Controversies and State-of-the Art Systemic Treatment in Soft Tissue Sarcoma

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Medical Oncology
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2 March 2013
• Principles of Systemic Therapy

• Systemic Treatment in Unselected Patients

• Systemic Treatment in Enriched Populations

• Adjuvant Therapy

• Genomics, Novel Therapeutics and the Way Ahead
• **Principles of Systemic Therapy**

• Systemic Treatment in Unselected Patients

• Systemic Treatment in Enriched Populations

• Adjuvant Therapy

• Genomics, Novel Therapeutics and the Way Ahead
Cancer treatment must be founded upon:

- Clear definition of **therapeutic objectives**

- Sound **biological** principles (pertaining to both disease and therapy)

- Scientifically and clinically meaningful **metric** of failure and success
<table>
<thead>
<tr>
<th>End point</th>
<th>Definition</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>Time from randomization to death from any cause</td>
<td>Objective, unambiguous</td>
<td>Requires large patient numbers and long follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Confounded by subsequent lines of therapy</td>
</tr>
<tr>
<td>PFS</td>
<td>Time from randomization to objective tumor progression or death</td>
<td>Not confounded by subsequent lines of therapy</td>
<td>Assessment of disease progression is subjective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smaller sample size than in OS assessment</td>
<td>Requires evaluations at frequent intervals</td>
</tr>
<tr>
<td>TTP</td>
<td>Time from randomization to objective tumor progression</td>
<td>Same as for PFS</td>
<td>Same as for PFS</td>
</tr>
<tr>
<td>ORR</td>
<td>Percentage of patients achieving CR or PR</td>
<td>Provides rapid assessment of antitumor activity</td>
<td>Influenced by tumor response criteria; can be subjective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Useful in initial Phase II trials</td>
<td>May not detect clinical benefit of cytostatic drugs</td>
</tr>
<tr>
<td>DCR; CBR</td>
<td>Percentage of patients achieving CR, PR and SD; CBR includes only SD lasting more than 3 to 6 months</td>
<td>May capture clinical benefit of cytostatic drugs</td>
<td>Confounded by natural history of malignancy (periods with little or slow growth)</td>
</tr>
<tr>
<td>TTF</td>
<td>Time from randomization to treatment discontinuation</td>
<td>Provides measure of efficacy/tolerability ratio</td>
<td>Confounded by multiple factors that can lead to discontinuation, including patient preference and physician decision</td>
</tr>
</tbody>
</table>

CBR: Clinical benefit rate; CR: Complete response; DCR: Disease control rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TTF: Time to treatment failure; TTP: Time to tumor progression.

Chmielowski et al Expert Rev Anticancer Ther 2012
Change in tumor size compared with baseline

<table>
<thead>
<tr>
<th>Sarcoma subtype</th>
<th>n</th>
<th>Median OS (weeks)</th>
<th>Median OS in patients with CBR (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone sarcomas</td>
<td>54</td>
<td>37.9</td>
<td>Not reached</td>
</tr>
<tr>
<td>Leiomyosarcomas</td>
<td>57</td>
<td>39.0</td>
<td>55.9</td>
</tr>
<tr>
<td>Liposarcomas</td>
<td>44</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Other soft-tissue sarcomas</td>
<td>57</td>
<td>44.1</td>
<td>72.3</td>
</tr>
<tr>
<td>All patients</td>
<td>212</td>
<td>40.1</td>
<td>67.6</td>
</tr>
</tbody>
</table>

*CBR was defined as a complete response, partial response or stable disease lasting ≥16 weeks. CBR: Clinical benefit rate; OS: Overall survival.
Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas

M. Van Glabbekea,*, J. Verweijb, I. Judsonc, O.S. Nielsend, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group

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bRotterdam Cancer Institute and University Hospital, Groene Hilledijk 301, Rotterdam, The Netherlands
cRoyal Marsden Hospital, Fulham Road 203, London, UK
dAarhus Kommunehospital, Noerrebrogade 44, Aarhus, Denmark

Received 27 September 2001; accepted 9 October 2001

Abstract

We have estimated progression-free rates (PFR) for various groups of soft-tissue sarcoma patients from our clinical trials database, to provide reference values for conducting phase II studies with PFR as the principal end-point. In 146 pretreated patients receiving an active agent, the PFR estimates were 39 and 14% at 3 and 6 months; with inactive regimens (234 patients), those estimates were 21 and 8% respectively. In 1154-non-pretreated patients, PFR estimates varied from 77% (synovial sarcoma) to 57% (malignant fibrous histiocytoma (MFH)) at 3 months, and from 56% (synovial sarcoma) to 38% (MFH) at 6 months. In 61 leiomyosarcomas from gastrointestinal origin, the corresponding figures were 44 and 30%, respectively. Consequently, for first-line therapy, a 6-month PFR of $\geq 30$–56% (depending on histology) can be considered as a reference value to suggest drug activity; for second-line therapy, a 3-month PFR of $\geq 40\%$ would suggest a drug activity, and $\leq 20\%$ would suggest inactivity. © 2002 Elsevier
Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas

M. Van Glabbekea,*, J. Verweijb, I. Judsonc, O.S. Nielsend, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group

... for first-line therapy, a 6-month PFR of ≥ 30-56% (depending on histology) can be considered as a reference value to suggest drug activity; for second-line therapy, a 3-month PFR of ≥ 40% would suggest a drug activity, and ≤ 20% would suggest inactivity.

Abstract

We have estimated progression-free rates (PFR) for various groups of soft-tissue sarcomas from our clinical trials database, to provide reference values for conducting phase II studies with PFR as the principal end-point. In 46 pretreated patients receiving an active agent, the PFR estimates were 39 and 14% at 3 and 6 months; with inactive agents (234 patients), those estimates were 21 and 8% respectively. In 1154 non-pretreated patients, PFR estimates varied from 15% (synovial sarcoma) to 57% (malignant fibrous histiocytoma (MFH)) at 3 months, and from 56% (synovial sarcoma) to 38% (MFH) at 6 months. In 61 leiomyosarcomas from gastrointestinal origin, the corresponding figures were 44 and 30%, respectively. Consequently, for first-line therapy, a 6-month PFR of ≥30–56% (depending on histology) can be considered as a reference value to suggest drug activity; for second-line therapy, a 3-month PFR of ≥40% would suggest a drug activity, and ≤20% would suggest inactivity. © 2002 Elsevier
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Sarcomas Are Uncommon Cancers Linked by Mesenchymal Origin
NCCS Sarcomas 2002 - 2012

N = 1245

- GIST: 23%
- UPS/MFH: 14%
- Leiomyosarcoma: 11%
- Lipo Sarcoma: 11%
- Angiosarcoma: 6%
- Osteosarcoma: 5%
- Synovial Sarcoma: 4%
- Myxofibrosarcoma: 3%
- Ewings / PNET: 3%
- Chondrosarcoma: 2%
- Rhabdomyosarcoma: 2%
- Hemangiopericytoma/SFT: 1%
- NCCS Sarcomas 2002 - 2012

- Dermatofibrosarcoma Protruberans
- MPNST
- Endometrial stromal sarcoma
- Hemangiopericytoma/SFT
- Desmoid/Fibromatosis
- Epitheloid sarcoma
- Fibrosarcoma
- Sarcoma, nos
- Chordoma
- Alveolar soft part sarcoma
- Fibromyxoid Sarcoma
- Giant Cell Tumour of Bone
- Others
NCCS Sarcomas 2002 - 2012

N = 1245

GIST 23%

UPS/MFH 14%

Leiomyosarcoma 11%

Lipo sarcoma 11%

Angiosarcoma 6%

Chondrosarcoma 2%

Myxofibrosarcoma 3%

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Endometrial stromal sarcoma

Hemangiopericytoma/SFT

Desmoid/Fibromatosis

Epitheloid sarcoma

Fibrosarcoma

Fibrosarcoma, nos

Chordoma

Alveolar soft part sarcoma

Fibromyxoid Sarcoma

Giant Cell Tumour of Bone

Others
NCCS STS 2002-2012

- Leiomyosarcoma: 17%
- Liposarcoma: 16%
- Angio-sarcoma: 8%
- Myxofibrosarcoma: 4%
- Rhabdomyosarcoma: 3%
- MPNST: 3%
- DFSP: 3%
- Hemangiopericytoma/SFT: 2%
- Desmoid/Fibromatosis: 2%
- Endometrial stromal sarcoma: 3%
- Epitheloid sarcoma: 2%
- Synovial sarcoma: 6%
- Others: 4%

N = 816
What are the Outcomes for Patients with Metastatic Soft-Tissue Sarcomas?

- Early hopes for chemotherapy that would yield similar survival benefits as noted in “chemotherapy sensitive sarcomas”
  - Osteosarcomas, Rhabdomyosarcomas and Ewing Sarcomas

- Metastatic soft tissue sarcomas present variable clinical behaviors but are nearly always incurable with any approach
  - Therefore, our intent is to palliate and to prolong life with the highest possible quality
What is the BEST FIRST-LINE THERAPY for Metastatic Soft-Tissue Sarcomas?

• Is it proper to “lump” together all soft tissue sarcomas?
  – Which soft-tissue sarcomas have reasonably similar behaviors when metastatic?

• Does combination chemotherapy meaningfully improve clinical outcomes compared with single agent chemotherapy?
Chemotherapy for Advanced and Metastatic Soft-Tissue Sarcomas: Evolution over the past 40 years

1972
- Doxorubicin and DTIC Activity Noted in Sarcomas

1982
- Combinations of Doxorubicin with DTIC and Cyclophosphamide
- Ifosfamide Activity Noted in Sarcomas (1987)

1992
- Combinations of Doxorubicin plus Ifosfamide
- HIGH DOSE Ifosfamide explored in Sarcomas with CSF support (1997)

2002
- GIST routinely removed from studies of "Soft Tissue Sarcomas"
Same Disease? Or Completely Different?
Same Disease? Or Completely Different?

Leiomyosarcoma

GIST
“Cancer biology trumps clinical empiricism”
Chemotherapy for Advanced and Metastatic Soft-Tissue Sarcomas:
Evolution over the past 40 years

- **1972**: Doxorubicin and DTIC Activity Noted in Sarcomas
- **1982**: Combinations of Doxorubicin with DTIC and Cyclophosphamide
- **2002**: HIGH DOSE Ifosfamide explored in Sarcomas with CSF support (1997)
- **2012**: Single Agent Doxorubicin same or better than Ifosfamide in 1st-line EORTC phase 3 study (2007)

ESMO 2012 plenary session from EORTC STBSG 62012
First-Line Chemo for Metastatic Soft Tissue Sarcomas (EORTC 62012)

Eligibility:
- Age 18-60
- High grade histology
- No previous chemo for advanced/metastatic disease
- WHO PS < 2

Stratification:
- Age (<50 vs ≥50)
- PS (0 vs 1)
- Liver metastases (0 vs +)
- Histological grade (2 vs 3)

Single-agent Doxorubicin
(75 mg/m² bolus or as a 72 hour continuous i.v. infusion)

Doxorubicin 25 mg/m² d 1-3
+ Ifosfamide 2.5 g/m² d 1-4
+ PEG-Filgrastim 6 mg s.c. d5

n = 455
Statistically Significant Difference in Progression-Free Survival

HR = 0.74 (95% CI 0.60 – 0.90)
Stratified logrank test, p = 0.003

Favors Combination Chemotherapy
Progression-Free Survival: Statistically Different ($p=0.003$) Favoring Dox+Ifos

- **Dox + Ifos**
  - Median PFS: 7.4 months (ORR 27%)

- **Dox**
  - Median PFS: 4.6 months (ORR 14%)

Since median OS is 13 months, this means that sarcoma is controlled for approx. 20% longer with combination chemo.
Overall survival

HR = 0.83 (95.5% CI 0.67 – 1.03)
Stratified logrank test, p = 0.076

Number of patients at risk:

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>188</td>
<td>228</td>
<td>Doxo</td>
</tr>
<tr>
<td>130</td>
<td>184</td>
<td>DxIf</td>
</tr>
</tbody>
</table>

12.8 m 14.3 m
1\textsuperscript{st} line
- Anthracycline +/- Ifosfamide

2\textsuperscript{nd} Line
- Gemcitabine - Docetaxel
- Trabectedin
- Pazopanib
- Gemcitabine-Navelbine, Dacarbazine, Temozolamide

N\textsuperscript{th} line
- Off label vs Trials if available
Targeting the VEGF Pathway with Tyrosine Kinase Inhibitors

Pazopanib

PALETTE Study

PAzopanib ExpLorEd in SofT-TissuE Sarcoma

- Non- adipocytic, non GIST
- ≥ 1 regimen containing anthracycline, ≤ 4 lines of systemic therapy for metastatic disease (≤ 2 lines of combination regimens).
- No previous anti-VEGF treatment

Sample Size: 369 patients enrolled and treated

Van der Graaf et al Lancet 2012
Pazopanib in STS: The PALETTE Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pazopanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>1.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.24, 0.40)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

ORR (Pazopanib): 6%

ORR (Placebo): 0%

Van der Graaf et al. Lancet 2012
OS in metastatic STS

Karavasilis et al. Cancer 2008

Minchom et al. Sarcoma 2010

1\textsuperscript{st} line chemo  
\( n = 488 \) (1991 – 2005)

2\textsuperscript{nd} line chemo  
\( n = 379 \) (1991 – 2005)

mOS 12m

mOS 8m

5y OS 10%
Improving OS with time?


Italiano et al. Cancer 2011
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Different Behaviour of Different Histological Subsets of STS Treated Similarly

n = 2185
All treated with anthracyclines in 1st line
Different Behaviour of Different Histological Subsets of STS Treated Similarly

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>A</th>
<th>A1</th>
<th>MAP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>42</td>
<td>10</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td>MFH</td>
<td>15</td>
<td>20</td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>5</td>
<td>20</td>
<td>8</td>
<td>88</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>7</td>
<td>57</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>4</td>
<td>25</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Spindle cell sarcoma</td>
<td>0</td>
<td>—</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>3</td>
<td>33</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>0</td>
<td>—</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>2</td>
<td>50</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other sarcoma</td>
<td>9</td>
<td>33</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>20</td>
<td>88</td>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histo / Regimen</th>
<th>Initially exciting results from small / retrospective series ....</th>
<th>More sobering data from prospective studies ....</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMS</strong>&lt;br&gt;Gem + Tax</td>
<td>In a single-arm phase II study (n=34) comprised primarily of pts with uterine LMS, <strong>ORR of 53%</strong> was achieved <em>(Hensley JCO 2002)</em>. Subsequent evaluation of the regimen in uterine LMS in both the first and second line continued to demonstrate promising activity.</td>
<td>In a randomised phase II study (n =90), of gemcitabine vs gemcitabine plus docetaxel in 2&lt;sup&gt;nd&lt;/sup&gt; line, there were no significant efficacy differences between the 2 arms. ORR was <strong>19% and 24%</strong> respectively for uterine, and <strong>14 % and 5%</strong> respectively for non-uterine. Median PFS was <strong>5.5 m and 4.7 m</strong> respectively for uterine, and <strong>6.3 m and 3.8 m</strong> respectively for non-uterine <em>(Pautier et al, Oncologist 2012)</em>.</td>
</tr>
<tr>
<td><strong>LPS</strong> (myxoid)&lt;br&gt;Trabectedin</td>
<td>A retrospective review (n=51) of international pts with myxoid LPS <strong>ORR of 51%</strong>, and a 6-mth PFR of <strong>88%</strong> <em>(Grosso et al, Lancet Oncol 2007)</em>. Longer term follow up of a single institution series corroborated these findings with <strong>median PFS of 17 m</strong> <em>(Grosso et al Annals of Oncology 2009)</em></td>
<td>In a single arm phase II study (n = 23) of neoadjuvant chemotherapy in locally advanced previously untreated myxoid LPS, the <strong>ORR was 24%</strong>, with 3 patients (13%) achieving pathological CR <em>(Gronchi et al, Annals of Oncology 2011)</em>.</td>
</tr>
<tr>
<td><strong>AS</strong>&lt;br&gt;Paclitaxel</td>
<td>A small retrospective study demonstrated major responses in 8 out of 9 patients with scalp or face AS treated with Paclitaxel <em>(Fata et al, Cancer 1999)</em>. A subsequent larger retrospective study demonstrated <strong>ORR of 75% in scalp AS and 58% in other primary sites</strong> <em>(Schlemmer et al, EJC 2008)</em>.</td>
<td>In a single arm Phase II study ( n= 30) for all-comers, <strong>ORR was 18%</strong>, with a 2, 4, ad 6 month PFR of 74%, 45% and 24% respectively <em>(Penel et al, JCO 2008)</em>.</td>
</tr>
</tbody>
</table>
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Adjuvant Chemotherapy in Sarcoma

- Adjuvant chemotherapy aims to eradicate micrometastatic disease to improve survival.

- In osteosarcoma and Ewing’s, cure rates improve from 20% to 60% with the addition of chemotherapy.

- In GIST, Imatinib remains the first and only tyrosine kinase inhibitor to improve survival in adjuvant setting.

- What of STS?
Adjuvant Chemotherapy in STS in last 2 decades

SMAC I: 1994-1997
SMAC II: 2008-2012

EORTC I: 62771
EORTC II: 62931

Small Prospective Studies
Adjuvant Chemotherapy in STS in last 2 decades

SMAC I: n = 1568, m f/up : 9 y

Interpretation: Positive study

10 y

<table>
<thead>
<tr>
<th></th>
<th>L-RFI</th>
<th>D-RFI</th>
<th>RFS</th>
<th>OS</th>
<th>OS extremity STS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.73</td>
<td>0.70</td>
<td>0.75</td>
<td>0.89</td>
<td>0.80</td>
</tr>
<tr>
<td>Absolute benefit</td>
<td>6%</td>
<td>10%</td>
<td>10%</td>
<td>4%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Bramwell et al JCO 1994
Adjuvant Chemotherapy in STS in last 2 decades

N = 351 (1995 – 2003) m f/up 8 y

Resected intermediate / high grade sarcoma

5 cycles (Doxo 75 mg/m² + Ifos 5g/m² )

+/-RT

EORTC II : 62931

2012

Woll et al Lancet Oncology 2012
Adjuvant Chemotherapy in STS in last 2 decades

Possible Limitations

Suboptimal Surgery ? - > 50% patients with unknown or close surgical margins (<5 mm)

Suboptimal Chemo ? - > Low ifosfamide dose (5g/m2)

Patient Heterogeneity ? - > (25% < 5 cm, central path grade High 46%, Intermediate 48%, Low 6%)

Interpretation : Negative study

Woll et al Lancet Oncology 2012
Even if decision made for adj. chemotherapy, questions remain ....

- Optimal *regimen*?
  - Choice of drugs
  - Number of cycles

- Optimal *patient selection*?
  - Impact of histology
  - Clinicopathologic risk factors

- *Neoadjuvant* approach?
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Cancer is a genomic disease, driven by pathological alterations – mutations – to our genes that regulate cellular survival.

Cancer bears certain molecular pathogenetic hallmarks.

Treating established cancer involves redressing these deviant cellular processes (e.g. abrogating aberrant proliferation or restoring pathologically shut-off apoptosis).

Hanahan and Weinberg, Cell 2011
A Genomic Approach to Sarcomas

**Genetically / Karyotypically Simple**
- Near diploid karyotypes
- Simple genetic alterations
- Usually arise de novo
- Single defining cytogenetic abnormality present at initiation, retained throughout clonal evolution

**Genetically / Karyotypically Complex**
- Genomically unstable
- Multiple genomic and chromosomal (numerical and structural) aberrations in single tumour; heterogeneity of aberrations across tumours of given type.
- Can arise from less aggressive form and pass through discrete stages of increasing complexity (*though most high grade ones arise de novo without antecedent lower grade lesions*).
- Reminiscent of most solid tumours

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<table>
<thead>
<tr>
<th>0 mutations</th>
<th>5 mutations</th>
<th>10 mutations</th>
<th>20 mutations</th>
<th>&gt; 100 mutations</th>
<th>&gt; 1000 mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST, DFSP</td>
<td>EWING’s, RMS, DD LPS</td>
<td>LMS, OSTEOSARC, PLEOMORPHIC LPS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Genomic Approach to Sarcomas

- **Genomically Simple**
  - Driven by pathognomonic translocations or point mutations

- **Genomically Intermediate**
  - Non translocation – associated sarcomas characterized by few, but highly recurrent amplifications (e.g. DD LPS)

- **Genomically Complex**
  - Karyotypically complex arcomas that are heterogeneous, unstable and profoundly altered in genomic copy number.
Molecular Mechanisms of Sarcomagenesis

Transcriptional Target Dysregulation
Aberrant transcriptional proteins resulting from gene fusions secondary to recurrent tumour specific translocations

Mutations in Key Genes and Signalling Pathways
Highly recurrent driver genes

Genomic Copy Number Alterations
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Translocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13)(q35;q14) PAX3-FOX01A</td>
</tr>
<tr>
<td></td>
<td>t(1;13)(p36;q14) PAX7-FOX01A</td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>t(X;17)(p11.2;q25) ASPL-TFE3</td>
</tr>
<tr>
<td>Angiomatoid fibrous histiocytoma</td>
<td>t(12;16)(q13;p11) FUS-ATF1 t(12;22)(q13;q12) ATF1-EWSR1 t(2;22)(q34;q12) CREB1-EWSR1</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)(q13;q12) ATF1-EWSR1 t(2;22)(q34;q12) CREB1-EWSR1</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>t(17;22)(q22;q13) COL1A1-PDGFB</td>
</tr>
<tr>
<td>Desmoplastic round cell tumor</td>
<td>t(11;22)(p13;q12) WT1-EWSR1</td>
</tr>
<tr>
<td>Endometrial stromal sarcoma</td>
<td>t(7;17)(p15;q21) JAZF1-JAZ1 t(6;7)(p21;p15) PHF1-JAZF1 t(6;10)(p21;p11) PHF1-EPC1</td>
</tr>
<tr>
<td>Ewing’s sarcoma/PNET</td>
<td>t(11;22)(q24;q12) EWSR1-FLI1</td>
</tr>
<tr>
<td></td>
<td>t(21;22)(q22;q12) EWSR1-ERG</td>
</tr>
<tr>
<td></td>
<td>t(7;22)(p22;q12) EWSR1-ETV1</td>
</tr>
<tr>
<td></td>
<td>t(17;22)(q12;q12) EWSR1-EIAF</td>
</tr>
<tr>
<td></td>
<td>t(16;21)(q13;q22) FUS-ERG</td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q33;q12) EWSR1-FEV</td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;22)(q22;q12) EWSR1-NR4A3 t(9;15)(q22;q21) TCF12-NR4A3</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>t(12;15)(p13;q25) ETV6-NTRK3</td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>t(2;19)(p23;p13.1) ALK-TPM4 t(1;2)(q22–23;p23) TPM3-ALK</td>
</tr>
<tr>
<td>Low grade fibromyxoid sarcoma</td>
<td>t(7;16)(q33;p11) FUS-BBF2H7 t(11;16)(p11;p11) FUS-CREB3L1</td>
</tr>
<tr>
<td>Myxoid-round cell liposarcoma</td>
<td>t(12;16)(q13;p11) FUS-DDIT3 t(12;22)(q13;q12) EWSR1-DDIT3</td>
</tr>
<tr>
<td>Pericytoma</td>
<td>t(7;12)(p22;q13) ACTB-GLI</td>
</tr>
<tr>
<td>Soft tissue myoepithelioma</td>
<td>t(1;22)(q23;q12) EWSR1-PBX1</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(X;18)(p11;q11) SS18-SSX1 SS18-SSX2 SS18-SSX4</td>
</tr>
</tbody>
</table>
Some Key Findings:

Mutations:
- **Tp53** (17% pl LPS)
- **NF1** (10.5% mxyF, 8% pl LPS)
- **PiK3CA** (18% MRC)

Pathway Validation:
- CDK4 in dD LPS
Pathway Driven Therapeutics in Sarcoma

- ALK in inflammatory myofibroblastic tumour
- MDM2 in liposarcoma
- Hedgehog in chondrosarcoma
- mTOR in PEComa
- IGF1-R in Ewing’s / Solitary fibrous tumour
- .......
- .......
MDM2 / CDK4 Pathway

- MDM
- 12q15
- p53
- 12q14
- CDK4
- RB
- G0
- G1
- S
- G2
- M

APOPTOSIS

Amplicon 12q14-15

Cell survival

↑ proliferation

Cancer cell
MDM2 / CDK4 Amplification in STS (LPS)
Phase I MDM2 inhibitor in MDM2 amp. WD/DD LPS (n = 20)
A Proposed Modern Phylogeny of Sarcoma

Proximal

Lineage

Prognosis

Driver alterations

Additional parameters.

Taylor et al Nat Rev Cancer 2011
Conclusions

• The median survival of advanced STS is 12-18 m.

• In unselected populations, traditional cytotoxics (anthracyclines +/- ifosfamide) remain the systemic therapy of choice in first line, with any of several agents (including novel cytotoxics and pathway inhibitors) showing meaningful benefit.

• In histologically selected populations, certain cytotoxic agents may have particular efficacy.

• The utility of adjuvant chemotherapy remains unproven.

• Improved apprehension of the genomic underpinnings of sarcomagenesis (leading to appropriate pathway driven therapeutics) has led to notable success, and holds much promise for the future.
Thank You

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