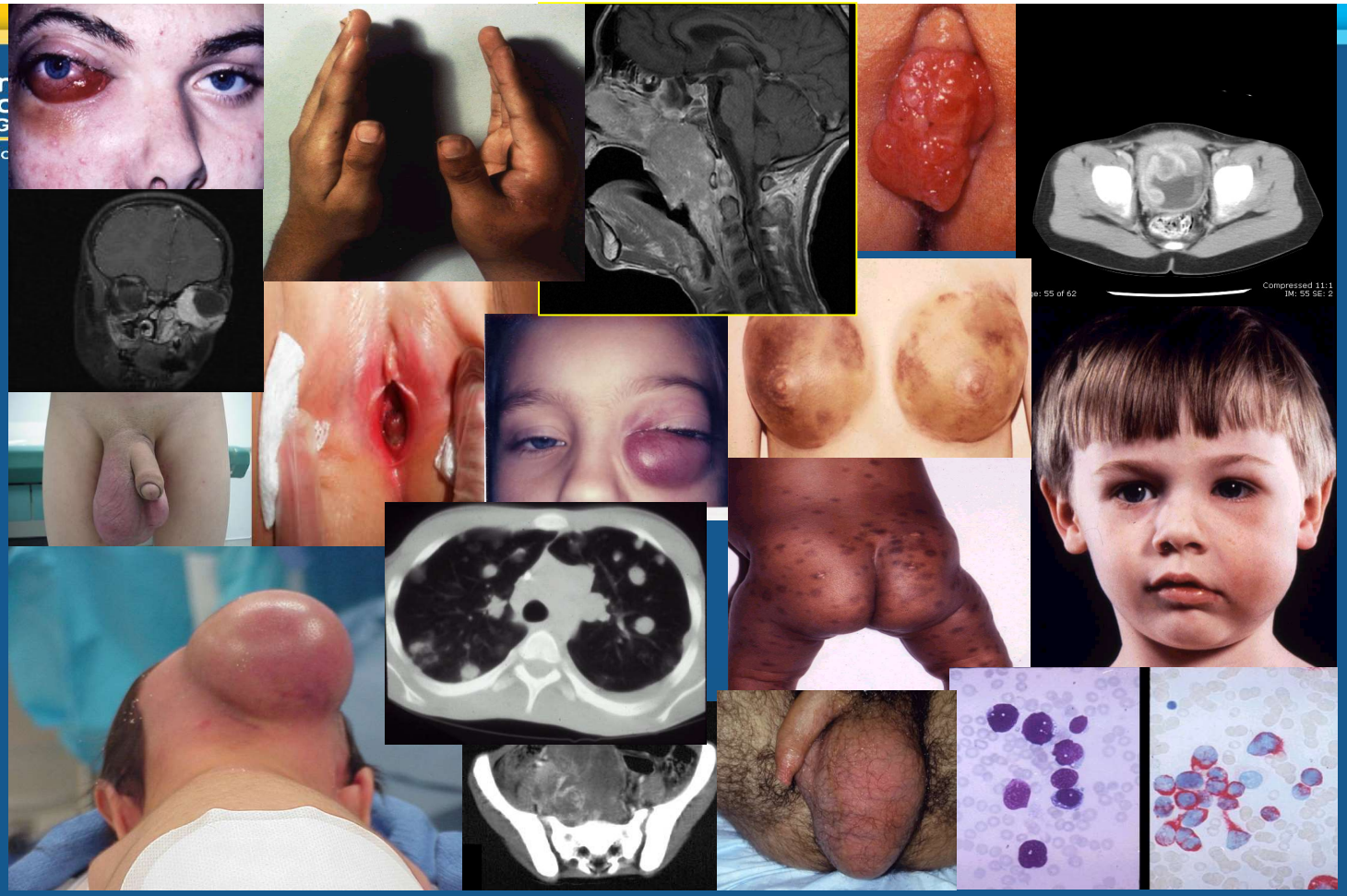


Patterns of Spread

Lymphatic: 40% of paratesticular and 20% of extremity tumors

Hematogenous: 10-20% at diagnosis (lung, bone, bone marrow, liver)

CNS extension: 50% of parameningeal (cranial nerve palsies, erosion of cranial bone, direct intracranial growth)


Compressed 11:1
IM: 55 SE: 2

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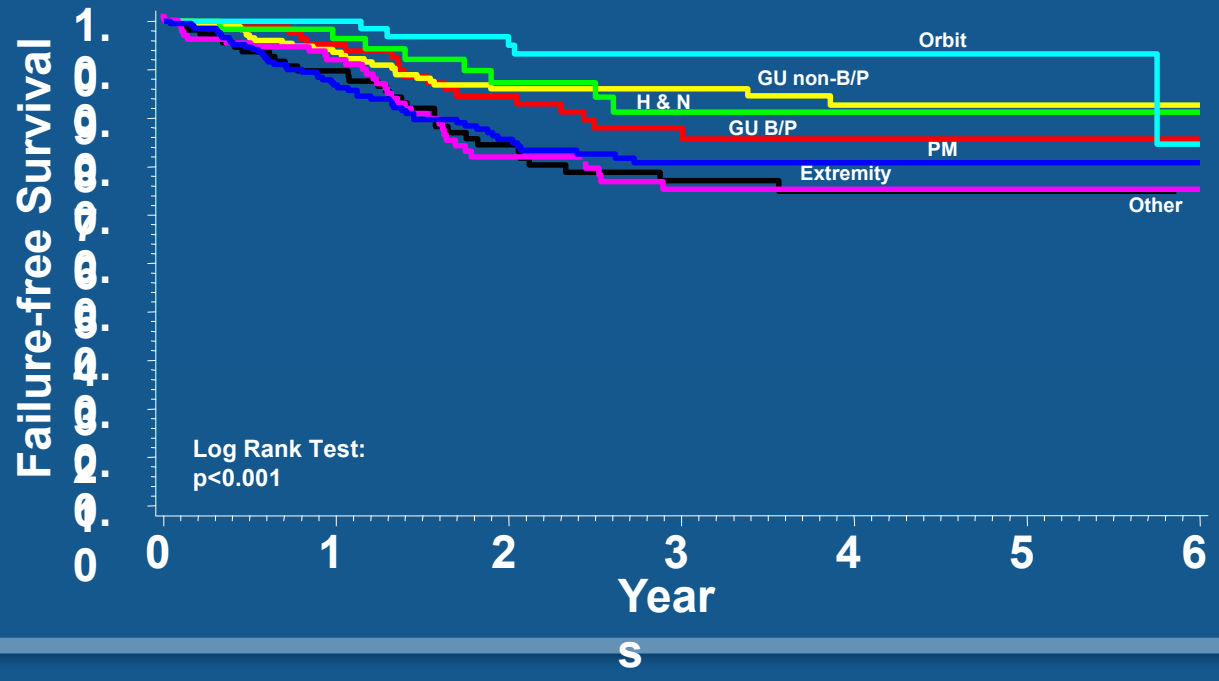
Failure-free Survival, IRS-IV for Patients with Local/Regional Tumors by Primary Site



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STAGING MADE EASY

Stage 1: Any tumor arising in a favorable site independent of size and lymph node involvement.

Stage 2: Tumors less than 5 cm in size arising from an unfavorable site without lymph node involvement.

Stage 3: Tumors greater than 5 cm in size arising from an unfavorable site or any size tumor arising from an unfavorable site with lymph node involvement.

Stage 4: Any tumor irrespective of site or size with distant metastases.

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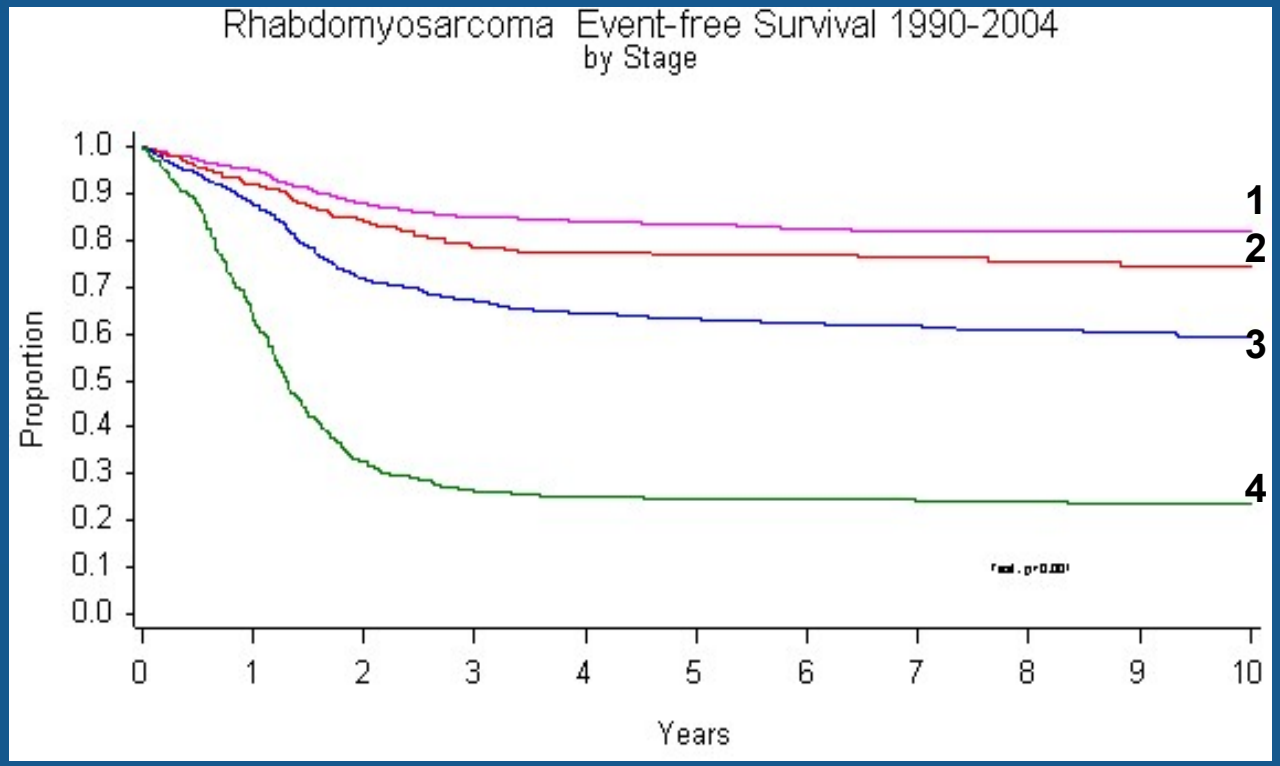

Courtesy J. Anderson Ph.D.
Statistician- STS Committee
Children's Oncology Group

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GROUPING MADE EASY

Group I: No residual disease (gross or microscopic).

Group II: Microscopic residual disease.

Group III: Gross residual disease.

Group IV: Distant metastases.

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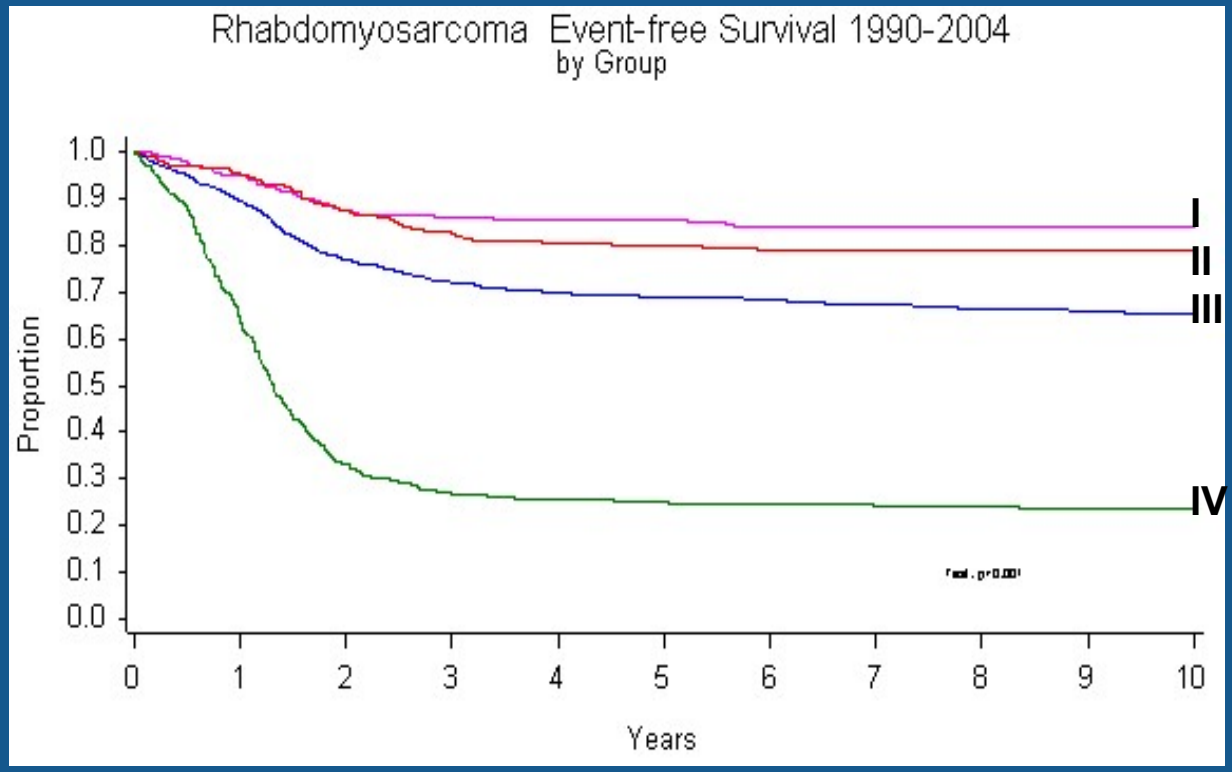

Courtesy J. Anderson Ph.D.
Statistician- STS

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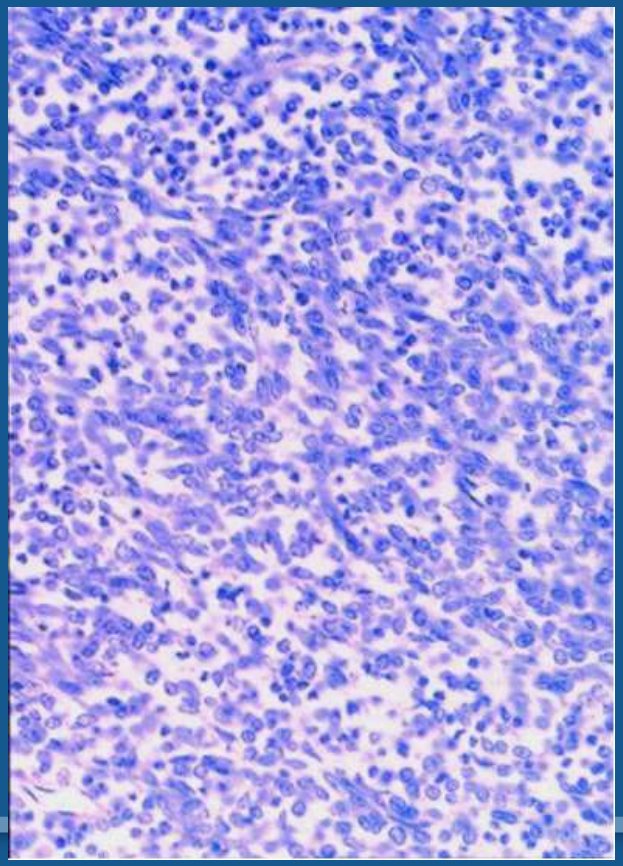
Embryonal RMS (ERMS)



Pathology

- 60-70% of cases
- Simulates immature skeletal muscle
- MyoD, Myogenin expressed

ERMS Variants:

- Solid ("embryonal"); favorable
- Botryoid (polypoid grossly); very favorable
- Spindle cell (leiomyomatous with cross striations); very favorable

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Alveolar RMS (ARMS)

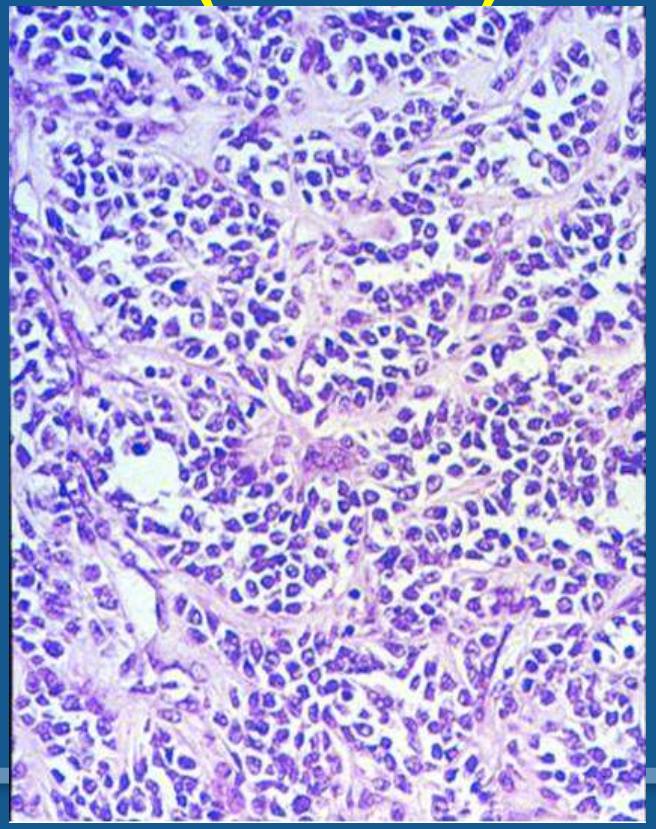
Pathology

20% of cases

Growth pattern reminiscent of pulmonary alveoli with fibrovascular septa

MyoD, Myogenin expressed

Associated with either a t(2;13)(q35;q14) or t(1;13)(p36;q14), extremity primary, lymph node involvement, and unfavorable prognosis



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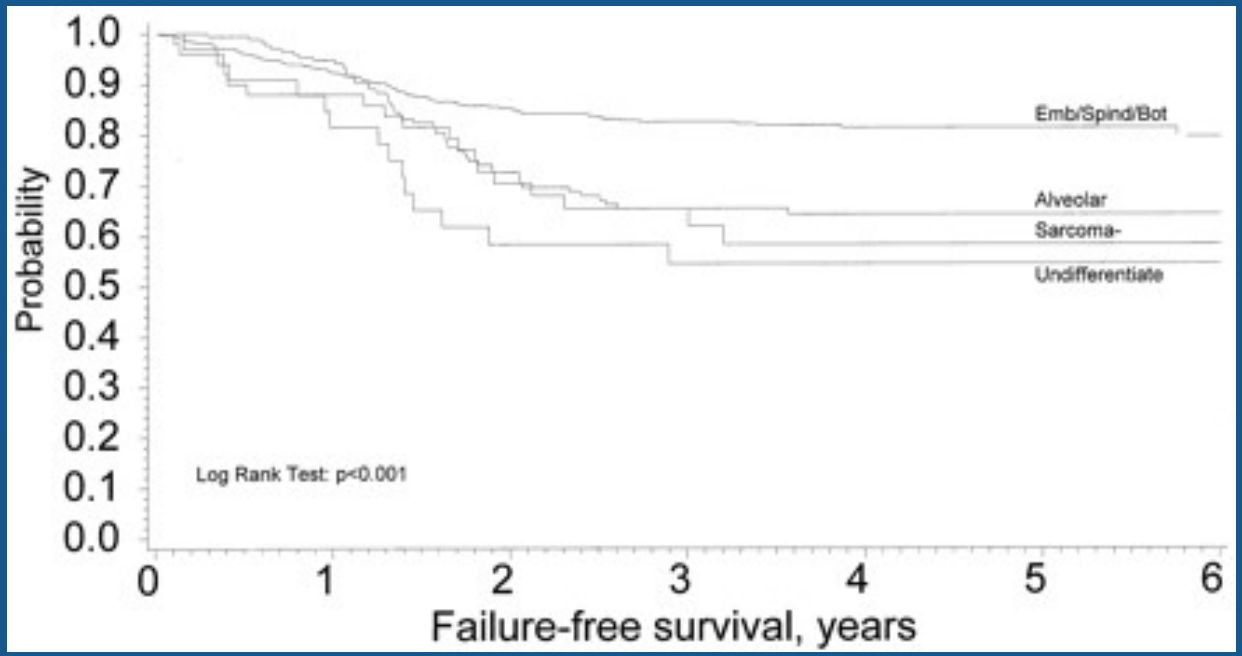
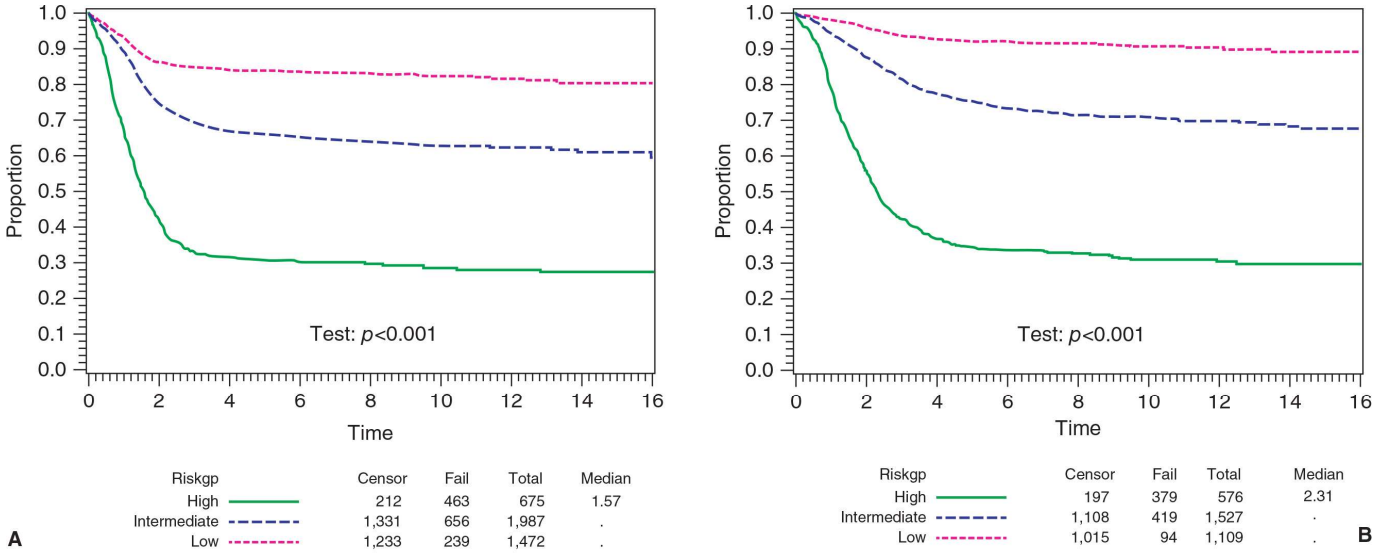
Outcome by histology, COG



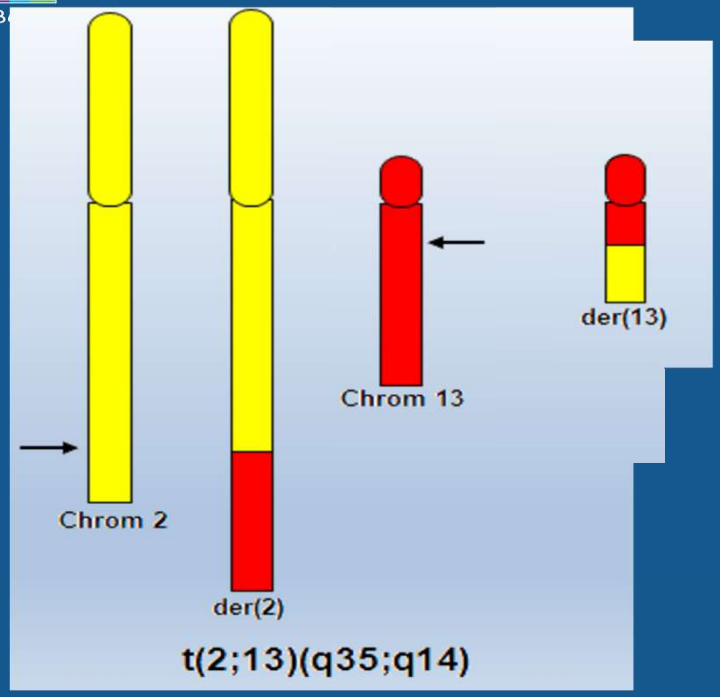
COG RMS Stratification, circa 2003-2015

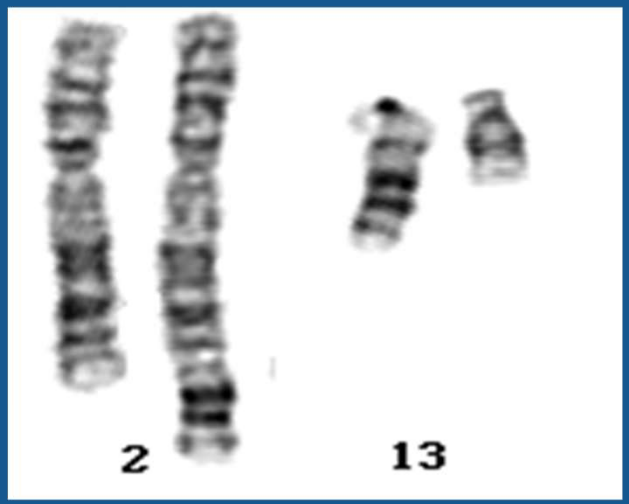
Risk Group	Stage	Group	Histology	COG study	Therapy
Low, subset 1	1	I-II	ERMS	ARST0331	VACx4, VAx4 24 weeks
	1	III (orbit)			
	2	I-II			
Low, subset 2	1	III (non-orbit)	ERMS	ARST0331	VACx4, VAx12 48 weeks
	3	I-II			
Intermediate	2-3	III	ERMS	ARST0531	VAC vs VAC/VI 42 weeks
	1-3	I-III	ARMS		
High	4	IV	ERMS	ARST08P1	VI/VDC/IE/VAC IGF-1R Ab, Temozolomide
			ARMS		

RMS Outcome by Risk Group: 1984-2012



Principles and Practice of Pediatric Oncology, Seventh Edition; data from James Anderson, Children's Oncology Group





First described by Turc-Carel et al 1987

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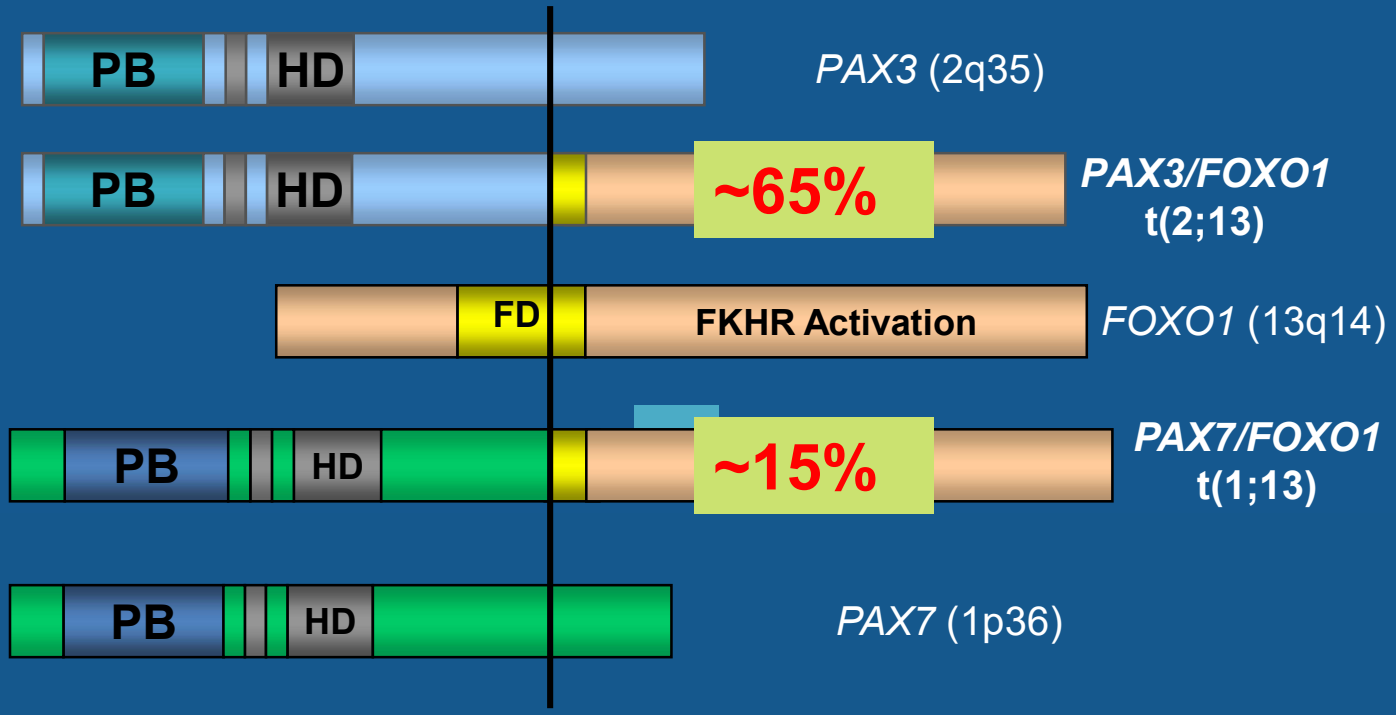
PAX/FOXO1 Fusion: ARMS



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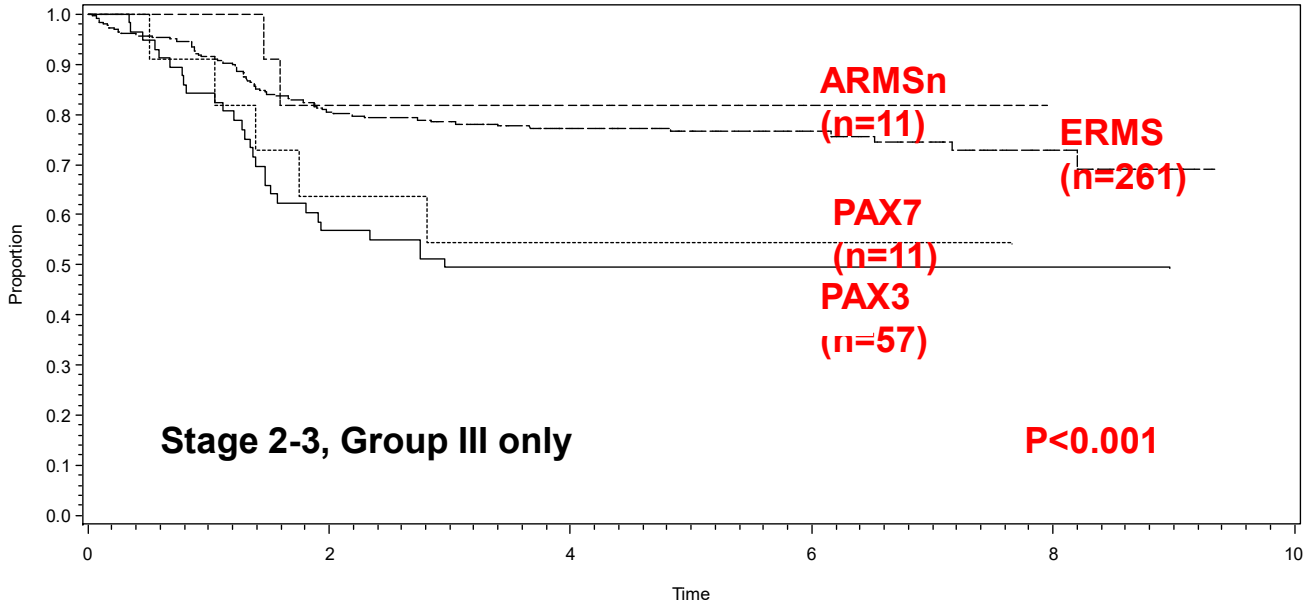
FOXO1 fusion and outcome



Skapek SX, Pediatr Blood Cancer 2013; 60:1411-1417

COG RMS Stratification, current

Risk Group	Stage	Group	Age	Fusion	COG study	Therapy
Low	1	I-II	Any	FOXO1-	None	VACx4, VAx4 24 weeks
	1	III (orbit)				
	2	I-II				
Intermediate	1	III (non-orbit)	Any	FOXO1-	ARST1431	VAC/VI +/- TEM 42 weeks, VRL/CY 24 weeks
	3	I-II		FOXO1-		
	2-3	III		FOXO1-		
	1-3	I-III		FOXO1+		
	4	IV	< 10 yr	FOXO1-		
High	4	IV	> 10 yr	FOXO1-	None currently	
			Any	FOXO1+		

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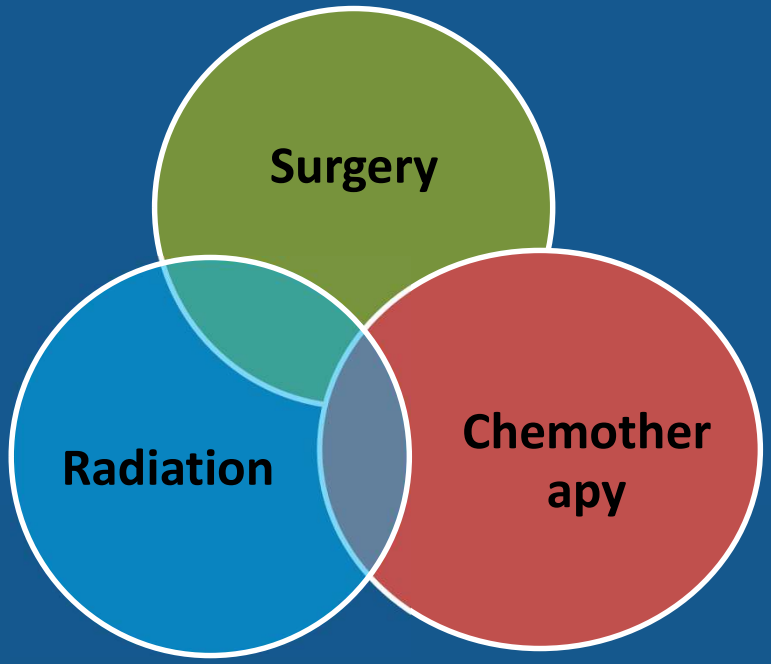
Treatment of RMS



Multimodality treatment with surgery, chemotherapy and radiotherapy has led to an overall survival of > 70% for all patients with rhabdomyosarcoma

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SURGERY

- Excision of primary tumor upfront whenever possible without causing major functional or cosmetic deficits
- Primary re-excision for residual tumor
- Special anatomic sites requiring surgical assessment of lymph nodes:
  - paratesticular (ISRLND/sampling)
  - extremity (node sampling)
- Second look surgery during treatment sometimes done for residual tumor

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RADIATION

- Local/regional relapse rates (IRS-IV): local (51%), regional (17%), and distant (32%)
- Patients with Group I embryonal tumors do not receive RT
- Treatment usually begins during weeks 3 – 18 of therapy
  - parameningeal (early for ICE)
  - vaginal
- Treatment volume is determined by pretreatment (pre-surgical) tumor size
- Doses of 3600 - 5040 cGy generally used; dose depends on Group (microscopic vs gross disease), primary site, nodal involvement, histology, and whether second look surgery performed

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Rhabdomyosarcoma is radiosensitive

IRS IV (1991-1997) radiation outcomes

5-yr local control for unresected RMS

- Extremity 96%
- Orbit 95%
- Bladder/prostate 90%
- Head and neck 88%
- Parameningeal 84%
- Other 90%.

Crist et al. JCO 19:3091, 2001
Donaldson et al. IJROBP 51:718,

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CHEMOTHERAPY

- Local and systemic tumor control
- Multi-agent/intensive/governed by risk-group
- Standard: vincristine, dactinomycin, and cyclophosphamide (VAC)
- Other active agents: irinotecan, topotecan, doxorubicin, etoposide, and ifosfamide

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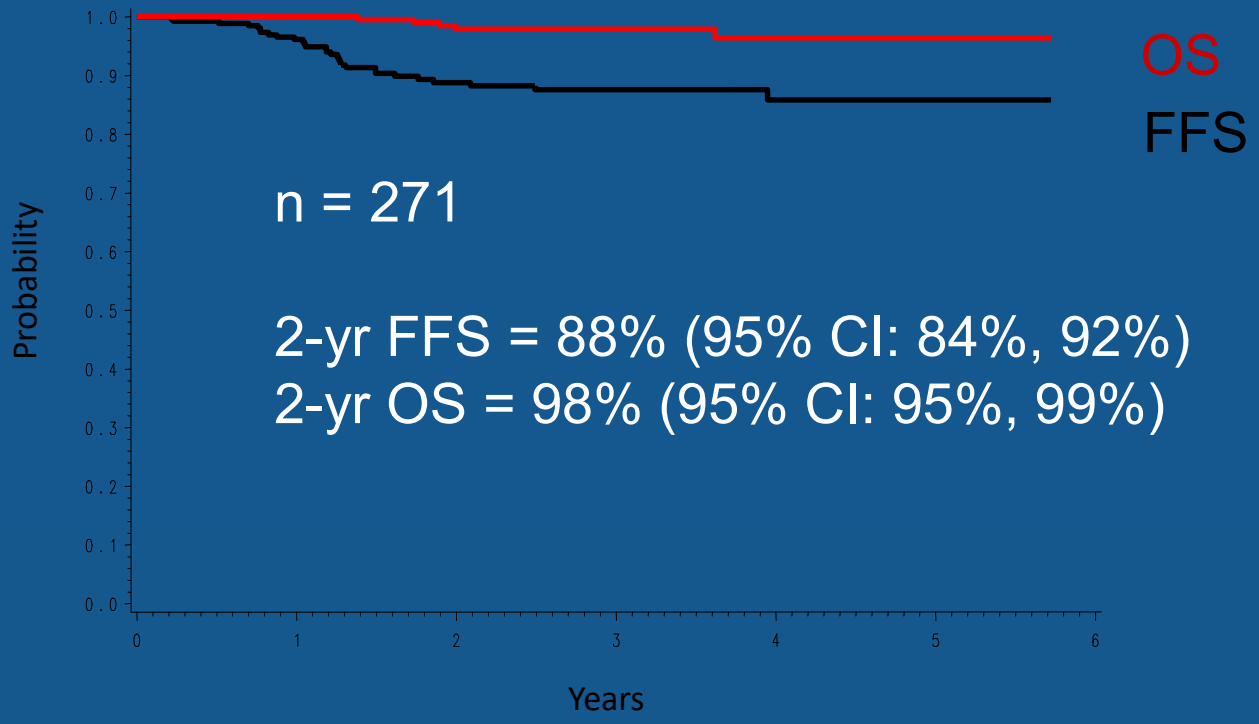
ARST0331: Subset 1



n = 271

2-yr FFS = 88% (95% CI: 84%, 92%)
2-yr OS = 98% (95% CI: 95%, 99%)

Walterhouse DO, JCO 2014 32:3547-3552

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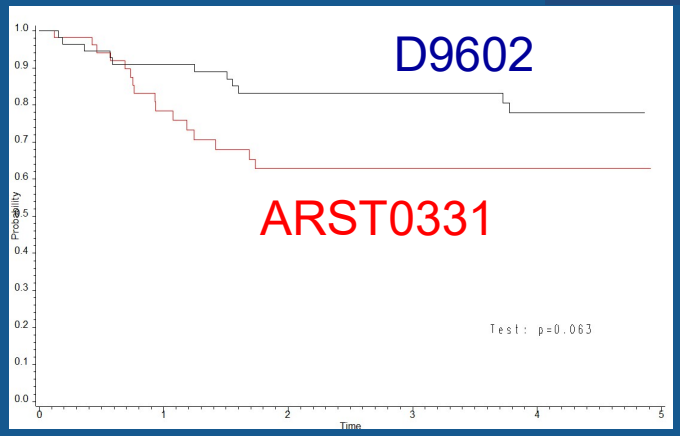
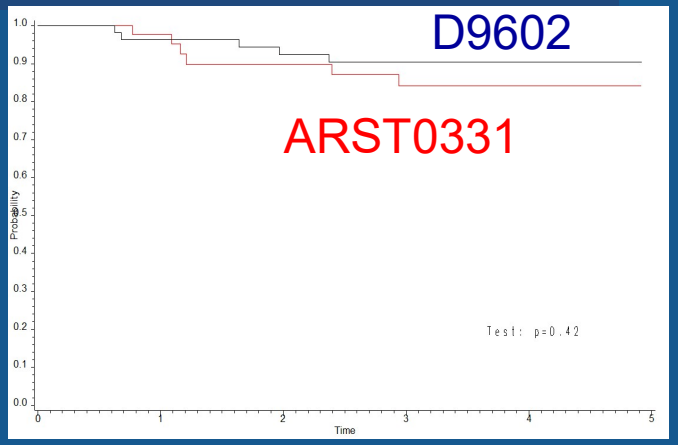
ARST0331: Subset 2





FFS **OS**

Walterhouse DO, Cancer. 2017 Jul 15;123(12):2368-2375

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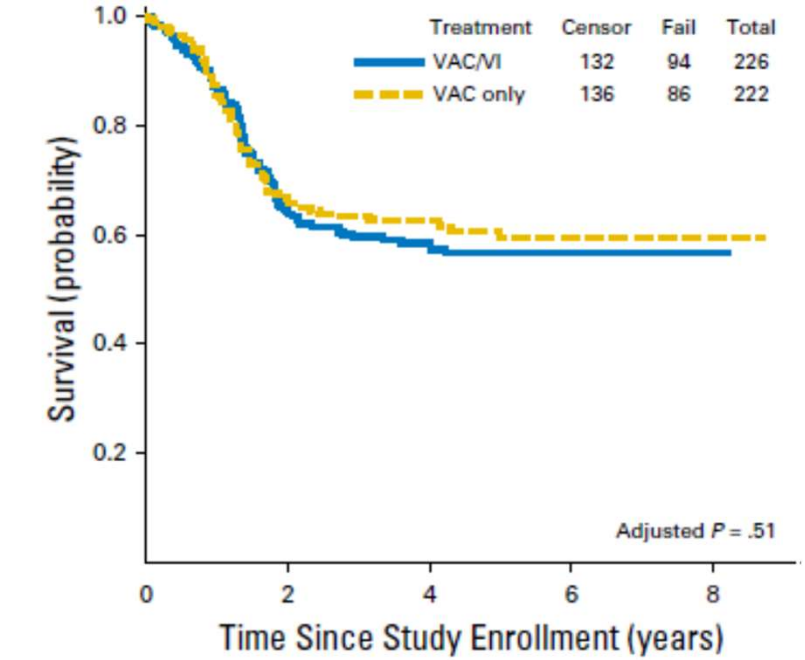
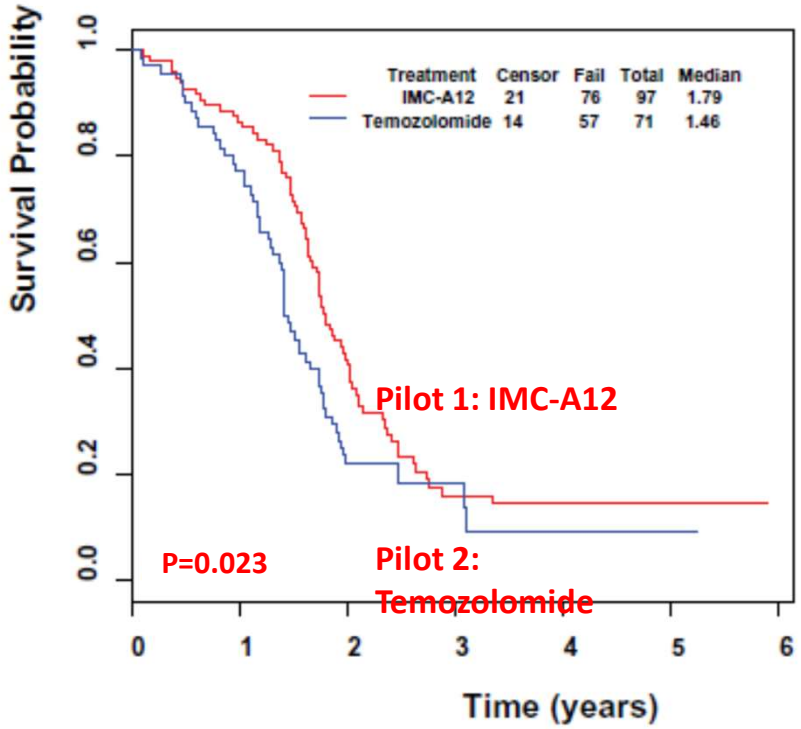
ARST0531: VAC, VAC/VI EFS similar



Hawkins DS, J Clin Oncol 2018 36:2770-2777

ARST08P1: Event-free survival



Malempati S, Cancer 2019; 125:290-297

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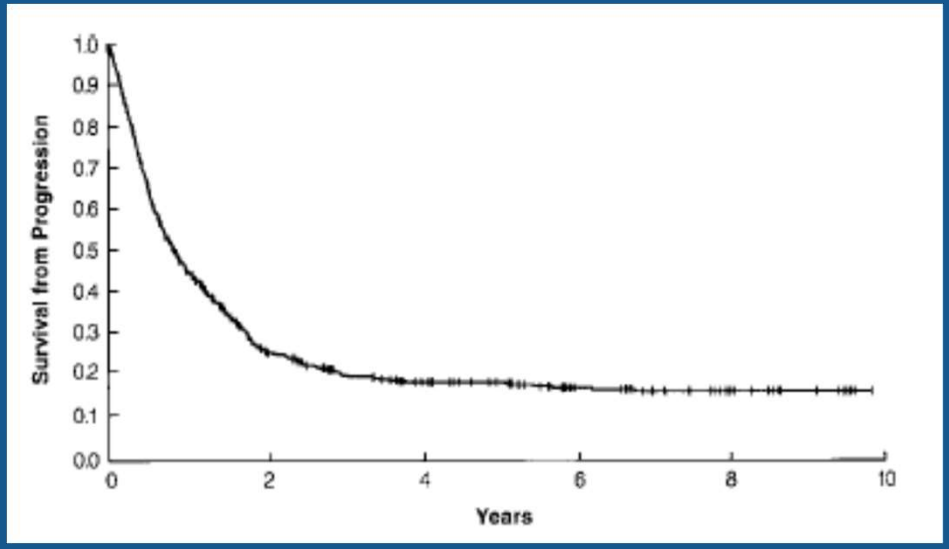
Relapsed Rhabdomyosarcoma

Majority of patient with relapsed rhabdomyosarcoma have a survival rate of less than 10% at 5 years.



Survival of patients with rhabdomyosarcoma treated on IRS-III, IRS-IVP and IRS IV after relapse or disease progression-

Pappo et al, JCO 17 (11) 1999: 3487-3493

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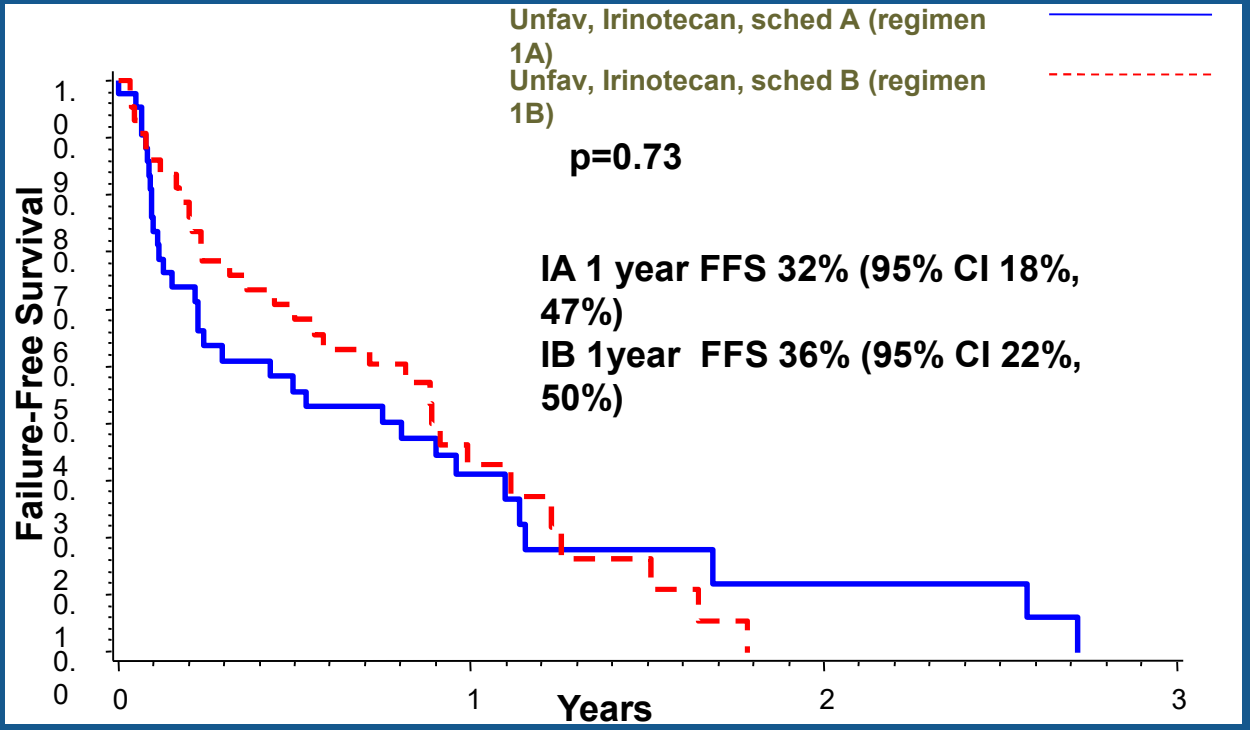
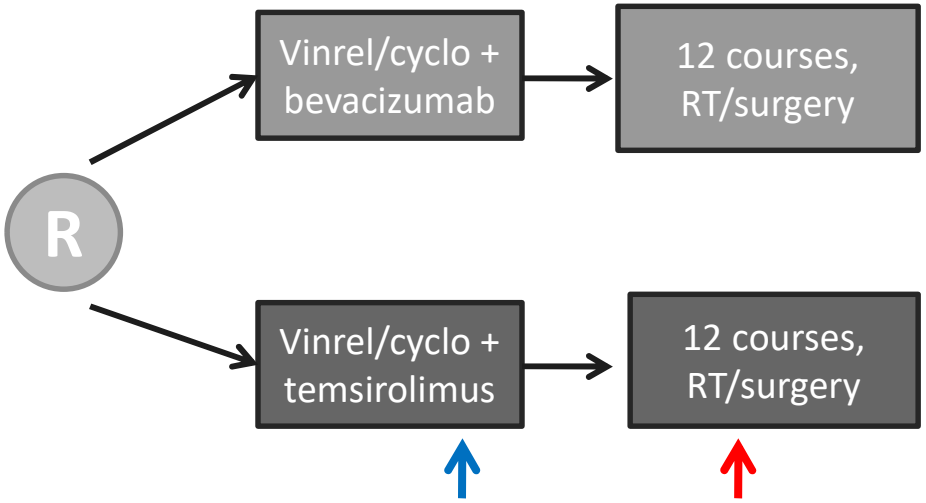
Failure-free Survival



Mascarenhas L et al,October 2010, JCO

ARST0921 Study Design



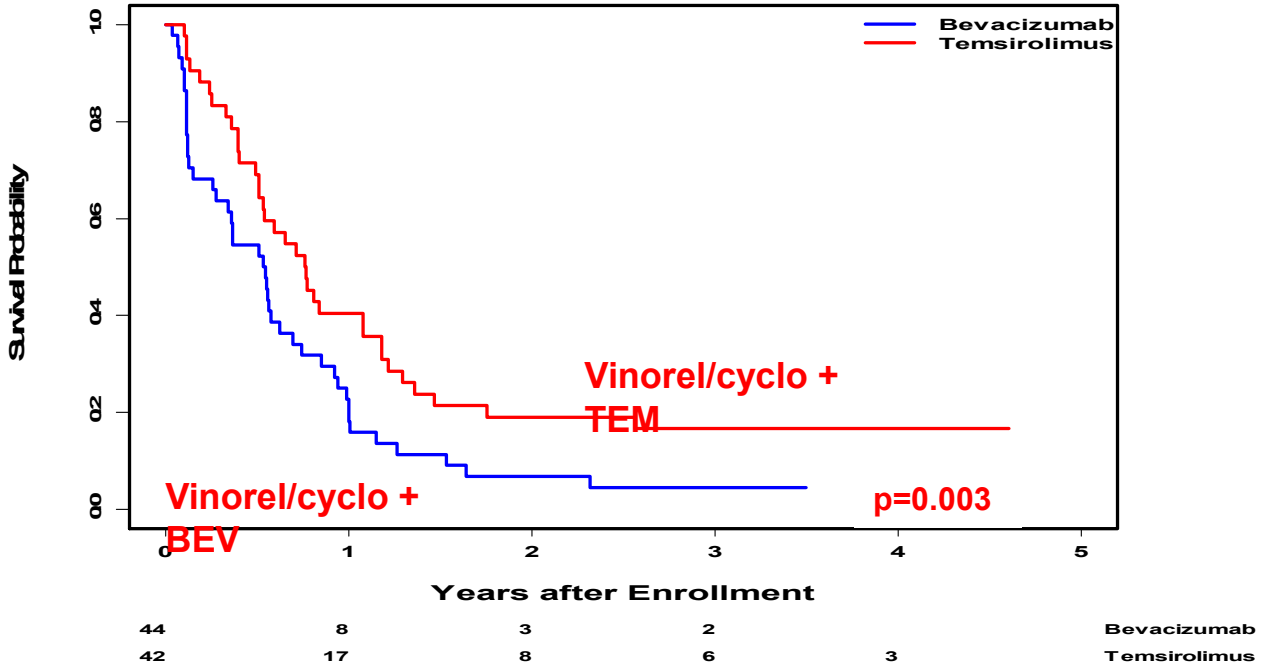
Secondary aim: RR @ 6 weeks **Primary aim: EFS**

Opened October 2010

Closed July 2013

Mascarenhas L, JCO 2019 Nov 1;37(31):2866-2874

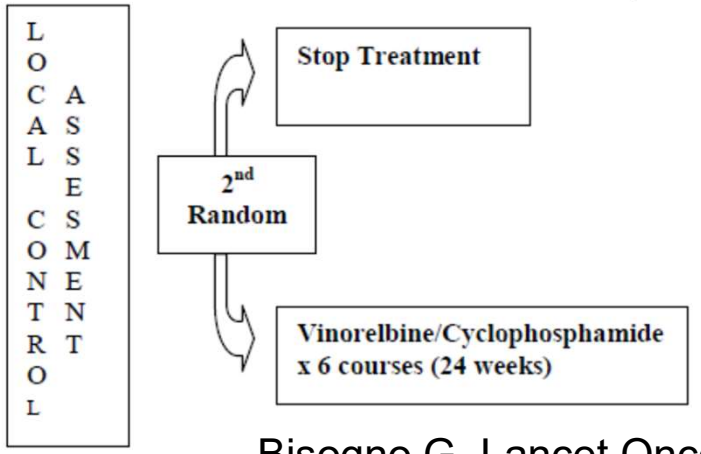
ARST0921: Event-free survival



Mascarenhas L, JCO 2019 Nov 1;37(31):2866-2874

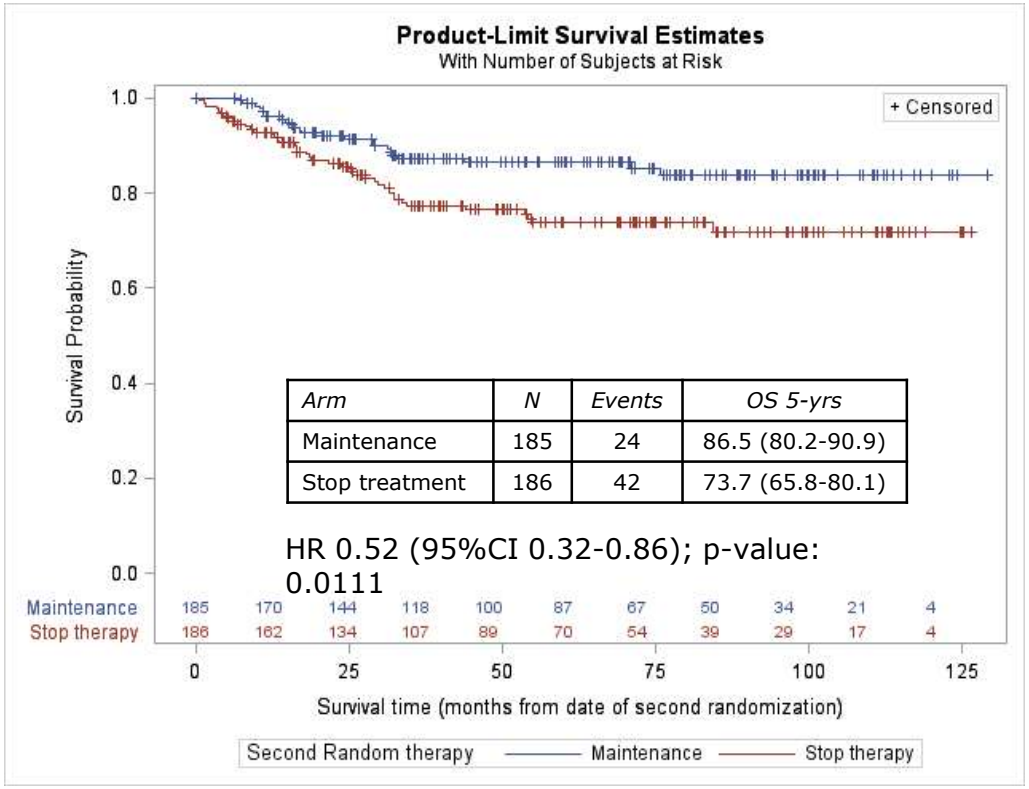
EpSSG RMS 2005: Study Design

- EpSSG RMS 2005 was a prospective phase III international, multi-institutional, non-blinded double randomized clinical trial.
- Patients in complete remission at the end of standard treatment will be randomized 1:1 (second randomization) to stop the therapy or to continue for 6 more months with the vinorelbine-cyclo regimen.
- Primary end point for the maintenance question is disease free survival, measured as time from date of second randomisation up to relapse or death.



Bisogno G, Lancet Oncol. 2019 Nov;20(11):1566-1575

EpSSG RMS 2005: Overall Survival

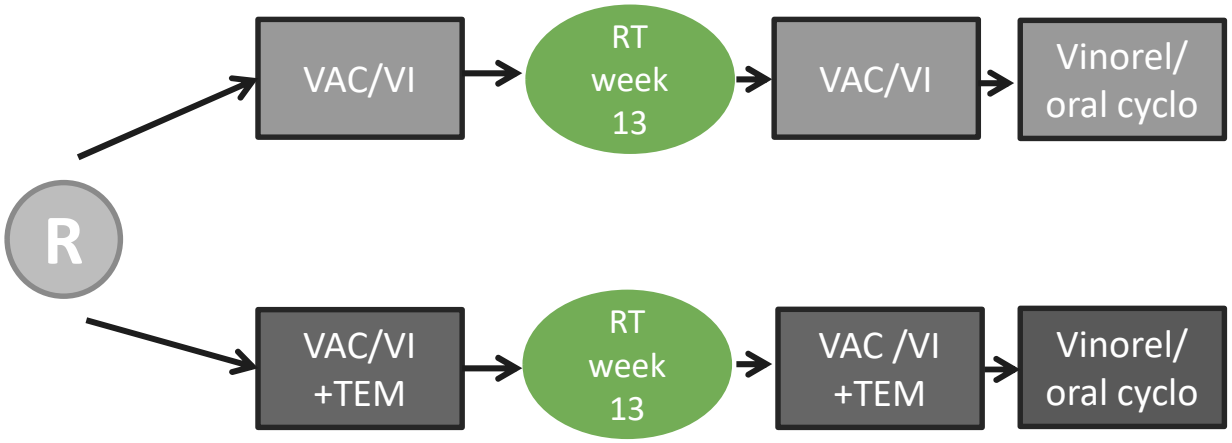


Arm	*N*	*Events*	*OS 5-yrs*
Maintenance	185	24	86.5 (80.2-90.9)
Stop treatment	186	42	73.7 (65.8-80.1)

HR 0.52 (95%CI 0.32-0.86); p-value: 0.0111

Bisogno G, Lancet Oncol. 2019 Nov;20(11):1566-1575

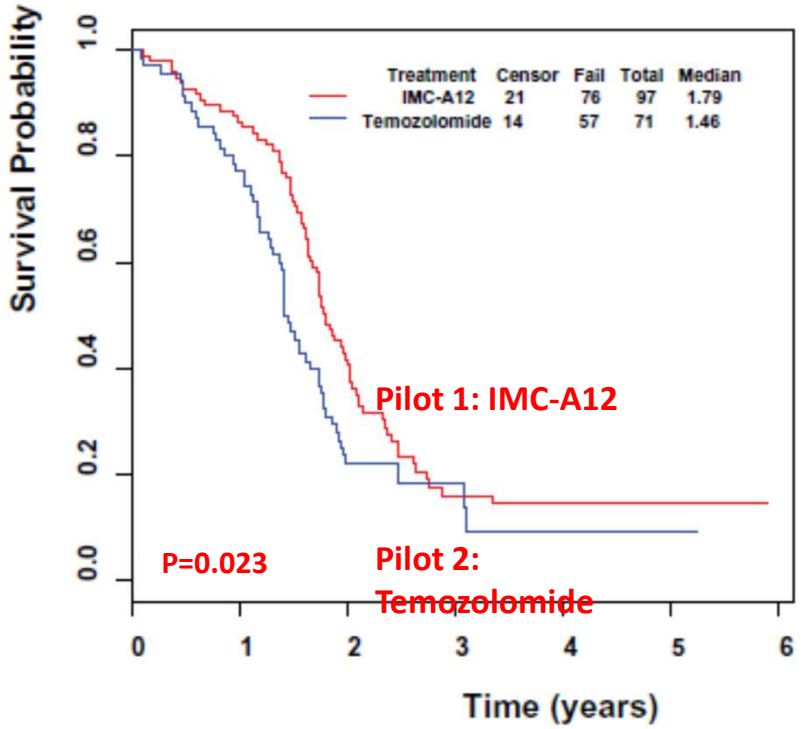
ARST1431 Study Design



Open: May 2016
Suspend: September 2016
Reopen: January 2018
Suspend: August 2018
Reopen: December 2018

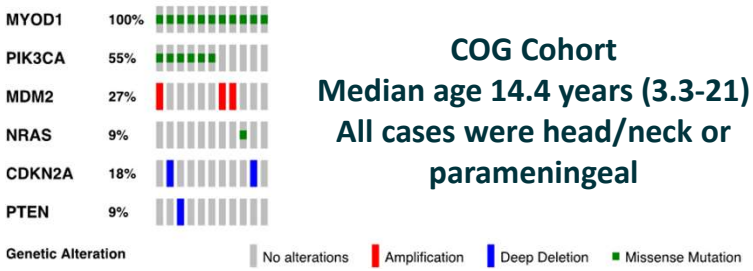
42 weeks + 24 weeks maintenance
12.6 g/m^2 total cyclophosphamide

ARST08P1: Event-free survival

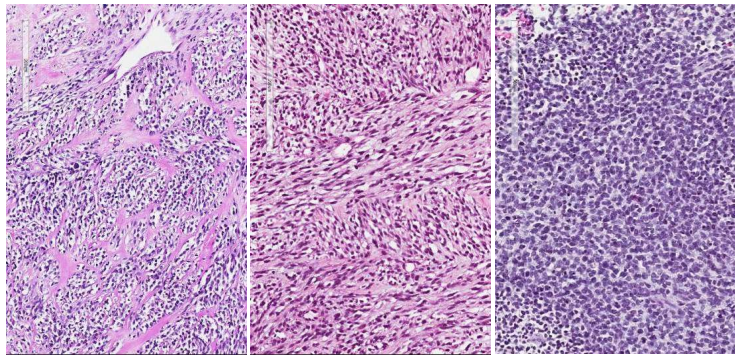


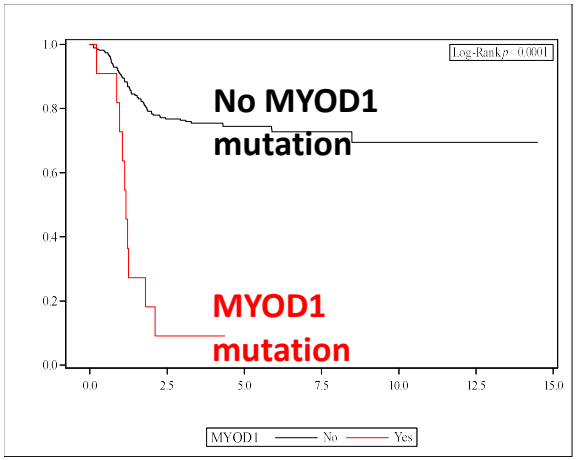
Malempati S, Cancer 2019; 125:290-297

FN: MYOD1 mutation very unfavorable

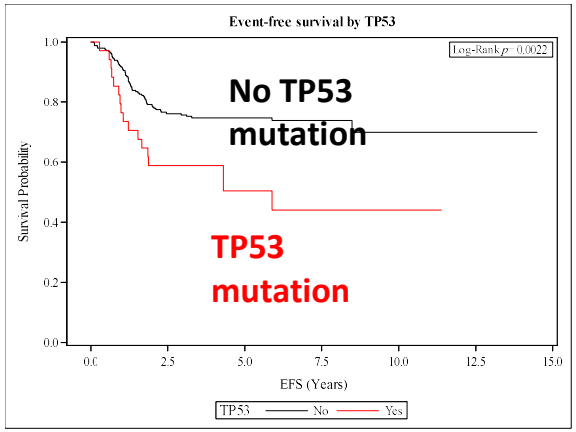


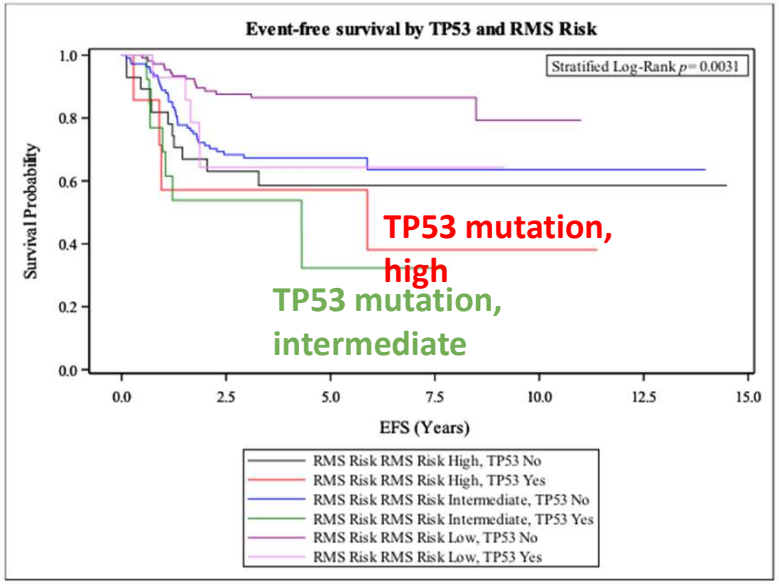
COG Cohort
Median age 14.4 years (3.3-21)
All cases were head/neck or parameningeal



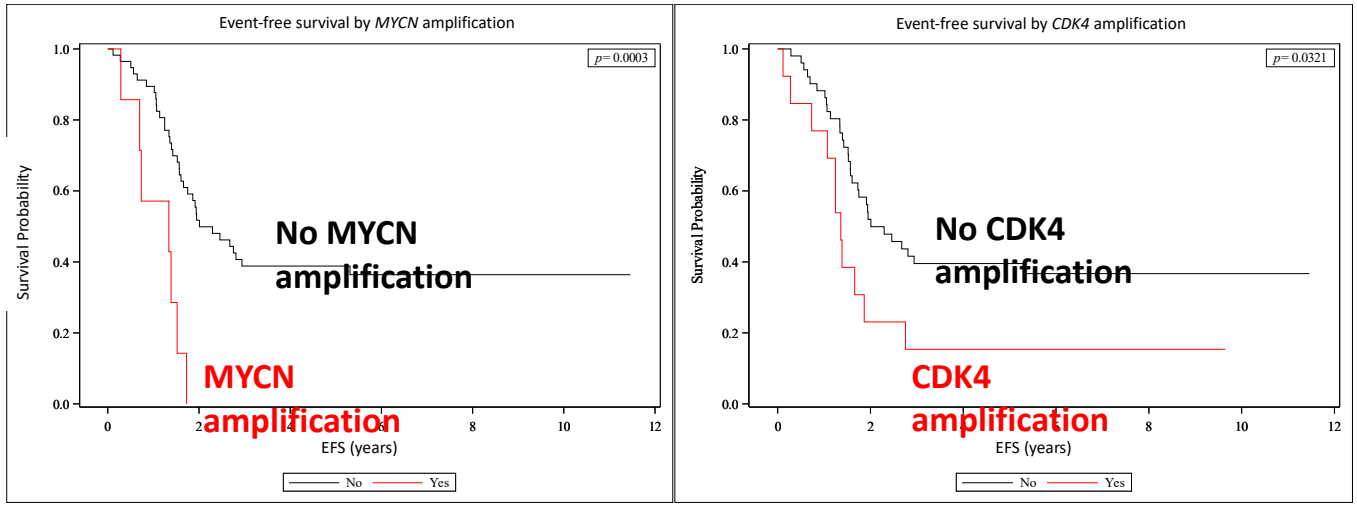


FN: TP53 mutation unfavorable





FP: MYCN, CDK4 amp unfavorable



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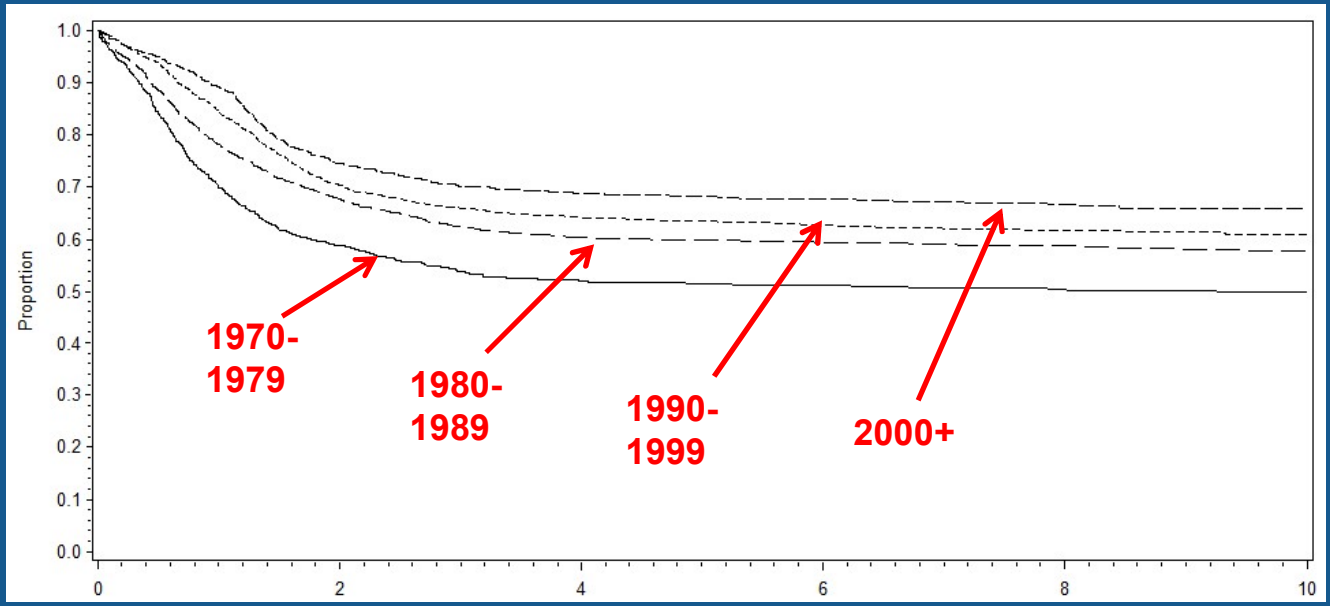
Improved RMS Outcome



CHILDREN'S ONCOLOGY GROUP

Courtesy of James Anderson, Children's Oncology Group

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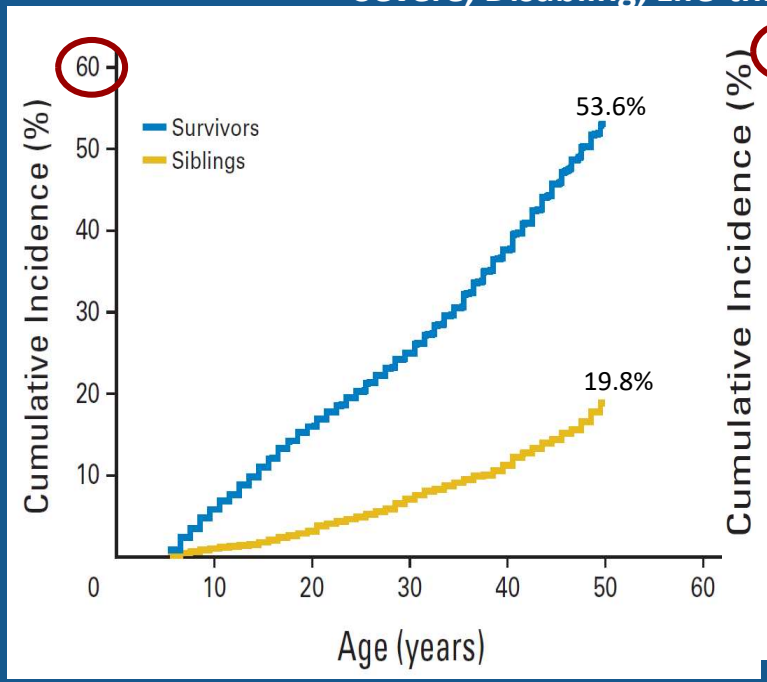
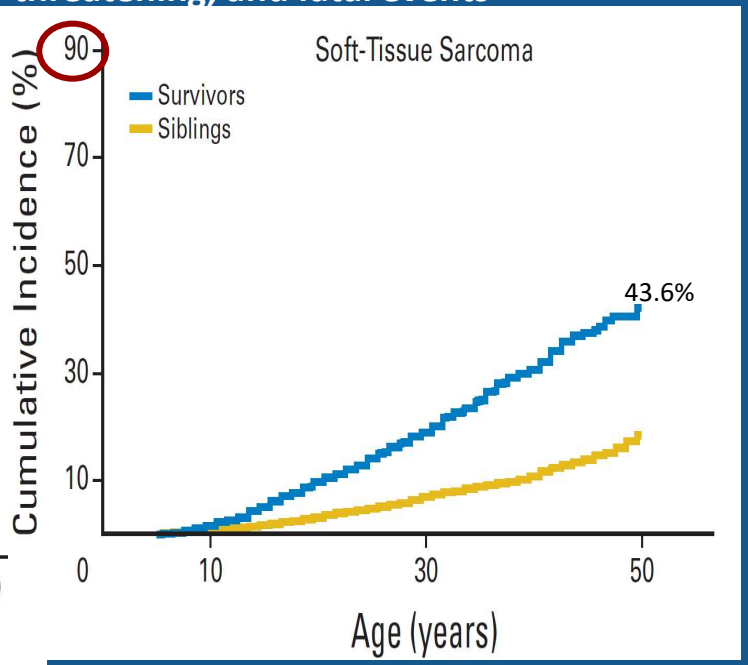
Long-term morbidity: aging cancer survivors

Severe, Disabling, Life-threatening, and fatal events





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Late Effects

- **Aging STS survivors have significantly increased risk of long-term health-related complications**
  - Tumor location
  - Young age at treatment
  - Multimodal approach for cure
- **Primary prevention is integral to decreasing the long-term burden due to health-related complications**
  - Limit radiation dose/field
  - Novel surgical approaches for local control
  - Reduce lifetime cumulative doses/exposures to treatments which can result in severe-disabling complications
- **Multi-disciplinary care and lifelong monitoring/ surveillance integral to maintaining well-being**

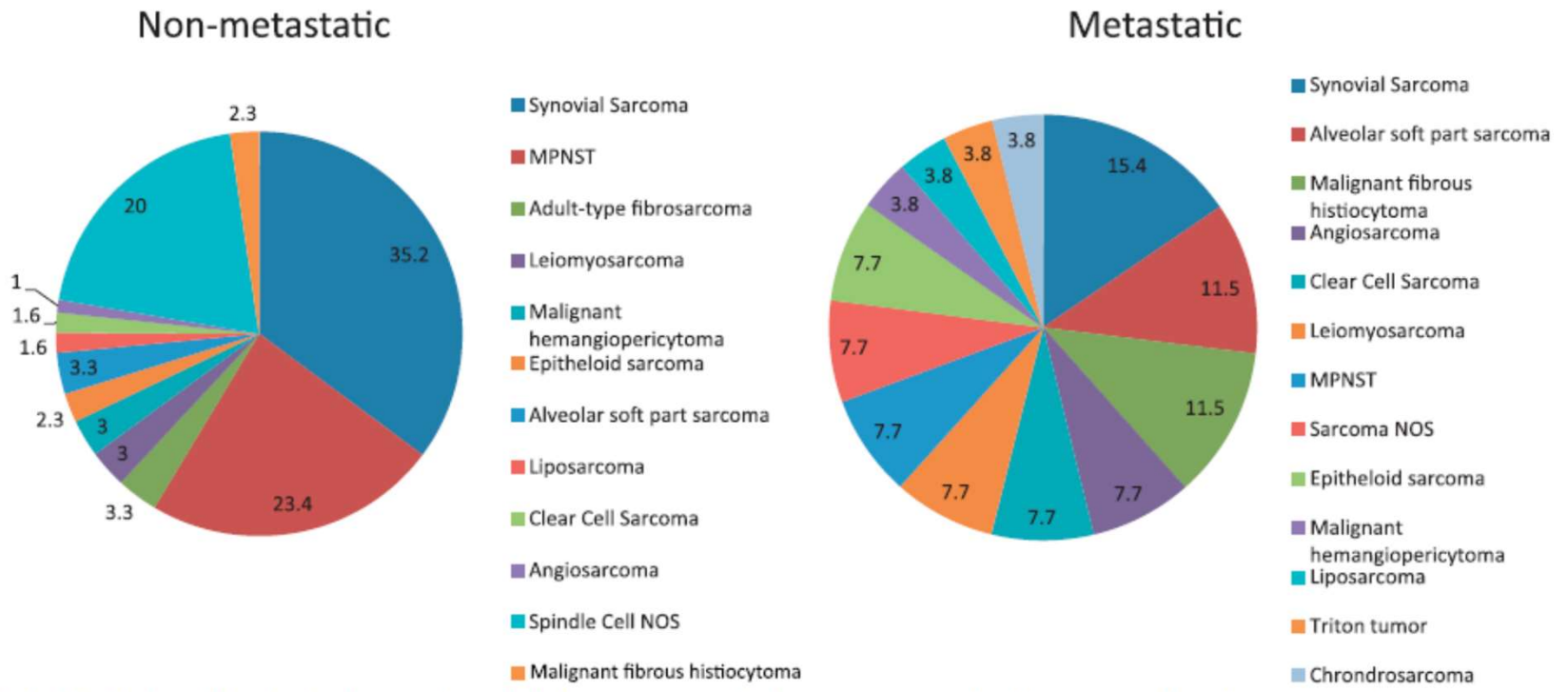

Fig. 3. Distribution of histologic subtypes of nonrhabdomyosarcoma soft-tissue sarcoma stratified into metastatic and nonmetastatic tumors at presentation. MPNST, malignant peripheral nerve sheath tumor; NOS, tumor not otherwise specified.

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A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study

Sheri L Spunt, Lynn Million, Yueh-Yun Chi, James Anderson, Jing Tian, Emily Hibbitts, Cheryl Coffin, M Beth McCarville, R Lor Randall, David M Parham, Jennifer O Black, Simon C Kao, Andrea Hayes-Jordan, Suzanne Wolden, Fran Laurie, Roseanne Speights, Ellen Kawashima, Stephen X Skapek, William Meyer, Alberto S Pappo, Douglas S Hawkins

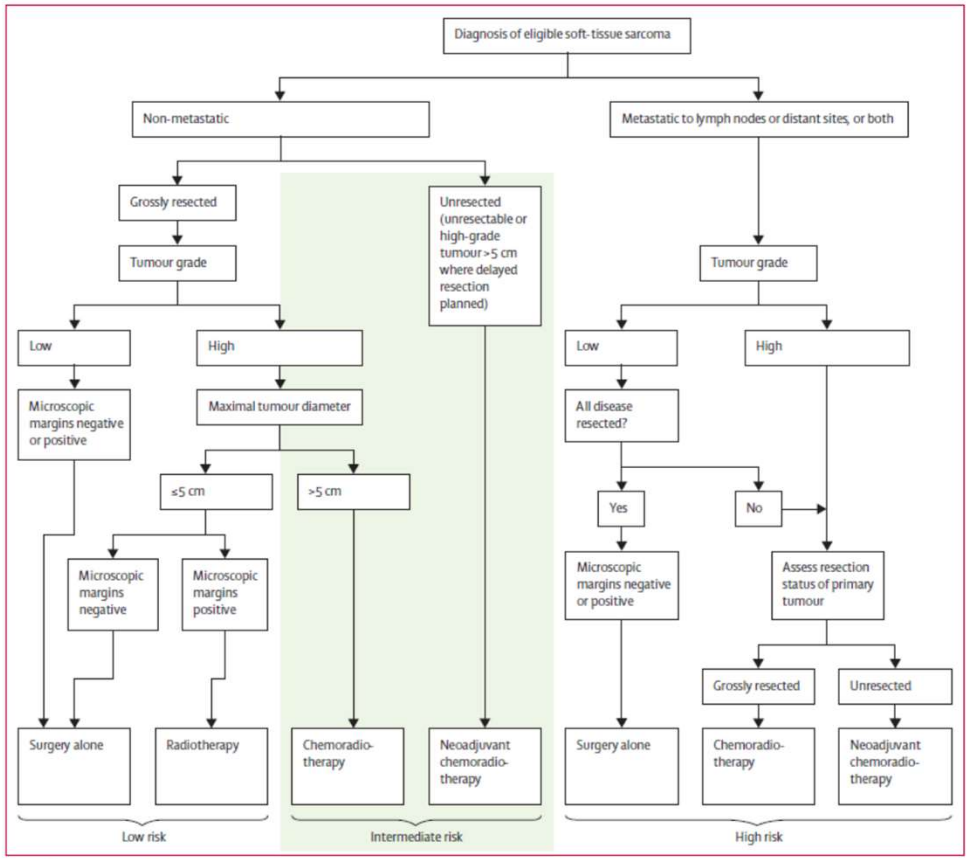

Figure 1: **Risk group and treatment assignment**

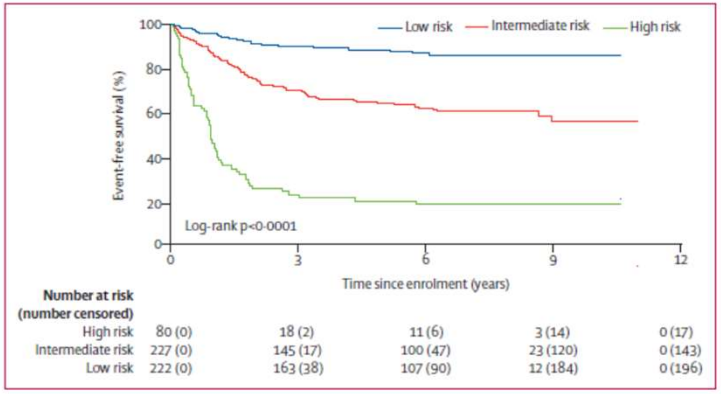

Figure 4: **Estimated event-free survival by risk group**

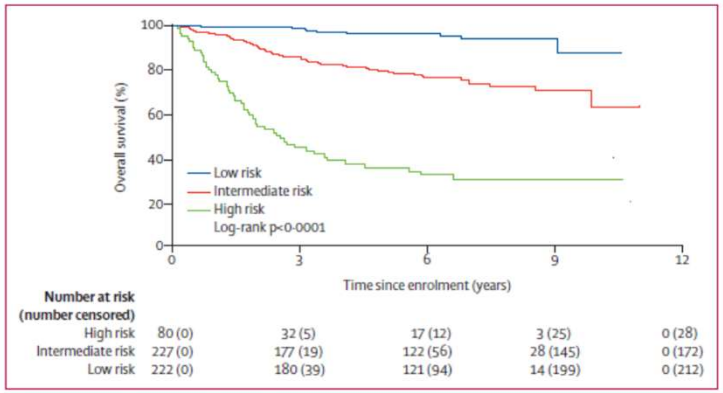

Figure 5: **Estimated overall survival by risk group**

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Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 trial

Aaron R Weiss, Yen-Lin Chen*, Thomas J Scharschmidt*, Yueh-Yun Chi, Jing Tian, Jennifer O Black, Jessica L Davis, Julie C Fanburg-Smith, Eduardo Zambrano, James Anderson, Robin Arens, Odion Binitie, Edwin Choy, Justin W Davis, Andrea Hayes-Jordan, Simon C Kao, Mark L Kayton, Sandy Kessel, Ruth Lim, William H Meyer, Lynn Million, Scott H Okuno, Andrew Ostrenga, Marguerite T Parisi, Daniel A Pryma, R Lor Randall, Mark A Rosen, Mary Schlapkohl, Barry L Shulkin, Ethan A Smith, Joel I Sorger, Stephanie Terezakis, Douglas S Hawkins†, Sheri L Spunt†, Dian Wang†*

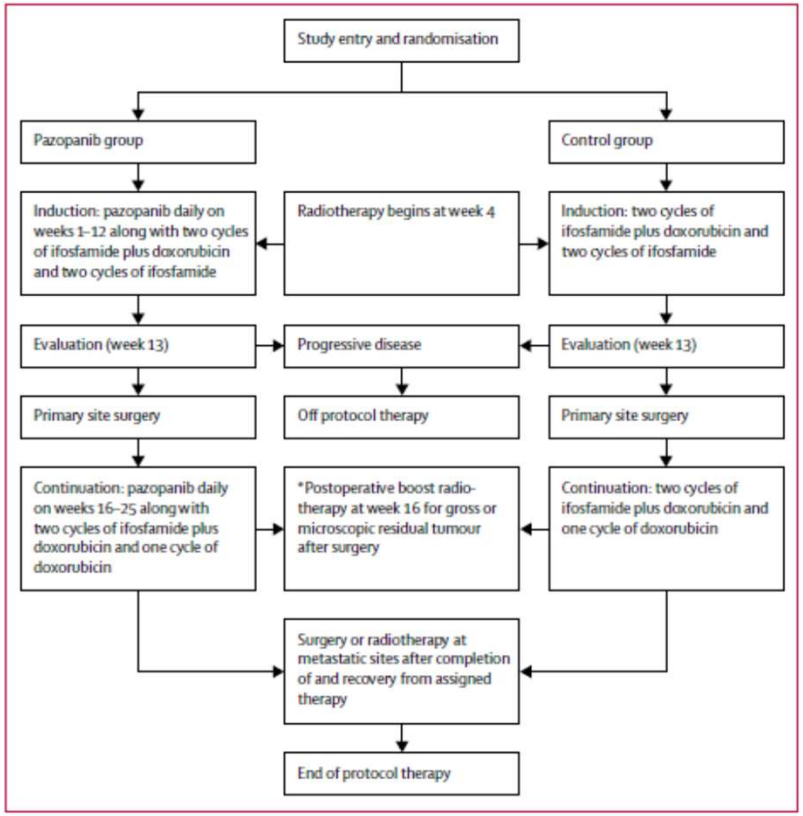

Figure 1: Study design

	Regimen A (n, %)	Regimen B (n, %)	p value
Pathologic response			
≥ 90%	14 (58.3%)	4 (22.2%)	0.029
< 90 %	10 (41.7%)	14 (77.8%)	

[1]Regimen A = Chemoradiation + Pazopanib
[2]Regimen B = Chemoradiation

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IGF1R/mTOR inhibitors/PARPi/LSDi
Spice Switch/GAMPER Oligos

IGF1R/? CHK1i

cMET/HGF inhibitor/PD-1i

TKIs/Trabectedin

Trabectidin/PI3Ki/NYESO(aTcell)/Eribulin

PDGFRAi/NYESO/EZH2i/TORC1-2i

Hormonal blockade

PDGFRB inhibitors

RANKL inhibitors

FGFR4 inhibitors

VEGF/METi/PD-1i

FMS/CSF inhibitors

IGF1R/mTORi/FGFRi

TKIs/MEK inhibitors

EZH2i

ALK inhibitors

MDM2/CDK4 inhibitors

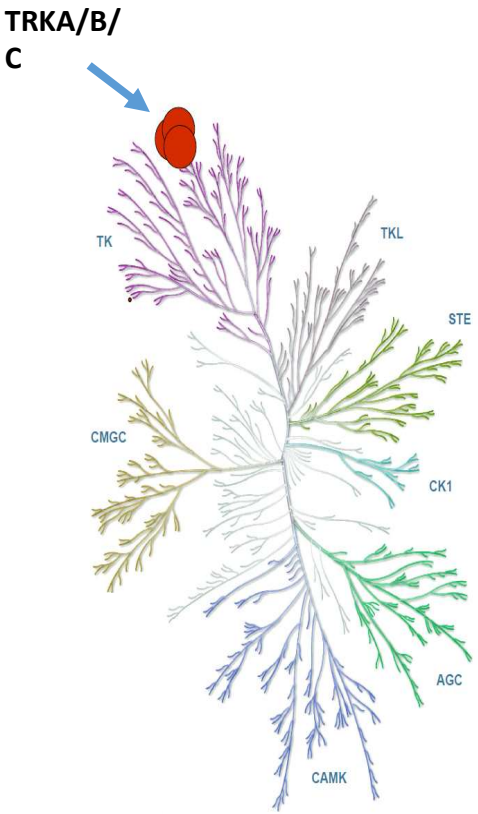
TKIs/GSI/Notchi

Sarcomas with fusion genes					
Fusion genes involving TET genes					
	Gene (N-C)	Chromosomal location	Clinical Significance	Proposed function of gene product	Detection Method
Ewings/PNET	*EWSR1- FLI1* *EWSR1- ERG* *FUS-FEV* *EWSR1-ZSG*	t(11;22)(q24;q12) t(21;22)(q22;q12)	Diagnostic EWSR1	Overexpression of Oncogene e.g. *MYC*	IHC (FLI1) Karyotype
Desmoplastic Small Round Cell Tumor	*EWSR1- WT1* *EV*	t(11;22)(p13;q12)	Diagnosis,	up-regulates oncogenic factors e.g. *PDGF, IL2RB, BAIALP3, TALLA1,MLF1*	IHC (WT1) FISH (EWSR1 break-apart probe) Karyotype
Clear cell sarcoma(CCS					FISH (EWSR1 break apart probe), PCR
Angiomatoid Fibrous Histiocytoma	*FUS-ATF1* *EWSR1-ATF1* *EWSR1-CREB1*	t(12;16)(q13;p11) t(12;22)(q13;q12) t(2;22)(q33;q12)	Diagnosis		FISH
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3* *TAF2N-NR4A3* *TCF12-NR4A3* *TFG-NR4A3*	t(9;22)(q22;q12) t(9;17)(q22;q11)	Diagnosis		FISH, RT-PCR (NR3A3-EWS fusion)
Myxoid/ round cell	*FUS-DDIT3*	t(12;16)(q13;p11)	Diagnosis,	Overexpression of	FISH
Low Grade Fibromyxoid Sarcoma / HSCT	*FUS-CREB3L2* *FUS-CREB3L1*	t(7;16)(q33;p11) t(11;16)(p11;p11	Diagnosis		FISH (FUS break-apart probe), RT-PCR
Fusion genes involving RTK genes					
Congenital mesoblastic nephroma	*ETV6-NTRK3*	t(12;15)(p13;q25)	Diagnosis		FISH, RT-PCR
Congenital fibrosarcoma	*ETV6-NTRK3*	t(12;15)(p13;q25)	Diagnosis		FISH, RT-PCR
Inflammatory myofibroblastic tumor	*TPM3-ALK* *TPM4-ALK* *CLTC-ALK* *RANBP2-ALK*	t(1 t(2 t(2 t(2;2)(p23;q13)			IHC (ALK protein) FISH, RT-PCR
Fusion genes involving chromatin remodeling genes					
Synovial sarcoma	*SS18-SSX1* *TLE1 gene*	t(X;18)(p11;q11)	Diagnosis,		FISH (SYT probe), RT-PCR, IHC (TLE1 protein)
Endometrial stromal sarcoma	*JAZF1-SUZ12* *JAZF1-PHF1* *EPC1-PHF1*	t(7;17)(p15;q21)	Diagnosis		RT-PCR
Fusion genes involving growth factors gene					
Dermatofibrosarcoma protuberans	*COL1A1-*		Diagnosis	Up-regulate the ssion of *PDGFR*	FISH, RT-PCR
Giant Cell Fibroblastoma	*COL1A1-PDGFB*		Diagnosis		FISH, RT-PCR
Other type of fusion genes					
Alveolar Rhabdomyosarcoma	*PAX3-* *PAX3-MLLT7*	t(2;13)(q35;q14)	Diagnostic		FISH (*FOXO1A* Break-apart probe), Karyotype, RT-PCR
Alveolar soft part sarcoma					IHC (TFE3), RT-PCR
Aneurysmal bone cyst	*CDH11-USP6* *THRAP3-USP6* *CNBP-USP6* *OMD-USP6*	t(16;17) t(1;17) t(3;17) t(9;17) t(17;17)	Diagnosis		FISH, RT-PCR
Tenosynovial giar tumor	*COL6A*				
Hemangiopericytoma					
Pericytoma	*ACTB-G*				
Sarcomas with specific oncogenic mutation					
Gastrointestinal Stromal Tumors	*KIT or*	*Occult 4q12*	Diagnosis, C-	Activation Tyrosine	IHC (C-Kit), PCR
Rhabdoid tumor			Diagnosis	LOH	IHC (loss of INI1)
Atypical lipomatous tumor/ Well-differentiated liposarcoma	*and* inMicatio3		Cyclin dependent kinase	FISH (MDM2, *CDK4 amplification*)	
Fibromatosis	APC inactivation	Trisomi 20 Deletio			IHC(β catenin)

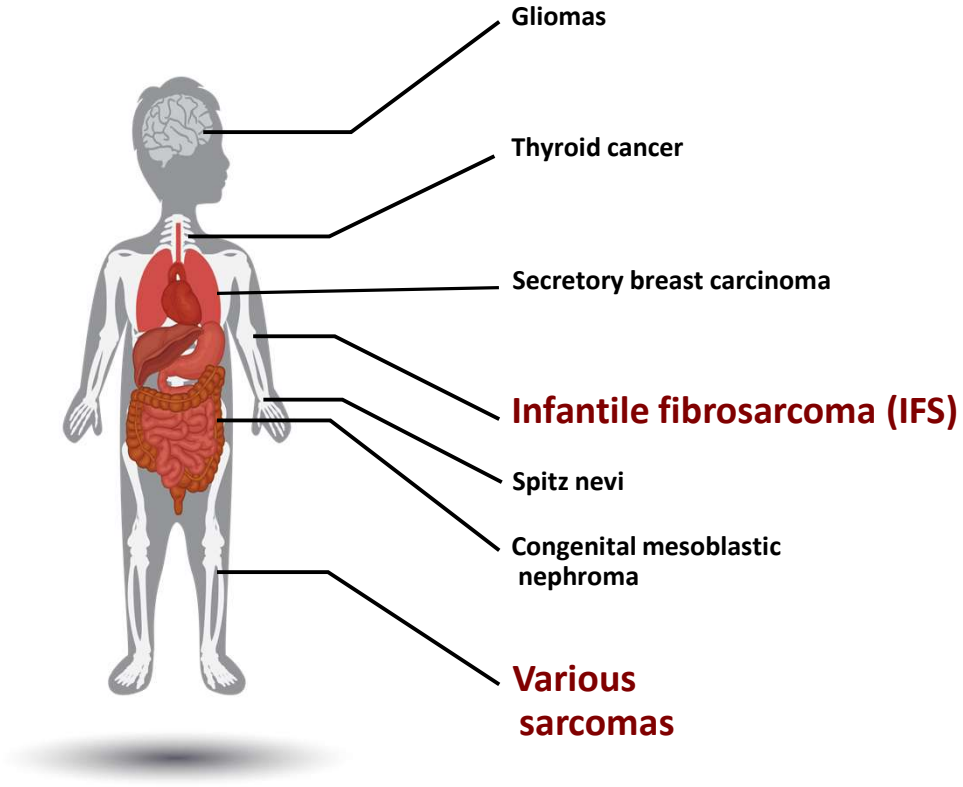
Int J Clin Exp Pathol 2010;3(4):416-429

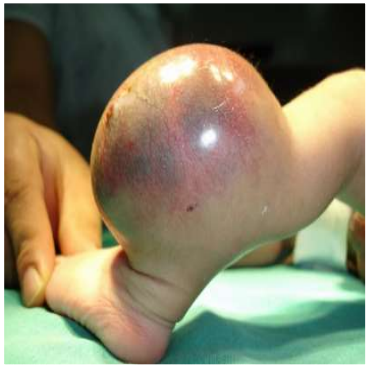
Larotrectinib (LOXO-101)

- Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC (5–11 nM IC_{50} in cellular assays)
- Highly selective
- High response rate in adult and pediatric patients with TRK fusions

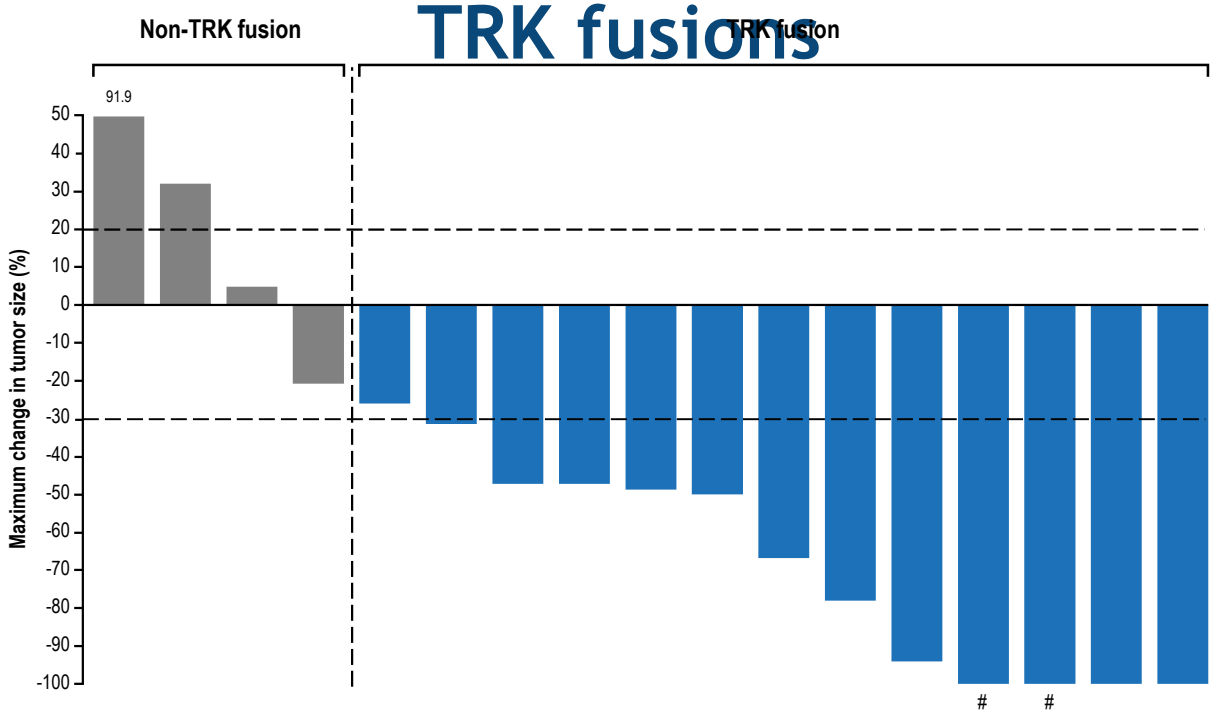


TRK fusions seen in diverse range of pediatric tumors

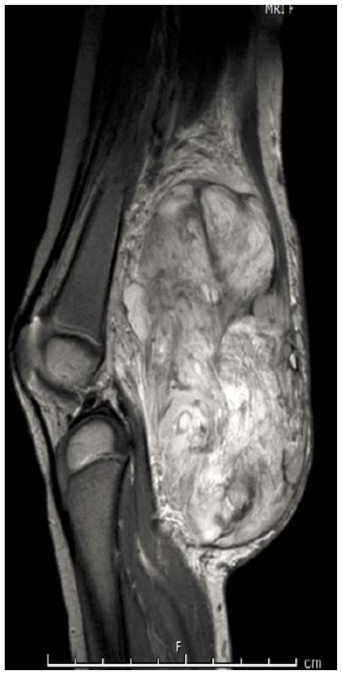




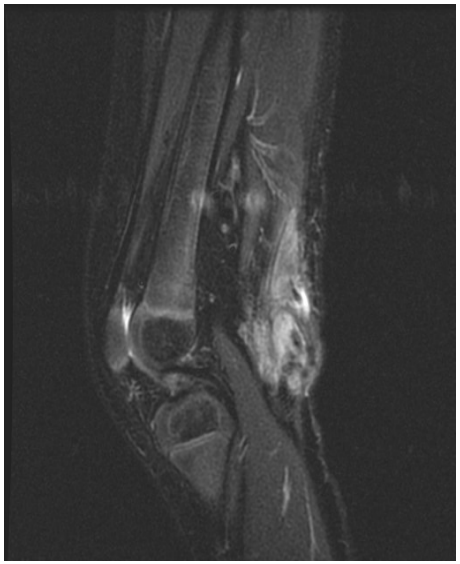
High response rate in children with TRK fusions



Note: 3 Non-NTRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2). #Pathologic CR



Baseline



Start of Cycle 3

2 yo girl with infantile fibrosarcoma

2 cycles of vincristine/ actinomycin-D/ cyclophosphamide → progression → amputation was only alternative

---

4 cycles larotrectinib → PR → referred for surgery

Pathologic complete response with clear margins (R0 resection); >98% necrosis

No functional deficit post-surgery

Off larotrectinib x 18 months and no evidence of disease

The NEW ENGLAND JOURNAL of MEDICINE

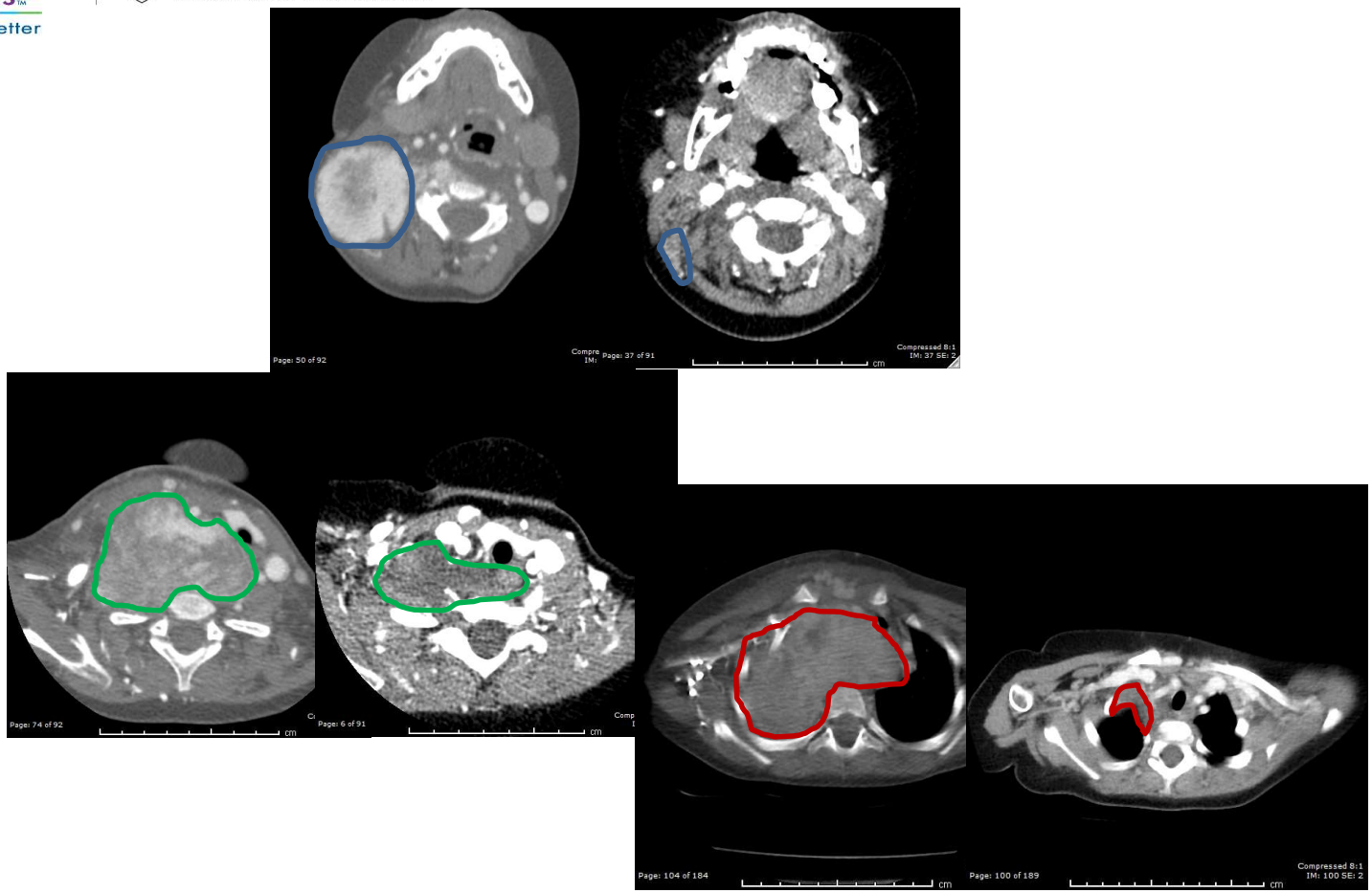
ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study

Theodore W Laetsch, Steven G DuBois*, Leo Mascarenhas, Brian Turpin, Noah Federman, Catherine M Albert, Ramamoorthy Nagasubramanian, Jessica L Davis, Erin Rudzinski, Angela M Feraco, Brian B Tuch, Kevin T Ebata, Mark Reynolds, Steven Smith, Scott Cruickshank, Michael C Cox, Alberto S Pappo*, Douglas S Hawkins**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Page: 37 of 91
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Page: 6 of 91
Page: 104 of 184
Page: 100 of 189
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IM: 100 SE: 2

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THE WALL STREET JOURNAL.

New Cancer Drugs Aim to Offer Alternatives To Chemo

Michelle shows a hang nail to Dr. Leo Mascarenhas, deputy director of the Children's Center for Cancer and Blood Diseases at CHLA and one of Michelle's doctors. Dr. Mascarenhas oversaw part of the clinical trial that Michelle is in.

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PEDIATRIC SARCOMAS

1. Are there patients where we can limit morbidity?

2. How do we pick which drug to study?

3. In which group of patients can we study them most efficiently?

4. What is the best method to study them?

5. What about tumor heterogeneity?