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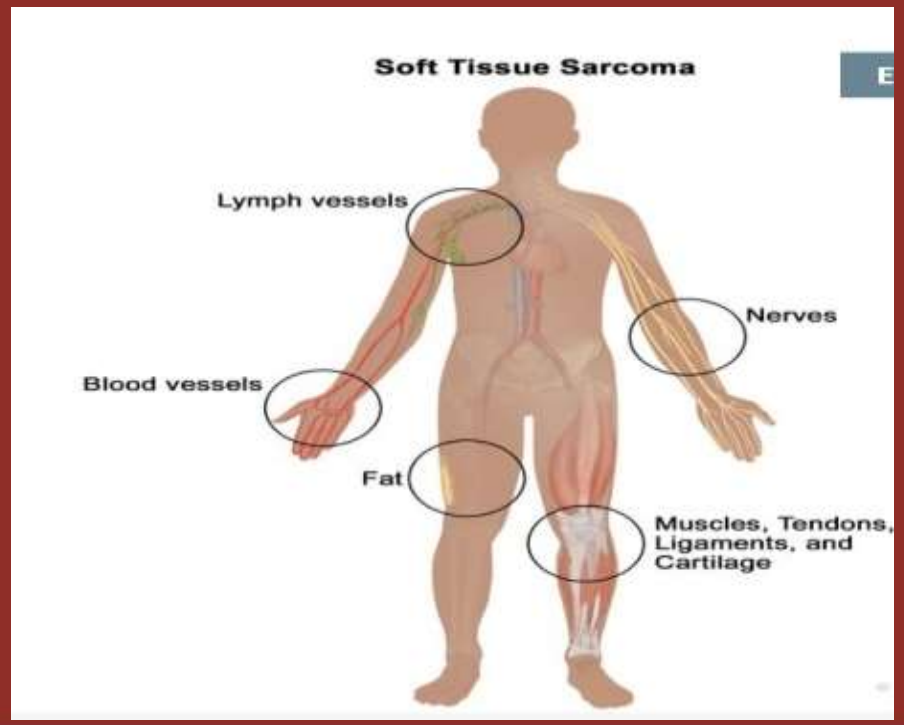
AMERICAN ONCOLOGY INSTITUTE
PRECISION CANCER CARE

ASCOMS
HOSPITAL

44th ICRO PG TEACHING COURSE

TOPIC: OVERVIEW OF SOFT TISSUE SARCOMAS IN PEDIATRIC POPULATION ? :



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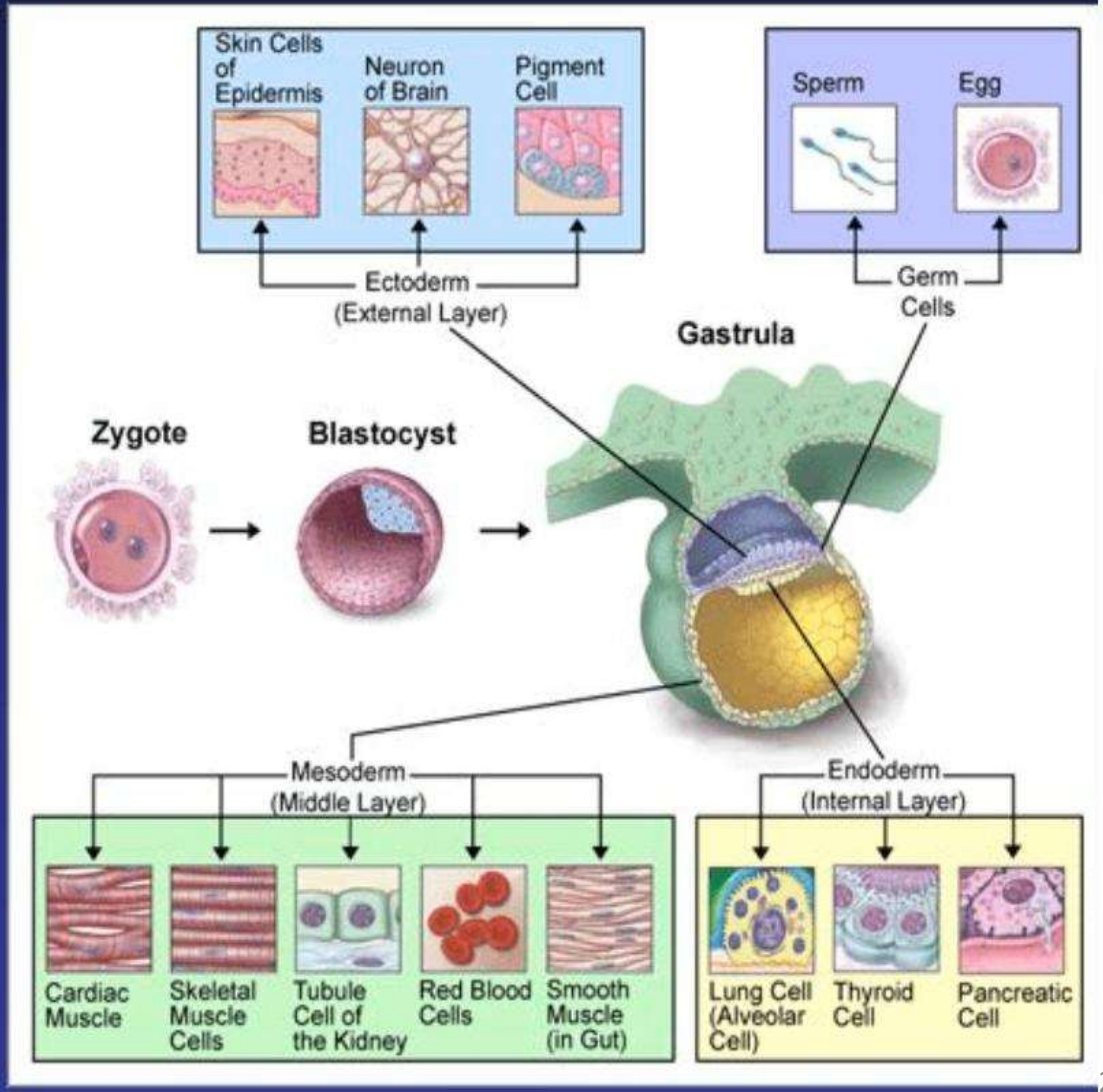
Tumors are named after their cell of origin and the embryonal layer that cell arose from

The middle embryonal layer – the mesoderm- gives rise to **mesenchymal tissues**- bone, muscle, cartilage, adipose tissue, blood vessels and more

Mesenchymal tumors are called **sarcomas**



Mesenchymal tumors

- Tumors of bone (Osteosarcoma, Ewing sarcoma)

- Tumors of soft tissues (Soft tissue sarcomas=STS)

  - Tumors of skeletal muscle (Rhabdomyosarcoma)

  - Tumors of smooth muscle (Leiomyosarcoma)
  - Tumors of adipose tissue (Liposarcoma)
  - Tumors of fibroblasts (Fibrosarcoma)
  - Tumors of cartilage (Chondrosarcoma, synovial sarcoma)
  - Tumors of blood vessels (Angiosarcoma)
  - MPNST, clear cell sarcoma, inflammatory myofibroblastic tumor, desmoid (fibromatosis), DSRCT, MFH

PEDIATRIC STS

- The most common form of soft-tissue sarcoma in childhood is rhabdomyosarcoma (50% of all STS)
- For convenience – all other soft-tissue sarcomas of childhood are called non-rhabdo soft tissue sarcomas (NRSTS) – and account for the remaining 50% of STS

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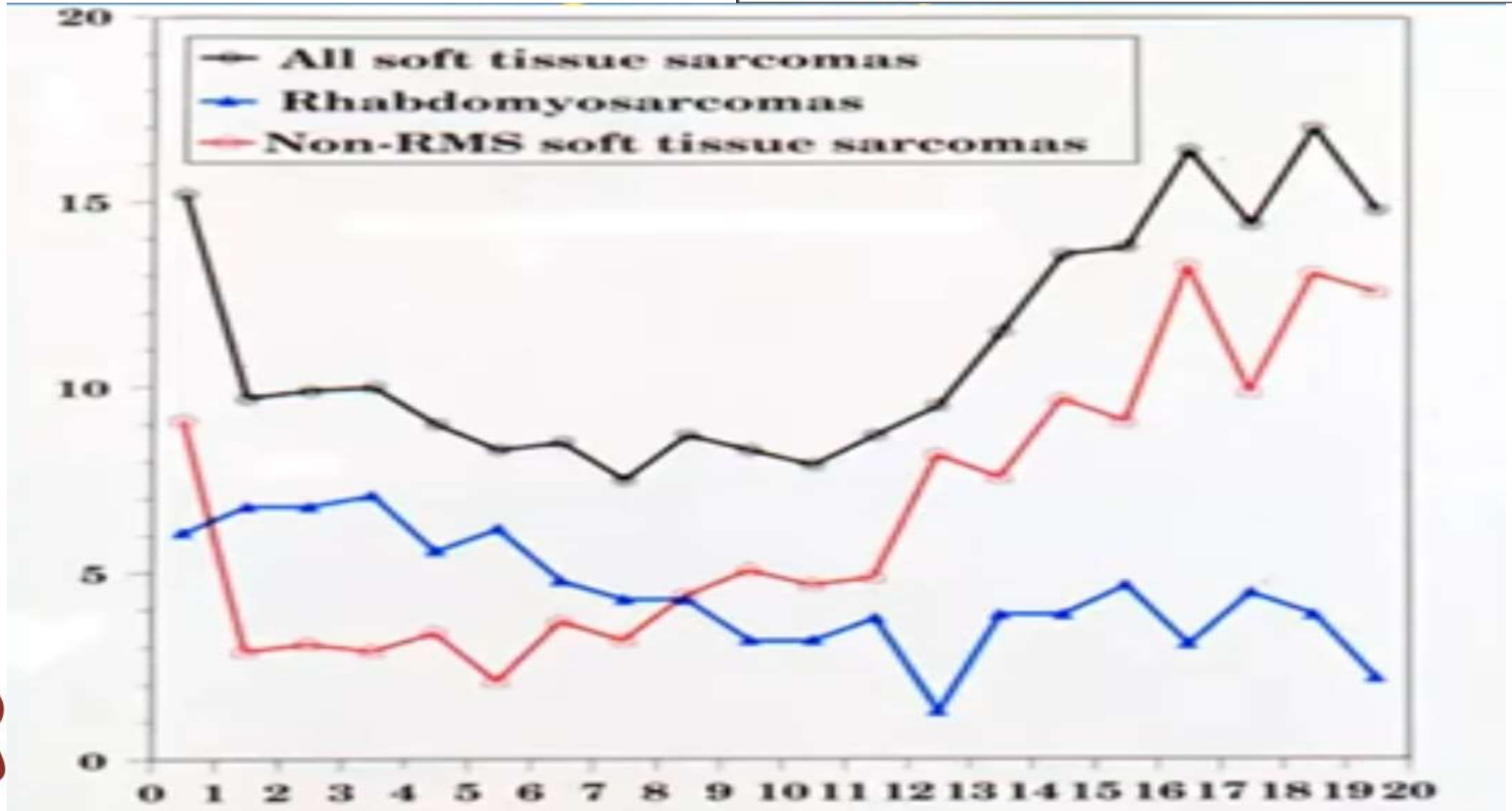
Cancer Types by Age Group

Tumor Type	Ages 0-14	Ages 15-19
Leukemia	28%	10%
CNS	22%	10%
Neuroblastoma	8%	0.2%
NHL	6%	8%
Hodgkin's	3.6%	16.8%
Wilm's tumor	6%	0.3%
Rhabdomyosarcoma	3.6%	1.7%
NRSTS	3.5%	5.1%
Osteosarcoma	2.6%	4.2%
Ewing sarcoma	1.5%	2.4%
Germ cell/gonadal	3.5%	12.4%
Retinoblastoma	3.2%	0%
Hepatoblastoma	1.3%	0%


All soft tissue sarcomas
Rhabdomyosarcomas
Non-RMS soft tissue sarcomas
20
15
10
5
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

RHABDOMYOSARCOMA

- 3 percent of childhood cancer.
- Most are Sporadic, Li Fraumeni , Neurofibromatosis 1 and Beckwith Wideman associated., Costello.
- Classic Histological Types are
- 1.Embryonal, 70 %
- 2.Alveolar, 20 to 40 %
- 3.Botryoid, 10 %
- 4.Undifferentiated and 5 %
- 5.Spindle cell 5 %

- Embryonal tumors typically arise in the orbit, head and neck, or genitourinary tract (OS 66%).
- Botryoid tumors often arise in the vagina, bladder, nasopharynx, and biliary tract (OS 95%).
- Spindle cell tumors most frequently occur in paratesticular sites (OS 88%).
- Alveolar tumors most commonly arise in the extremity, trunk, or retroperitoneum of adolescents (OS 54%).

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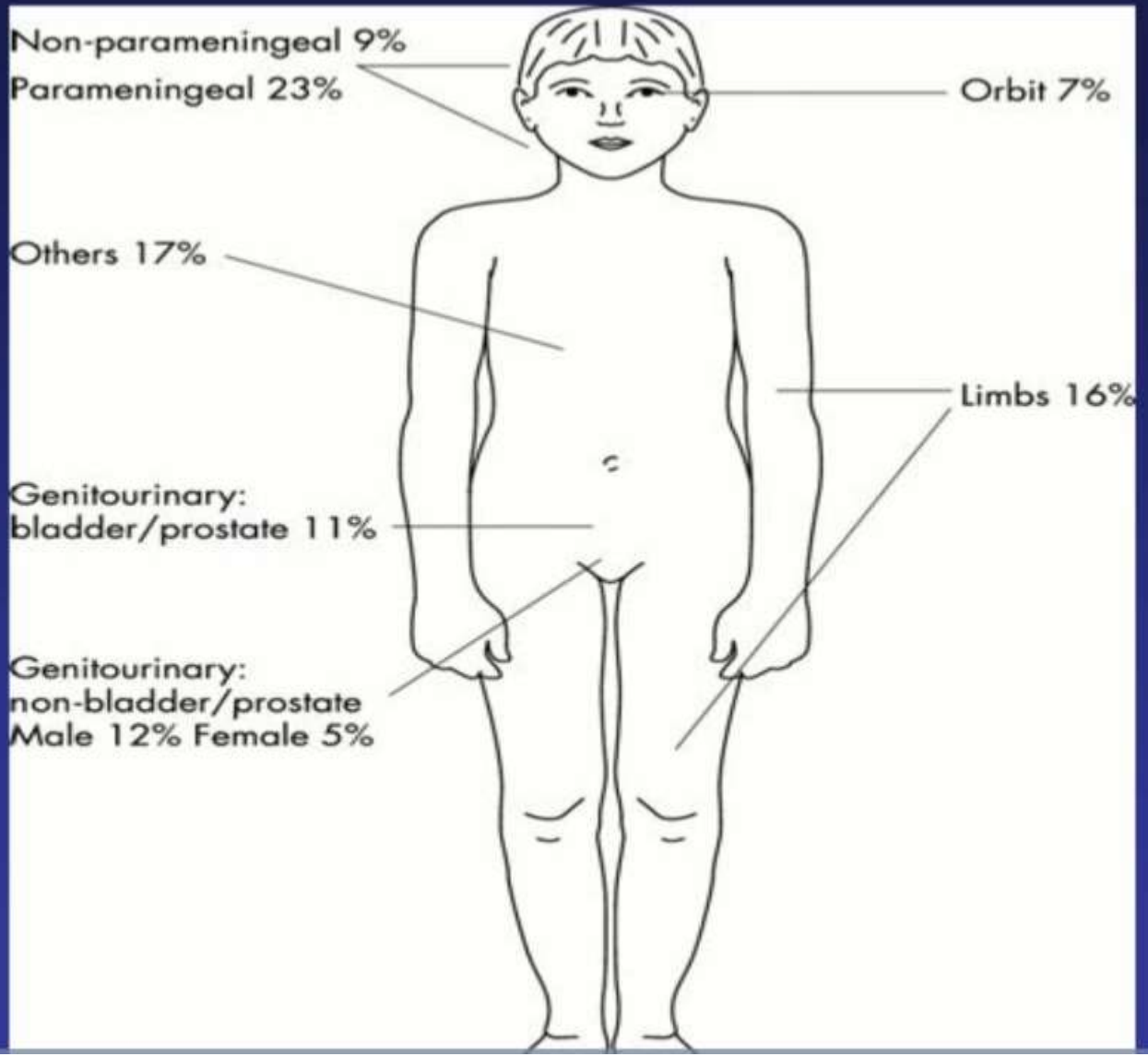
Rhabdomyosarcoma Sites of disease

- **Head & Neck**
  - Orbit
  - Parameningeal
  - Non-Parameningeal
- **Genitourinary**
  - Bladder
  - Prostate
  - Para-testicular
  - Vagina/uterus
- **Extremity**
- **Others**



Cytogenetic abnormalities in soft tissue sarcomas

Diagnosis	Cytogenetic abnormality	Genes involved
Alveolar RMS	t(2;13) or t(1;13)	FKHR on chromosome 13 and PAX3 (chromosome 2) or PAX7 (chromosome 1)
Infantile fibrosarcoma	t(12;15)	TEL (ETV6) on chromosome 12 and NTRK3 (TRKC) on chromosome 15
Dermatofibrosarcoma Protuberans	t(17;22)	PDGF β-chain on chromosome 17 and collagen type Ia on chromosome 22
Synovial sarcoma	t(X;18)	SYT on chromosome 18 and SSX-1 or SSX-2 on the X chromosome
Liposarcoma	t(12;16)	FUS gene on chromosome 16 and CHOP gene on chromosome 12
Myxoid chondrosarcoma	t(9;22)	EWS on chromosome 22 and TEC gene on chromosome 9
Alveolar soft part sarcoma	t(X;17)	Unidentified genes, esp. at chromosome band 17q25

EMBRYONAL RMS

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

ALVEOLAR RMS

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

RMS – Clinical Presentation is Site Dependent

- Orbit - Proptosis, ophthalmoplegia
- Other head and neck/parameningeal – nasal or aural obstruction, cranial nerve palsies
- Genitourinary tract – Bladder: Hematuria, urinary obstruction
  Paratesticular – painless scrotal mass
  Vaginal – Vaginal mass, discharge
- Extremities – Swelling, pain, lymph node involvement

WORKUP

- H&P: EUA may be required for pelvic tumors; cystoscopy should be performed for GU sites.
- Labs include CBC, LFTs, BUN/Cr, and LDH.
- Imaging includes CT/MRI of primary, CT of the chest and abdomen, and bone scan.
- If parameningeal site → lumbar puncture; obtain neuraxis MRI for positive CSF cytology.
- Bone marrow biopsy.

IRS PREOPERATIVE STAGING SYSTEM

Stage 1: Favorable site, any T, N0–1, M0
Stage 2: Unfavorable site, T1a/T2a, N0 M0
Stage 3: Unfavorable site, T1b/T2b, N0 M0, or any T, N1 M0
Stage 4: Any M1

Favorable sites: Orbit, nonparameningeal H&N (scalp, parotid, OPX, oral cavity, larynx), GU nonbladder-prostate (paratestes, vagina, vulva, uterus), and biliary tract

Unfavorable sites: Parameningeal (NPX, nasal cavity, paranasal sinuses, middle ear, mastoid, pterygopalatine fossa, infratemporal fossa), bladder, prostate, extremity, and others (trunk, retroperitoneum, etc.)

T1: Tumor is confined to site/organ of origin (a ≤5 cm, b >5 cm)
T2: Tumor extends beyond site/organ of origin (a ≤5 cm, b >5 cm)
N1: Regional lymph node involvement
M1: Distant metastases at diagnosis

STAGING MADE EASY

Stage 1: Any Tumor arising in a favorable site independent of size and lymphnode involvement

Stage 2: < 5cm , unfavorable site, without lymph node involvement.

Stage 3: > 5 cm , unfavorable site. Any size unfavorable site with lymph node involvement.

Stage 4: Any site , Any size, Distant Metastasis.

Rhabdomyosarcoma clinical group definitions

Group	Definition
Group I	Localized disease completely resected
Group IIa	Gross total resection with microscopic residual disease
Group IIb	Regionally involved lymph nodes, completely resected with the primary
Group IIc	Regional disease with involved nodes, totally resected with microscopic residual disease or histologic evidence of involvement of the most distant lymph node in the dissection
Group III	Incomplete resection
Group IV	Distant metastases

Risk stratification in rhabdomyosarcoma

Histology	Clinical group	Stage	Risk group
Embryonal	I, II, III	1	Low
Embryonal	I, II	2, 3	Low
Embryonal	III	2, 3	Intermediate
Embryonal	IV	4	High
Alveolar	I, II, III	1, 2, 3	Intermediate
Alveolar	IV	4	High

~3-year OS by risk group
Low >90–95%
Intermediate 55–70%
High 30–50%

~5-year OS by histology
Botryoid 95%
Spindle cell 88%
Embryonal 66%
Alveolar 54%
Undifferentiated 40%

~5-year OS by site
Orbit >90%
Parameningeal 75%
H&N nonparameningeal: 80%
Genitourinary sites 82%
Paratesticular 69–96%
Gynecologic sites 90–98%
Extremity 70%

IRS TREATMENT

- All patients require multimodality therapy consisting of surgery (if possible) followed by chemo ±RT. Treatment is based on stage, group, and primary site.
- Chemotherapy agents include VCR, AMD, CY, topotecan, and irinotecan.
- VA = VCR/AMD; VAC = VCR/AMD/CY; VTC = VCR/topotecan/CY; VCPT = VCR/irinotecan.

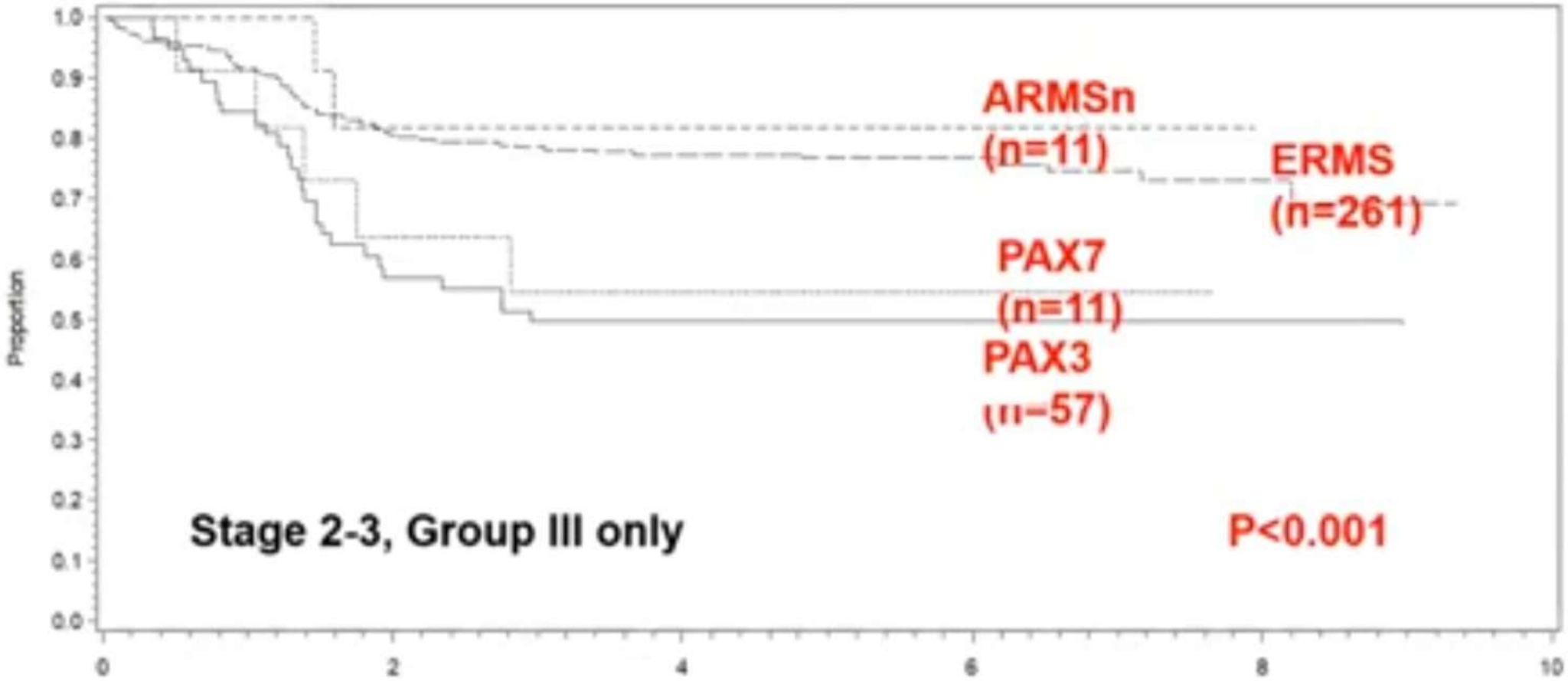
Group/stage	Treatment	3-year OS	Findings
I paratesticular	VA	90%	No difference from IRS III
I orbit	VA	100%	No difference from IRS III
II orbit	VA + RT	100%	No difference from IRS III
I, stage 1–2	VAC vs. VAI vs. VIE; no RT	84–88%	No difference between chemo regimens
I, stage 3; all II	VAC vs. VAI vs. VIE + RT	84–88%	No difference between chemo regimens
III	VAC vs. VAI vs. VIE, + RT (qd vs. b.i.d.)	72–83% (3-year FFS)	No difference between chemo regimens. b.i.d. RT did not improve LC (~87%) or OS vs. qd RT
IV	VM vs. IE → VAC, + RT	27 vs. 55%	IE improved FFS, OS vs. VM chemo

COG RMS STRATIFICATION

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		

COG RMS STRATIFICATION

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+		



TP 53 AND MYOD1 SHOW UNFAVORABLE PROGNOSIS

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

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

RADIATION TECHNIQUES

Simulation and Field Design

- Many patients may require pediatric anesthesia.
- Excellent immobilization is required, and 3DCRT or IMRT is encouraged to limit doses to normal structures.
- In IRS-V RT, volumes were to the prechemotherapy, presurgical tumor plus a 2 cm margin with inclusion of involved lymph nodes (prophylactic nodal RT not used). For Group III patients requiring 50.4 Gy, the volume is reduced to the prechemotherapy, presurgical tumor plus a 0.5 cm margin at 36 Gy for N0 patients or at 41.4 Gy for N1 patients.

- The timing of RT is described in the IRS-V treatment summary table above and always given at 1.8 Gy/day.
- Dose limitations are as follows: kidney <14.4 Gy, whole liver <23.4 Gy, bilateral lungs <15 Gy in 1.5 Gy fractions, optic nerve and chiasm <46.8 Gy, spinal cord <45 Gy, GI tract <45 Gy, whole abdomen 24 Gy in 1.5 Gy fractions, heart <30.6 Gy, lens <14.4 Gy, and lacrimal gland and cornea <41.4 Gy.
- Uninvolved ovaries or testicles should be shielded or moved in patients with pelvic or paratesticular primaries.

FOLLOW-UP

- H&P and CXR every 2 months for first year with repeat imaging studies that were positive at diagnosis every 3 months, then H&P and CXR every 4 months for second and third years, then H&P annually for years 5–10, and annual visit or phone contact after 10 years.

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NRSTS

EPIDMIOLOGY AND ETIOLOGY

- INCIDENCE OF STS CHILDREN - 11/MILLION
- APPROXIMATELY 7.4%
- UPTO 60% ARE NRSTS
- MORE COMMON WITH INCREASING AGE AND OLDER ADOLESCENTS.
- NO SINGLE HISTOLOGY > 15%
- NO KNOWN CAUSES OR RISK FACTORS.

NRSTS ACCORDING TO INTERNATIONAL CLASSIFICATION OF CHILDHOOD CANCER

- FIBROSARCOMA CATEGORY
- KAPOSIS SARCOMA
- OTHER SPECIFIED STS
- UNSPECIFIED STS

Histologic subtypes of nonrhabdomyosarcoma soft tissue sarcomas in pediatric patients

Histology	Normal counterpart	Incidence
Fibrosarcoma	Fibroblast	0.6
Infantile fibrosarcoma	Fibroblast	0.2
Malignant fibrous histiocytoma	Fibroblast	0.8
Dermatofibrosarcoma protuberans	Fibroblast	1.0
Malignant peripheral nerve sheath tumor	Schwann cell	0.6
Kaposi's sarcoma	Blood vessels	0.1
Liposarcoma	Adipocyte	0.1
Leimyosarcoma	Smooth muscle	0.3
Synovial sarcoma	Synovial cells	0.7
Hemangiosarcoma	Blood vessels	0.2
Malignant hemangiopericytoma	Vessel pericytes	0.1
Alveolar soft part sarcoma		0.1
Chondrosarcoma	Chondrocytes	0.1

CHROMOSOMAL ALTERATIONS

- T(17;22) in Dermatofibrosarcoma Protuberans
- Inhibition of this receptor with Imatinib has been evaluated.

CLINICAL PRESENTATION

- PAINLESS MASS WHICH ARE SLOW GROWING
- SYMPTOMS DEPENDS ON LOCATION

EVALUATION AND MANAGEMENT

- CT SCAN
- MRI
- PET SCAN
- BIOPSY
- BIOPSY SITE TO BE CHOSEN TO INCLUDE TRACK LINES IN FIELD OF RESECTION.

SURGERY MAINSTAY

- A 1 cm MARGIN CONSIDERED APPROPRIATE
- LOCAL CONTROL RATES WITH ADJUVANT CT RT FOR LIMBSPARING IS APPROACHING 95%
- AMPUTATION IS BEING RESERVED FOR MAJOR ARTERY AND NERVE INVOLVEMENT

CHEMOTHERAPY

- For Patients Deemed at high risk of Metastasis
- Doxorubicin and Ifosfamide.

NOMOGRAMS FOR ADJUVANT TREATMENT

- Usefulness depends on risk of relapse and sarcoma specific death.
- Prognosis depends on Age, size of Tumor, histologic grade and subtype and location of tumor.
- In pediatric population TUMOR SIZE is most important.
- OTHER IMPORTANT THINGS ARE
    1. Localized versus metastatic disease
    2. Extent of Tumor resection
    3. Maximum Tumor Diameter
    4. Tumor Grade

ROLE OF RADIATION

- ALMOST ALWAYS USED IN COMBINATION WITH SURGERY.
- ADJUVANT OR NEOADJUVANT
- PREOPERATIVE 5000 cGY OR POSTOPERATIVE 6600cGY
- LOCAL CONTROL IDENTICAL , TOXICITIES DIFFERENT
- TREATMENT VOLUME ENCOMPASS PREOPERATIVE TUMOR VOLUME OR POST OPERATIVE TUMOR BED WITH 5CM LONGITUDINAL AND 2CM RADIAL MARGINS.

TREATMENT COMPLICATIONS

- 1. Physical disabilities and Functional limitations.
- 2. Emotional and psychological challenges.
- 3. Cognitive and Learning disabilities.
- 4. Risk of Secondary cancers.
- 5. Cardiac and Pulmonary complications

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

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†

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

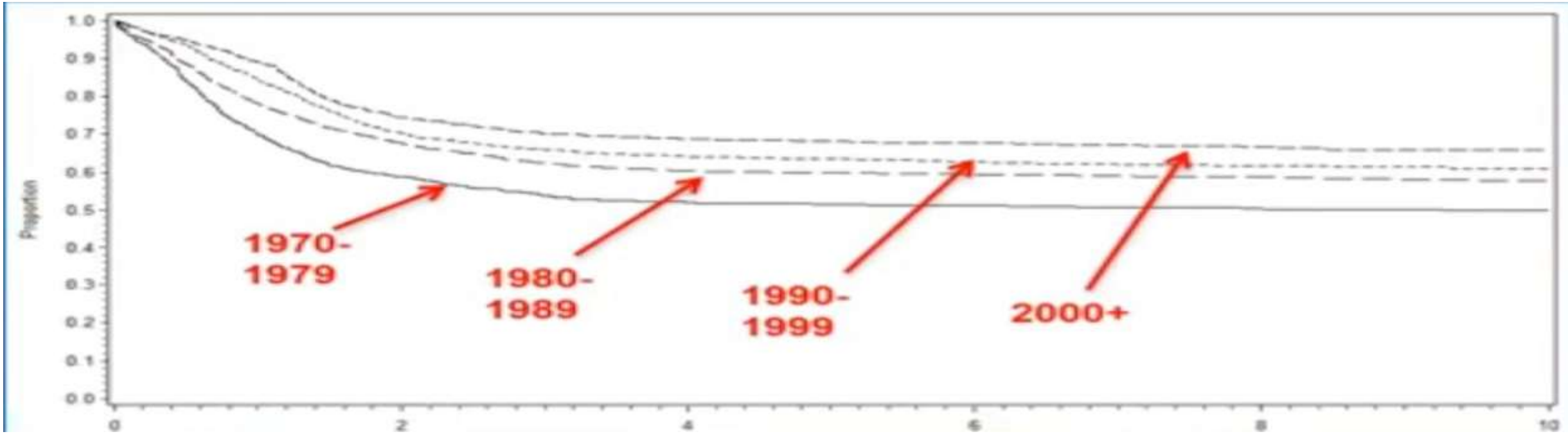
Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

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**

QUESTIONS TO PONDER UPON……


Proportion
1.0
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0.7
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0.5
0.4
0.3
0.2
0.1
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2
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6
8
10
1970-
1979
1980-
1989
1990-
1999
2000+