PEDEIATRIC 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
**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)

**Clinical Presentation**

Mass, +/- pain, +/- disturbance in function
Failure-free Survival, IRS-IV for Patients with Local/Regional Tumors by Primary Site

Year

Failure-free Survival

Log Rank Test: 
p<0.001
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.
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.
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 (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
Outcome by histology, COG
## COG RMS Stratification, circa 2003-2015

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

**COG RMS Stratification, circa 2003-2015**

**Soft Tissue Sarcoma**
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
PAX/FOXO1 Fusion: ARMS

PAX3 (2q35)

PAX3/FOXO1 t(2;13) ~65%

FOXO1 (13q14) FKHR Activation

PAX7/FOXO1 t(1;13) ~15%

PAX7 (1p36)

PB HD

～65%

PB HD

～15%

PB HD

PAX3 (2q35)

PAX3/FOXO1 t(2;13)

FOXO1 (13q14) FKHR Activation

PAX7/FOXO1 t(1;13)

PAX7 (1p36)
**FOXO1 fusion and outcome**

![Graph showing survival rates for different categories of soft tissue sarcoma patients.](image)

**Stage 2-3, Group III only**  
P<0.001

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

Soft Tissue Sarcoma
## COG RMS Stratification, current

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Stage</th>
<th>Group</th>
<th>Age</th>
<th>Fusion</th>
<th>COG study</th>
<th>Therapy</th>
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</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
<td>I-II</td>
<td>Any</td>
<td>FOXO1-</td>
<td>None</td>
<td>VACx4, VAXx4 24 weeks</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>III (orbit)</td>
<td>Any</td>
<td>FOXO1-</td>
<td>ARST1431</td>
<td>VAC/VI +/- TEM 42 weeks, VRL/CY 24 weeks</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I-II</td>
<td></td>
<td>FOXO1+</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
<td>III (non-orbit)</td>
<td>Any</td>
<td>FOXO1-</td>
<td>ARST1431</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I-II</td>
<td>Any</td>
<td>FOXO1-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>III</td>
<td></td>
<td>FOXO1-</td>
<td>ARST1431</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>I-III</td>
<td></td>
<td>FOXO1+</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>IV</td>
<td>&lt; 10 yr</td>
<td>FOXO1-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>IV</td>
<td>&gt; 10 yr</td>
<td>FOXO1-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any</td>
<td>FOXO1+</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td>IV</td>
<td></td>
<td>FOXO1-</td>
<td>None currently</td>
<td></td>
</tr>
</tbody>
</table>

**Soft Tissue Sarcoma**
Multimodality treatment with surgery, chemotherapy and radiotherapy has led to an overall survival of >70% for all patients with rhabdomyosarcoma.
• 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
• 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
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, 2001
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
n = 271

2-yr FFS = 88% (95% CI: 84%, 92%)
2-yr OS = 98% (95% CI: 95%, 99%)
Walterhouse DO, Cancer. 2017 Jul 15;123(12):2368-2375
ARST0531: VAC, VAC/VI EFS similar
ARST08P1: Event-free survival

Pilot 2: Temozolomide

P = 0.023

Malempati S, Cancer 2019; 125:290-297

Soft Tissue Sarcoma
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
Unfav, Irinotecan, sched A (regimen 1A)

Unfav, Irinotecan, sched B (regimen 1B)

$p=0.73$

Failure-Free Survival

IA 1 year FFS 32% (95% CI 18%, 47%)

IB 1 year FFS 36% (95% CI 22%, 50%)
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

Soft Tissue Sarcoma
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.

EpSSG RMS 2005: Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>OS 5-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>185</td>
<td>24</td>
<td>86.5 (80.2-90.9)</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>186</td>
<td>42</td>
<td>73.7 (65.8-80.1)</td>
</tr>
</tbody>
</table>

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

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/m² total cyclophosphamide

Soft Tissue Sarcoma
ARST08P1: Event-free survival

Pilot 1: IMC-A12
P = 0.023

Pilot 2: Temozolomide

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

No MYOD1 mutation

MYOD1 mutation

Shern J, ASCO 2018
Soft Tissue Sarcoma
FN: TP53 mutation unfavorable

Shern J, ASCO 2018

Soft Tissue Sarcoma
FP: MYCN, CDK4 amp unfavorable

Event-free survival by MYCN amplification

No MYCN amplification

MYCN amplification

Event-free survival by CDK4 amplification

No CDK4 amplification

CDK4 amplification

Shern J, ASCO 2018

Soft Tissue Sarcoma
Improved RMS Outcome

- Soft Tissue Sarcoma
- 1990-2005

1990-1999
1980-1989
1970-1979
2000+

Courtesy of James Anderson, Children’s Oncology Group
Long-term morbidity: aging cancer survivors

Severe, Disabling, Life-threatening, and fatal events

Cumulative Incidence (%) vs Age (years)

- Survivors
- Siblings

60-year Incidence:
- 53.6% for Survivors
- 19.8% for Siblings

90-year Incidence:
- 43.6% for Survivors
- 19.8% for Siblings

Soft-Tissue Sarcoma
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.
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

Figure 1: Risk group and treatment assignment
Figure 4: Estimated event-free survival by risk group

Figure 5: Estimated overall survival by risk group
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

Figure 1: Study design

Study entry and randomisation

Pazopanib group

Induction: pazopanib daily on weeks 1-12 along with two cycles of ifosfamide plus doxorubicin and two cycles of ifosfamide

Evaluation (week 13)

Primary site surgery

Continuation: pazopanib daily on weeks 16-25 along with two cycles of ifosfamide plus doxorubicin and one cycle of doxorubicin

Surgery or radiotherapy at metastatic sites after completion of and recovery from assigned therapy

End of protocol therapy

Control group

Radiotherapy begins at week 4

Progressive disease

Off protocol therapy

Primary site surgery

Induction: two cycles of ifosfamide plus doxorubicin and two cycles of ifosfamide

Evaluation (week 13)

Continuation: two cycles of ifosfamide plus doxorubicin and one cycle of doxorubicin

*Postoperative boost radiotherapy at week 16 for gross or microscopic residual tumour after surgery
<table>
<thead>
<tr>
<th>Pathologic response</th>
<th>Regimen A (n, %)</th>
<th>Regimen B (n, %)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 90%</td>
<td>14 (58.3%)</td>
<td>4 (22.2%)</td>
<td>0.029</td>
</tr>
<tr>
<td>&lt; 90 %</td>
<td>10 (41.7%)</td>
<td>14 (77.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Regimen A = Chemoradiation + Pazopanib
Regimen B = Chemoradiation
<table>
<thead>
<tr>
<th>Genes with fusion genes</th>
<th>Genes with chromosomal aberrations</th>
<th>Clinical significance</th>
<th>Gene product</th>
<th>Detection method</th>
<th>Gene product</th>
<th>Gene product</th>
<th>Gene product</th>
<th>Gene product</th>
<th>Gene product</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF1R/mTOR inhibitors</td>
<td>PARPi/LSDi</td>
<td>Spice Switch/GAMPER Oligos</td>
<td>IGF1R/? CHK1i</td>
<td>cMET/HGF inhibitor/PD-1i</td>
<td>TKIs/Trabectedin</td>
<td>Trabectedin/Pi3Ki/NYESO(aTcell)/Eribulin</td>
<td>TKIs/MK inhibitors</td>
<td>EZH2i</td>
<td>MDM2/CDK4 inhibitors</td>
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<tr>
<td>PDGFRA inhibitors</td>
<td>FGFR4 inhibitors</td>
<td>VEGF/METi/PD-1i</td>
<td>RANKL inhibitors</td>
<td>FMS/CSF inhibitors</td>
<td>IGF1R/mTORi/FGF4i</td>
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</tr>
<tr>
<td>PI3Ki/NYESO</td>
<td>PDGFRB inhibitors</td>
<td>PD-1i</td>
<td>TKIs</td>
<td>TKIs</td>
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<td></td>
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</tbody>
</table>
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 IC₅₀ in cellular assays)

- Highly selective

- High response rate in adult and pediatric patients with TRK fusions

  Recommended phase 2 TRKA/B/C
TRK fusions seen in diverse range of pediatric tumors

- Gliomas
- Thyroid cancer
- Secretory breast carcinoma
- Infantile fibrosarcoma (IFS)
- Spitz nevi
- Congenital mesoblastic nephroma
- Various sarcomas
High response rate in children with TRK fusions

Maximum change in tumor size (%)

Non-TRK fusion

TRK fusion

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
Case 1: 2 yo with progressive ETV6-NTRK3 IFS

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

Courtesy of L. Mascarenhas, CHLA
Data cutoff: 17 July 2017
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*
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.
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?