Management of Soft Tissue Sarcomas: Current Therapies and Future Directions

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Medicine Grand Rounds
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Disclosures

• No relevant disclosures
Outline

• Background
• Work-up of a soft tissue mass
• Staging and prognosis
• Treatment
  – Localized extremity sarcoma
  – Retroperitoneal sarcoma
  – Metastatic disease
• Targeted therapies
• New strategies
Sarcomas Background

- Rare group of tumors
  - 1% of all adult malignancies
  - 12% of pediatric cancers
- From the Greek “sarkos” = “fleshy”
- Tumors of connective tissue
  - Muscle, bone, fat, fascia, cartilage, etc.
- Tumors of mesodermal origin
  - Ectodermal: Ewing’s/PNET, neurosarcoma
- 80% originate from soft tissues, the rest from bone

Fletcher, CDM. WHO Classification. 2002.
Miller, RW. Cancer 1995;75(1 Suppl):395.
# US Cancer Cases

<table>
<thead>
<tr>
<th>System</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary System</td>
<td>481,790</td>
<td>87,690</td>
</tr>
<tr>
<td>Digestive System</td>
<td>284,680</td>
<td>142,510</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>244,180</td>
<td>164,770</td>
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<tr>
<td>Breast</td>
<td>229,060</td>
<td>39,920</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>79,190</td>
<td>20,130</td>
</tr>
<tr>
<td>Leukemia</td>
<td>47,150</td>
<td>23,540</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>11,280</td>
<td>3900</td>
</tr>
<tr>
<td>Bone</td>
<td>2890</td>
<td>1410</td>
</tr>
</tbody>
</table>

Etiology

• Most arise de novo
  – Not from a benign soft tissue mass
• Potential predisposing factors:
  – Genetic predisposition
    • Li Fraumeni syndrome
    • Neurofibromatosis type I
  – Exposure to radiation therapy or chemotherapy
  – Exposure to chemical carcinogens
  – Chronic irritation
  – Lymphedema

Fletcher, CDM. WHO Classification. 2002.
Histopathology

There are more than 50 different histologic subtypes of soft tissue sarcoma.

Classification based on:
- Morphology
- IHC
- FISH and RT-PCR for translocations

<table>
<thead>
<tr>
<th>Most Common histologic subtypes of soft tissue sarcoma (non-GIST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated pleomorphic sarcoma (Malignant Fibrous Histiocytoma)</td>
</tr>
<tr>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td><strong>Rhabdomyosarcoma</strong></td>
</tr>
<tr>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td><strong>Primitive neuroectodermal tumor/Extraskeletal Ewing tumor</strong></td>
</tr>
<tr>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
</tr>
<tr>
<td>Malignant mesenchymoma</td>
</tr>
</tbody>
</table>

Fletcher, CDM. WHO Classification. 2002.
# Translocation-Driven Sarcomas
Primed for “Targeted Therapies”

<table>
<thead>
<tr>
<th>Sarcoma Subtype</th>
<th>Translocation</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>t(17;22)(q22;q13)</td>
<td>COL1A1-PDGFB</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>t(11;22)(q24;q12)</td>
<td>EWSR1-FLI1</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ATF1</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(X;18)(p11;q11)</td>
<td>SYT-SSX1</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>t(12;16)(q13;p11)</td>
<td>FUS-DDIT3</td>
</tr>
<tr>
<td>Alveolar soft parts sarcoma</td>
<td>t(X;17)(p11.2;q25)</td>
<td>ASPL-TFE3</td>
</tr>
</tbody>
</table>
Presentation

Enlarging painless mass

Anatomic Distribution

- Thigh, buttock, and groin: 46%
- Upper extremity: 13%
- Torso: 18%
- Retroperitoneum: 13%
- Head and neck: 9%

Work-up of a soft tissue mass

• Which soft tissue masses require further evaluation:
  – Soft tissue mass >5 cm (golf ball size)
  – Painful lump
  – A soft tissue lump that is increasing in size
  – A lump of any size that is deep to the muscle fascia
  – Recurrence of a lump after previous excision

Sinha S. BMJ. 2010;341:c7170.
Work-up of a soft tissue mass

• Imaging
  – MRI if the mass is in an extremity
  – CT if the mass is in the abdomen
  – PET/CT not routinely recommended

• If imaging is suspicious for sarcoma...
  – Early referral to a center specializing in the treatment of sarcoma is recommended
Biopsy of a soft tissue mass

• General recommendations
  – Obtain biopsy after MRI to minimize edema
  – Biopsy should be carefully planned by the surgeon performing the resection

• Incisional biopsy vs core needle biopsy vs FNA
  – Core needle biopsy preferred
  – Incisional biopsy if diagnosis not made with core
  – FNA not recommended for initial diagnosis
Metastatic Disease

• Only 10% of patients present with distant metastatic disease
• 80% of metastases are found in the lungs
  – Chest imaging recommended as part of work-up
• After successful treatment of their primary tumor, 25% of patients will develop metastatic disease
  – Incidence increased to 40 to 50% in tumors that are:
    • >5 cm in size
    • Deep to the fascia
    • Intermediate or high grade

**AJCC Staging (7th Edition)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor (T)</th>
<th>Nodes (N)</th>
<th>Metastasis (M)</th>
<th>Grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1a,b</td>
<td>N0</td>
<td>M0</td>
<td>G1</td>
</tr>
<tr>
<td>IB</td>
<td>T2a,b</td>
<td>N0</td>
<td>M0</td>
<td>G1</td>
</tr>
<tr>
<td>IIA</td>
<td>T1a,b</td>
<td>N0</td>
<td>M0</td>
<td>G2,G3</td>
</tr>
<tr>
<td>IIB</td>
<td>T2a,b</td>
<td>N0</td>
<td>M0</td>
<td>G2</td>
</tr>
<tr>
<td>III</td>
<td>T2a,b</td>
<td>N0</td>
<td>M0</td>
<td>G3</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any G</td>
</tr>
</tbody>
</table>

**Tumor**
- T1 \(\leq 5\) cm
- T2 \(> 5\) cm
  - a: superficial
  - b: deep

**Nodes**
- N0: no nodes
- N1: regional nodes

**Grade**
- G1
- G2
- G3

**Metastasis**
- M0: no metastasis
- M1: + metastasis
Prognosis: Sarcoma Nomogram

Postoperative nomogram for 12-year sarcoma-specific death based upon data from 2,163 patients treated at memorial Sloan-Kettering cancer center

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (cm)</td>
<td>≤5</td>
<td>5-10</td>
<td>&gt;10</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Depth</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td>Lower Extremity</td>
<td>Thoracic/Trunk</td>
<td>Head/Neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper Extremity</td>
<td>Visceral</td>
<td>Retro/Intra-abdominal</td>
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<td></td>
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<tr>
<td>Histology</td>
<td>Fibro</td>
<td>Lipo</td>
<td>Leiomyo</td>
<td>Synovial</td>
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<td></td>
<td>MFH</td>
<td>Other</td>
<td>MPNT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>16</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total points</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
<td>160</td>
<td>180</td>
<td>200</td>
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<tr>
<td>Low grade 12 year SSD</td>
<td>0.04</td>
<td>0.06</td>
<td>0.08</td>
<td>0.1</td>
<td>0.15</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
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<tr>
<td>High grade 12 year SSD</td>
<td>0.04</td>
<td>0.06</td>
<td>0.08</td>
<td>0.1</td>
<td>0.15</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Nomogram Website

http://nomograms.mskcc.org/sarcoma/PostSurgery.aspx

Sarcoma Nomogram: Post-Surgery

In consultation with a physician, this tool can be used to predict the chances that an individual with sarcoma will have died from sarcoma up to 12 years after receiving surgical treatment for the disease. The tool also predicts the chances that patients with recurrent soft-tissue sarcoma (sarcoma that has returned after initial treatment success) will be alive up to 5 years following recurrence of the disease. These tools may be useful for patient counseling, follow-up scheduling, and clinical trial eligibility determination.

Enter Your Information

Age
Enter your current age.
36 years old (16 to 93)

Histology
Select the type of sarcoma diagnosed.
Syncytiom

Site
Select the location of the body where the sarcoma was located.
Lower Extremity

Grade
Enter a description of how the cancer cells appear under a microscope.
High

Depth
From the pathology report, enter the depth at which the sarcoma was located.
Deep

Tumor Size
7.2 cm (0 to 10)

Clear

Calculate

Your Results

Learn more about your results below.

Post Operative
Probability of Death
from Sarcoma

4 Year 28%
8 Year 38%
12 Year 42%

Probability of Death
from Sarcoma
Following Local
Recurrence

1 Year 23%
3 Year 51%
5 Year 61%

Print These Results

Make An Appointment

Call us to schedule an appointment or contact us online
contact us
Soft Tissue Sarcoma Treatment

• Stage I-IIB (small, low grade, superficial)
  – Surgery +/- RT
• Stage IIB-III (large, high grade, deep)
  – Surgery + RT
  – ? Chemotherapy (neoadjuvant or adjuvant)
• Stage IV (metastatic)
  – Chemotherapy
  – Metastectomy
Treatment of Localized Extremity Soft Tissue Sarcomas
Surgery

- Surgical resection with wide margins
  - Limb salvage
  - Amputation
    - required in 5% of patients

- Local recurrence after surgery alone
  - 60-90% with narrow margins
  - 8-30% with wide margins
  - 10-20% with compartmental resection

Radiation Therapy

- Improves local control rates by 20-25% compared to limb salvage surgery alone
- No improvement in overall survival
- Radiation recommended for:
  - Tumors > 5 cm
  - High grade tumors
  - Deep tumors

**Preop vs. Postop RT**

**Treatment Sequencing Trade-Off Issues**

**Preop RT**
- Lower dose (50 Gy)
- Smaller field size
- Reduced fibrosis
- Reduced edema
- Increased wound complications (35%)

**Postop RT**
- Higher dose (60-66 Gy)
- Larger field size
- Increased fibrosis
- Increased edema
- Wound complication risk as high as 17%

Adjuvant Chemotherapy

• Over 20 randomized trials and 2 meta-analyses with conflicting data
  – “First generation”
    • Doxorubicin based chemotherapy
  – “Second generation”
    • Ifosfamide incorporated
    • Doses intensified + growth factors
    • More restricted selection criteria

Antman KH. Semin Oncol. 1997;24(5):556.
SMAC Meta-analysis in 1997

14 trials
1568 patients

Extremity Tumors:
7% OS benefit at 10 years
p=.029

**Italian Adjuvant Study**

- >5 cm
- High grade Extremity/Girdle tumors
- Epirubicin + Ifosfamide
- Median F/U 89.6 months

![Graph showing survival rates](image)

**Fig. 1.** Overall survival of 104 randomized patients.

Updated Meta-analysis in 2008

- 18 trials
- 5 included anthracycline + ifosfamide
- OS benefit for anthracycline + ifosfamide
  - Absolute risk reduction was 11%
- No OS benefit for doxorubicin alone

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Citation</th>
<th>Treated</th>
<th>Control</th>
<th>PValue</th>
<th>0.01</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
<th>Effect</th>
<th>Lower</th>
<th>Upper</th>
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</thead>
<tbody>
<tr>
<td>Type II</td>
<td>Brodowicz et al</td>
<td>1 / 31</td>
<td>3 / 28</td>
<td>.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.26</td>
<td>.03</td>
<td>2.84</td>
</tr>
<tr>
<td>Type II</td>
<td>Furnstahl et al</td>
<td>20 / 53</td>
<td>28 / 51</td>
<td>.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.50</td>
<td>.23</td>
<td>1.09</td>
</tr>
<tr>
<td>Type II</td>
<td>Gorzalka et al</td>
<td>22 / 67</td>
<td>26 / 67</td>
<td>.29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.68</td>
<td>.34</td>
<td>1.38</td>
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<td>Type II</td>
<td>Petrioli et al</td>
<td>13 / 45</td>
<td>23 / 43</td>
<td>.02</td>
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<td></td>
<td></td>
<td></td>
<td>.35</td>
<td>.15</td>
<td>.85</td>
</tr>
<tr>
<td>Type II</td>
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<td>5 / 14</td>
<td>3 / 15</td>
<td>.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.22</td>
<td>.42</td>
<td>11.83</td>
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<tr>
<td>Fixed Type II</td>
<td>(5)</td>
<td>61 / 210</td>
<td>85 / 204</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.56</td>
<td>.36</td>
<td>.85</td>
</tr>
<tr>
<td>Fixed Combined</td>
<td>(18)</td>
<td>364 / 963</td>
<td>446 / 966</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.77</td>
<td>.64</td>
<td>.93</td>
</tr>
</tbody>
</table>

Neoadjuvant Chemotherapy

• Theoretical advantages
  – Tumor cytoreduction
    • Allow for limb salvage in borderline patient
  – Immediate treatment of micrometastases
  – Early indication of effectiveness of therapy

• Chemoradiotherapy
Neoadjuvant Chemoradiotherapy: Phase II Study by Ryan, et al

- 25 patients with STS of extremity and trunk > 5 cm and grade 2 or 3

- The rate of 95% pathologic necrosis was 40%
- 2-year overall survival rate was 84% (95% CI, 66–100%)

Summary of Adjuvant Chemotherapy

• Limited and conflicting data
• Anthracycline + ifosfamide appears to be better than anthracycline alone
• Adjuvant chemo is a category 2B recommendation on the NCCN guidelines
• Must discuss risks and benefits with the patient
Treatment of Localized Retroperitoneal Soft Tissue Sarcomas
Retroperitoneal Soft Tissue Sarcomas

- Most common histologies:
  - Liposarcoma
    - Well-differentiated
    - Dedifferentiated
  - Leiomyosarcoma

- Can metastasize to the liver or lungs
  - Local failure more common
Surgery

• Often difficult to achieve R0 resection
  – Large tumors
  – Anatomic constraints
• Commonly require resection of adjacent organs such as kidneys, colon, or spleen
• Five-year local recurrence rates after complete resection ~ 50%

Radiation

• No randomized trials
• Retrospective data suggests decreased risk of local recurrence but no survival benefit
• Preop vs Postop RT
  – Postop can be difficult due to bowel falling into resection cavity
  – Advantages to preop RT:
    • Precisely define tumor volume
    • Tumor displaces bowel
    • Can give higher doses
    • May decrease risk of tumor dissemination at surgery
    • Possibly convert unresectable tumor to resectable

Adjuvant or Neoadjuvant Chemotherapy

• No randomized trials showing a benefit
  – Not routinely recommended
• Neoadjuvant chemotherapy for unresectable tumors
  – May see a response in leiomyosarcomas
  – Response unlikely in well-differentiated or dedifferentiated liposarcomas
  – Anthracycline + ifosfamide regimen likely most active

Treatment of Metastatic Disease
Pulmonary Metastectomy

Median survival 33 months

Median survival 11 months

# Single Agent Chemotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>10-25%</td>
<td>12 months</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>20-25%</td>
<td>12 months</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>8%</td>
<td>12 months</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>18%</td>
<td>NR</td>
</tr>
</tbody>
</table>

Other agents with <20% RR include Vinorelbine, Methotrexate, Doxil, Temazolomide
## Combination Chemotherapy

**Intergroup Randomized Phase III study of 340 patients**

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Response Rate (p&lt;0.002)</th>
<th>Median Overall Survival (NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin + DTIC</td>
<td>17%</td>
<td>13 months</td>
</tr>
<tr>
<td>Doxorubicin + DTIC + Ifosfamide</td>
<td>32%</td>
<td>12 months</td>
</tr>
</tbody>
</table>

EORTC Combination Study 1995

663 patients randomized to:
- Doxorubicin
- Doxorubicin + Ifosfamide
- Cyclophosphamide, vincristine, doxorubicin, DTIC

No difference in RR or OS

**EORTC 62012**

Randomized Phase III trial of 455 patients

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Response Rate</th>
<th>Median Overall Survival (p=0.076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin 75 mg/m²</td>
<td>13.2%</td>
<td>12.8 months</td>
</tr>
<tr>
<td>Doxorubicin 75 mg/m² + ifosfamide 10 g/m² days 1-4</td>
<td>24.7%</td>
<td>14.3 months</td>
</tr>
</tbody>
</table>

Van Der Graaf et al. ESMO 2012.
Gemcitabine + Docetaxel

Baysian designed randomized phase II study of 119 patients

40% of patients in the combination arm discontinued treatment by 6 months due to toxicity

Higher activity in LMS and MFH

## Histology Driven Chemotherapy

<table>
<thead>
<tr>
<th>Histology</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial sarcoma</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>Trabectedin</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Gemcitabine + Docetaxel</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Paclitaxel</td>
</tr>
</tbody>
</table>

Alveolar soft part sarcoma and clear cell sarcoma are generally not sensitive to chemotherapy.

Targeted Therapies
Angiogenesis in Soft Tissue Sarcomas

- Overexpression of PDGFR, VEGF, and VEGFR
- More commonly seen in:
  - Angiosarcomas
  - Solitary fibrous tumors
- Clinical correlation unclear


VEGF Inhibitors in Soft Tissue Sarcomas

• Several Phase II studies using bevacizumab, sunitinib, sorafenib, and pazopanib
  – Low response rates
  – Some activity in vascular sarcoma subtypes
Phase III RCT of Pazopanib in Soft Tissue Sarcoma

Adipocytic histologies excluded based on insufficient activity in Phase II study

No OS benefit

Pazopanib now FDA approved for non-adipocytic metastatic STS

Van Der Graaf, WT. Lancet 2012 May 19;379(9829):1879-86.
Multicenter Phase II RCT of Gemcitabine + Pazopanib

- N = 80
- Advanced STS
- Previous doxorubicin

**Randomize** 1:1

- Gemcitabine 1000 mg/m² days 1,8
- Pazopanib 800 mg PO daily
- q21 days

- Placebo PO daily
- q21 days

- Cross-over at progression

- Primary Endpoint: PFS
- Stratification Factor: Liposarcoma vs all other subtypes
# Histology Driven Targeted Therapies

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Targeted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary fibrous tumor/hemangiopericytoma</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Alveolar soft parts sarcoma</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Perivascular epithelioid cell neoplasms (PEComas, recurrent angiomyolipoma/lymphangioleiomyomatosis)</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Pigmented villonodular synovitis/tenosynovial giant cell tumor</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Desmoid tumors</td>
<td>Imatinib, sorafenib</td>
</tr>
<tr>
<td>Chordoma</td>
<td>Imatinib, sunitinib</td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor (IMT) with ALK translocation</td>
<td>Crizotinib</td>
</tr>
</tbody>
</table>

New Treatment Strategies
Trabectedin

- Derived from a sea squirt
- Poisons the DNA nucleotide excision repair machinery
- RR highest in the myxoid/round cell liposarcoma and leiomyosarcoma subtypes
- Several nonrandomized studies showing promising PFS and OS results
- Approved in Europe
- Phase III study ongoing in the US
Eribulin

- Derived from a sea sponge
- Microtubule inhibitor
- Approved for treatment of metastatic breast cancer
- Phase II study with activity in leiomyosarcoma and liposarcoma histolgies
- Phase III study ongoing


Halichondria panicea
Palifosfamide

- Composed of the active metabolite of ifosfamide
- Lacks the hemorrhagic cystitis and CNS toxicity seen with ifosfamide
- Randomized Phase II study of doxorubicin + palifosfamide compared to doxorubicin alone showed doubling of PFS with combination
- Phase III study of doxorubicin + palifosfamide vs doxorubicin recently completed accrual

Verschraegen CF. J Clin Oncol 28:15s, 2010 (suppl; abstr 10004)
TH-302

• Hypoxia activated prodrug
• Releases the DNA-alkylating dibromo isophosphoramide mustard moiety within hypoxic regions of tumors
• Targets levels of hypoxia that are common in tumors but are rare in normal tissues
• Encouraging antitumor activity in combination with doxorubicin in STS
• Phase III study of TH-302 + doxorubicin vs doxorubicin alone is ongoing
CDK4 inhibitor

- Cyclin-dependent kinase 4 (CDK4) is amplified in ~ 90% of well-differentiated/de-differentiated liposarcomas
- Promising PFS in a Phase II study of the selective CDK4/CDK6 inhibitor PD0332991
- Phase III study planned

CDK4 forms a complex with cyclin D1 which results in phosphorylation of the retinoblastoma protein allowing the release of E2F transcription factors that activate G1/S-phase gene expression.

Dickson MA. J Clin Oncol 30, 2012 (suppl; abstr 10002).
Summary of Treatment of Metastatic Disease

• Metastectomy for limited disease
• Clinical trial if available
• Chemotherapy
  – Single agent doxorubicin
  – Doxorubicin + ifosfamide
  – Gemcitabine + docetaxel
  – Pazopanib
  – Targeted therapies for specific histologies
Questions?