Sarcoma

Thomas Brodowicz

Bucharest, 18 June 2015
Meeting Objectives

• Gain insight and feedback on the existing and emerging clinical data in sarcomas landscape
  – Soft Tissue Sarcoma
  – GIST
  – EWING Family
  – Osteosarcoma
Soft Tissue Sarcomas: Current Landscape and Emerging Data
Soft Tissue Sarcoma (STS)

- ~11,000 newly diagnosed STS/year in the EU (10%M1)
- ~50% of the patients experience M1
- Median OS in M1: 8-12 months
- Localisation:
  - Lower Extremities: ~40%
  - Upper Extremities: ~20%
  - Retroperitoneal and intra-peritoneal: ~20%
  - Trunk: ~10%
  - Head & Neck: ~10%
Relative frequency of sarcoma subtypes

- Bone primary (osteosarcoma/chondrosarcoma) (8%)
- GIST (18%)
- Liposarcoma (15%)
- Soft-tissue Ewing sarcoma/pNET (4%)
- Kaposi sarcoma (3%)
- Dermatofibrosarcoma (5%)
- Unclassified sarcoma (16%)
- Leiomyosarcoma (11%)
- Rhabdomyosarcoma (3%)
- Angiosarcoma (3%)
- Myxofibrosarcoma (2%)
- Synovial sarcoma (2%)
- Endometrial stromal sarcoma (2%)
- Other very rare subtypes (8%)
Incidence of sarcoma in 3 European regions

- Others
- Osteosarcoma
- Solitary Fibrous Tumors
- Fibrosarcoma
- MPNST
- LG Fibromyxoid sarcomas
- Angiosarcomas
- Ewing sarcomas
- Synovial sarcomas
- Rhabdomyosarcomas
- Myxofibrosarcomas
- MFH
- Uterine LMS
- Dermatofibrosarcoma
- Kaposi
- Non Uterine LMS
- Sarcoma NOS
- Liposarcoma
- GIST

Comparative study in three different European regions

- ConTiCanet: European network of excellence (Connective Tissue Cancer Network)
- Collaboration between Aquitaine, Rhône-Alpes & Veneto
- Inclusion criteria: STS and visceral

→ 3 exhaustive data bases of incident cases of sarcoma during 2 years

Rhône-Alpes: 6 M inhab. 10% French popul.
Aquitaine: 3 M inhab. 5% French popul.
Vénétro: 5 M inhab. 8% Italian popul.

Incidence / 100,000 / yr
Resection with tumor free margins

Classification of Margins

- Intralesional: Margin runs through the tumor and therefore tumor remains.
- Marginal: Surgical plane is between the tumor capsule (reactive zone). The local recurrence rate is high because of tumor satellites in the reactive tissue.
- Wide: Surgical plane is in normal tissue in the same compartment as the tumor. The recurrence rate is low and is related only to skip lesions in the affected compartment.
- Radical: The tumor is removed including affected compartments and there is a minimal risk of local recurrence.

Irradiation, Chemotherapy
Tumor Grading

- Grade according to the histologic type
- Grading according to the FNCLCC grading system

**Table 1: FNCLCC histological grading criteria**

<table>
<thead>
<tr>
<th>Tumour differentiation</th>
<th>Necrosis</th>
<th>Mitotic count ($n/10$ high power fields)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: well</td>
<td>0: absent</td>
<td>1: $n &lt; 10$</td>
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<tr>
<td>2: moderate</td>
<td>1: $&lt;50%$</td>
<td>2: $10–19$</td>
</tr>
<tr>
<td>3: poor (anaplastic)</td>
<td>2: $\geq 50%$</td>
<td>3: $n \geq 20$</td>
</tr>
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</table>

The sum of the scores of the three criteria determines the grade of malignancy. Grade 1: 2, 3; Grade 2: 4, 5; Grade 3: 6, 7, 8.
Sarcomas and aggressive connective tissue tumors

<p>| Translocations (DFSP; SyS; Ewing) | Mutations kinases (GIST) | Amplifications 12q13-15 MDM2/CDK4 (WD/DDLPS) | TSG loss NF1, TSC1/2 (MPNST; PEComas) | Complex Genomic (LMS; UPS) | Mutations APC/bCat (Desmoids) |</p>
<table>
<thead>
<tr>
<th>Sarkom</th>
<th>Translokation</th>
<th>fusionierte Gene</th>
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<tbody>
<tr>
<td><strong>EWING Sa</strong></td>
<td>t(11;22)(q24;q12)</td>
<td><em>FLI1</em> - <em>EWSR1</em></td>
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<td></td>
<td>t(21;22)(q22;q12)</td>
<td><em>ERG</em> – <em>EWSR1</em></td>
</tr>
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<td></td>
<td>t(7;22)(p22;q12)</td>
<td><em>ETV1</em> – <em>EWSR1</em></td>
</tr>
<tr>
<td></td>
<td>t(17;22)(q12;q12)</td>
<td><em>E1AF</em> – <em>EWSR1</em></td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q33;q12)</td>
<td><em>FEV</em> – <em>EWSR1</em></td>
</tr>
<tr>
<td><strong>Klarzellen Sa</strong></td>
<td>t(12;22)(q13;q12)</td>
<td><em>ATF1</em> - <em>EWSR1</em></td>
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<td><strong>DSCRT</strong></td>
<td>t(11;22)(p13;q12)</td>
<td><em>WT1</em> - <em>EWSR1</em></td>
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<td><strong>EMC</strong></td>
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<td></td>
<td>t(9;22)(q22;q12)</td>
<td><em>NR4A3</em> - <em>EWS</em></td>
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<td>t(9;17)(q22;q11)</td>
<td><em>NR4A3</em> – <em>TAF2N</em></td>
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<td>t(9;15)(q22;q21)</td>
<td><em>NR4A3</em> – <em>TCF12</em></td>
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<td><strong>myx. Lipo Sa</strong></td>
<td>t(12;16)(q13;q11)</td>
<td><em>DDIT3</em> - <em>TLS</em></td>
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<td>t(12;22)(q13;q12)</td>
<td><em>DDIT3</em> - <em>EWSR1</em></td>
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<td>t(2;13)(q35;q14)</td>
<td><em>PAX3</em> – <em>FOXO1A</em></td>
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<td><strong>alveoläres RMS</strong></td>
<td>t(1;13)(p36;q14)</td>
<td><em>PAX7</em> – <em>FOXO1A</em></td>
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<td>t(X;18)(p11.2;q11.2)</td>
<td><em>SSX1</em> - <em>SYT</em></td>
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<td><strong>Synovial Sa</strong></td>
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<td>t(11;16)(p11;p11)</td>
<td><em>CERB3L1 – FUS</em></td>
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<td><strong>angiomat. (M) FH</strong></td>
<td>t(12;16)(q13;p11)</td>
<td><em>ATF1</em> - <em>FUS</em></td>
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Meta-analysis

14 Randomized Trials: 1568 Patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>p-value</th>
<th>HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Local RFI</td>
<td>0.016</td>
<td>0.73</td>
<td>(0.56-0.94)</td>
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<td>RFS</td>
<td>0.0001</td>
<td>0.75</td>
<td>(0.64-0.87)</td>
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<tr>
<td>OS</td>
<td>0.12</td>
<td>0.89</td>
<td>(0.76-1.03)</td>
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</table>
STS: adjuvant chemotherapy

- Meta-analysis of 14 randomized, doxorubicin-based adjuvant chemotherapy trials (n=1586)
  - 6% benefit for local recurrence-free survival (p=0.016)
  - 10% benefit for distant recurrence-free survival (p=0.0003)
  - 10% benefit for overall recurrence-free survival (p=0.0001)
  - 4% benefit for overall survival (p=0.12)

  - STS of extremities (n=886) HR for OS 0.80
  - 7% benefit at 7 years (p=0.029)

## Meta-analysis 2008 - OS

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<thead>
<tr>
<th>Chemotherapy</th>
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Pervaiz et al., Cancer 2008
• Retrospective analysis of 1,513 patients with localised soft tissue sarcoma
• Central review of histology and grading according FNCLCC system
• Median follow-up 9 years
• Impact of adjuvant chemotherapy:
  – Multivariate analysis shows a significant improvement in
    5-year MFS: 58% vs 49%, HR 0.7, p = 0.01
    5-year OS: 58% vs 45%, HR 0.6, p = 0.0002
    for patients with grade 3 soft tissue sarcomas only
    (no difference in patients with grade 2 soft tissue sarcomas)

Italiano et al., Ann Oncol 2010
**Interpretation** Adjuvant chemotherapy with doxorubicin and ifosfamide in resected soft-tissue sarcoma showed no benefit in relapse-free survival or overall survival. Future studies should focus on patients with larger, grade III, and extremity sarcomas.

Woll et al., Lancet Oncology 2012
Regionale Hyperthermie
Lokaltherapie mit RHT: Ergebnisse RHT 95 - LPFS

>120 Mo vs 75 Mo

Issels R, et al., Lancet Oncology 2010
STS: adjuvant chemotherapy

2015: Standard of care? → NO!

- Improvement of local/distant tumor control
- Delay of distant metastases
- (Marginal) survival benefit
- Selection of patients: High-risk, localisation, age, sex
- Individualized decision: benefit vs toxicity
Postoperative Nomogram for 12-Year Sarcoma-Specific Death

Points

Size (cm)
- <=5
- 5-10
- >10

Depth
- Superficial
- Deep

Site
- Lower Extremity
- Thoracic/Trunk
- Head/Neck
- Upper Extremity
- Visceral
- Retro/Intra-abdominal

Histology
- Fibro
- Lipo
- MFH
- Leiomyo
- Other
- Synovial
- MPNT

Age (years)
- 16
- 20
- 30
- 40
- 50
- 60
- 70
- 80
- 90

Total Points

12yr Low Gr. SSD

12yr High Gr. SSD

Instructions for Physician: Locate the patient’s tumor size on the Size axis. Draw a line straight upwards to the Points axis to determine how many points towards sarcoma-specific death the patient receives for his tumor size. Repeat this process for the other axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to either the Low Grade or High Grade axis to find the patient’s probability of dying from sarcoma within 12 years assuming he or she does not die of another cause first.

Instruction to Patient: “If we had 100 patients exactly like you, we would expect between <predicted percentage from nomogram – 8%> and <predicted percentage + 8%> to die of sarcoma within 12 years if they did not die of another cause first, and death from sarcoma after 12 years is still possible.”

http://www.mskcc.org/mskcc/html/6181.cfm
• Biopsy first
  – Management by a trained team
  – En bloc resection
  – Planning R0
  – If R1: re resection?
  – If R2: re esrection

• Post op RT
  – (G2-3 and/or deep seated T, and/or >5cm)

• Pre operative RT
Treatment algorithm for localized and metastatic disease

1 L
- Doxorubicin
- Ifosfamide
- Combination
  - OS 12-18 mths

2 L
- Ifosfamide
- Doxorubicin
  - PFS 4-6 mths

3/5 L
- Trabectedin / pazopanib / Gem DTIC / Gem-Tax
  - PFS 4 mths

Surgery R0/R1+ Radiotherapy

Cure (~50 %)

Metastasis (~60 %)

Surgery (~10 %)
Systemic Treatment of Sarcomas 2005-2015

**2005**
- All sarcomas
  - Doxorubicin
  - Ifosfamide
  - DTIC
- Subtypes
  - Dactinomycin
  - CDDP
  - Vinca-alcaloids
  - Cyclophosphamide
  - HDMTX

**2015**
- Trabectedin
- Gem Tax
- Gem DTIC
- Other than LPS: Pazopanib
- LMS: Gem,
- EWS: AcD, Topol inh, VCR
- A/E RMS: AcD, Topol inh, VCR
- Angio: Paclitaxel
- SFT: Temozolomide + Bevacizumab
- GIST: Imatinib, sunitinib, regorafenib
- Osteosarcomas: MTPPE
- LPS: Dox, ET743 (MRCL++)
- ESS: Aromatase inh.
- PEComa: mTOR
- DFSP: Imatinib
- PVNS: Imatinib, MCSFR Ab or TKI
- TD/FA: HT, imatinib, sorafenib
Pivotal Study STS-201 Trabectedin in STS

Randomized study with 270 STS patients comparing two dosing schedules, leading to EU indication in 2007

PFS

HR: 0.755
p = 0.0418

q3wk 24-h:
Median 3.3 months

qwk 3-h:
Median 2.3 months

OS

HR: 0.783
p = 0.0965

q3wk 24-h:
Median OS = 13.9 months

qwk 3-h:
Median OS = 11.8 months

1-year survival:
61% vs. 49%, p = 0.06

Historical context: PFS vs EORTC-Database*

Trabectedin vs BSC in Translocation-Related Sarcomas (TRS)

Progression Free Survival (Independent Assessment)

- Statistically significant improvement in PFS
- 29/36 BSC patients received Trabectedin after progression with similar PFS benefit

Takahashi S et al. ASCO 2014 abstract #10524; Yonemoto T et al. ESMO2014 abstract #1422PD
T-DIS study – Drug Holiday and Rechallenge
Interruption vs Continuation in Responding Patients After 6 Courses of Trabectedin

6 Cycles Trab
N=50

Responders

No Chemotherapy

Primary endpoint:
- PFR 24 weeks post Randomization

Secondary endpoints:
- ORR
- PFR at 12 & 54 weeks
- Survival at 12 & 24 months

N=156 at inclusion
® = 50

Le Cesne et al, ASCO 2014 Abs Nº 10523;
Le Cesne et al, Lancet Oncol 2015
T-Dis Maintenance Study
Results: Progression Free Survival (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Arm A (cont)</th>
<th>Arm (discont)</th>
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<tbody>
<tr>
<td>3-m PFS</td>
<td>81.5% (61.1-91.8)</td>
<td>53.9% (33.3-70.6)</td>
</tr>
<tr>
<td>6-m PFS</td>
<td>51.9% (31.9-68.6)</td>
<td>23.1% (9.4-40.3)</td>
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<tr>
<td>9-m PFS</td>
<td>33.3% (16.8-50.9)</td>
<td>19.2% (7.0-36.0)</td>
</tr>
</tbody>
</table>

Logrank test: $p=0.02$
Median f.u: 21 m from 

Le Cesne et al, ASCO 2014 Abs Nº 10523;
Le Cesne et al, Lancet Oncol 2015
## Retrospectyon – Retrospective Analysis of Trabectedin in Real Practice in France

### Efficacy observed by histotype in clinical practice

<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<td></td>
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<td>Median</td>
<td>95% CI</td>
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<td>PFS at 3 months (%)</td>
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<tr>
<td>Chondrosarcoma</td>
<td>13</td>
<td>6.267</td>
<td>.000–15.935</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>161</td>
<td>6.067</td>
<td>4.488–7.645</td>
</tr>
<tr>
<td>DSCRT</td>
<td>5</td>
<td>3.400</td>
<td>.000–9.126</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>20</td>
<td>2.833</td>
<td>1.471–4.196</td>
</tr>
<tr>
<td>Sarcoma NOS</td>
<td>82</td>
<td>2.367</td>
<td>1.977–2.756</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>89</td>
<td>2.300</td>
<td>.968–3.632</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>3</td>
<td>1.967</td>
<td>.000–5.061</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>9</td>
<td>.933</td>
<td>.836–1.031</td>
</tr>
</tbody>
</table>

CI: confidence intervals; DSCRT, Desmoplastic Small Round Cell Tumour; MPNST, Malignant Peripheral Nerve Sheath Tumours; OS, overall survival; PFS, progression-free survival.
SAR-3007: A randomized phase III study of trabectedin (T) or dacarbazine (D) for the treatment of patients (pts) with advanced liposarcoma (LPS) or leiomyosarcoma (LMS).

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>D</th>
<th>HR/OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>4.2</td>
<td>1.5</td>
<td>HR=0.550</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Benefit observed across all subgroups, and validated by independent radiologists audit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP (months)</td>
<td>4.2</td>
<td>1.5</td>
<td>HR=0.522</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CBR (%) (CR+PR+SD ≥ 18wks)</td>
<td>34.2</td>
<td>18.5</td>
<td>OR=2.291</td>
<td>0.0002</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>9.9</td>
<td>6.9</td>
<td>OR=1.467</td>
<td>0.3269</td>
</tr>
<tr>
<td>DOR (months)</td>
<td>6.5</td>
<td>4.2</td>
<td>HR=0.471</td>
<td>0.1415</td>
</tr>
<tr>
<td>IA of OS (64% censored) (months)</td>
<td>12.4</td>
<td>12.9</td>
<td>HR=0.872</td>
<td>0.3741</td>
</tr>
</tbody>
</table>

• The safety profiles were consistent with the well-characterized toxicities of both agents, with the most common grade 3-4 toxicities in T vs. D arm being ANC (40% vs 25%), platelets (19% vs 20%), increased ALT (29% vs 1%), and drug-related death (2.1% vs 0%). Patient-reported outcomes were similar across the arms, with low symptom scores during treatment.

Demetri et al. J Clin Oncol 33, 2015 (suppl; abstr 10503)
Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

### Previous studies of gemcitabine and docetaxel

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study type</th>
<th>Histology</th>
<th>Line of treatment</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hensley et al, 2002</td>
<td>34</td>
<td>Phase II</td>
<td>Leiomyosarcoma</td>
<td>1st/2nd</td>
<td>5.6</td>
<td>17.9</td>
</tr>
<tr>
<td>Leu et al, 2004</td>
<td>35</td>
<td>Retrospective</td>
<td>All STS</td>
<td>1st/2nd</td>
<td>6.7 (TTP)</td>
<td>13</td>
</tr>
<tr>
<td>Bay et al, 2006</td>
<td>133</td>
<td>Retrospective</td>
<td>All STS</td>
<td>Any</td>
<td>-</td>
<td>12.1</td>
</tr>
<tr>
<td>Maki et al, 2007</td>
<td>122</td>
<td>Randomised phase II (GvG)</td>
<td>All STS</td>
<td>2nd</td>
<td>GD: 6.2</td>
<td>GD: 17.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G: 3.0</td>
<td>G: 11.5</td>
</tr>
<tr>
<td>Hensley et al, 2008</td>
<td>42</td>
<td>Phase II</td>
<td>Uterine leiomyosarcoma</td>
<td>1st</td>
<td>4.4</td>
<td>16+</td>
</tr>
<tr>
<td>Hensley et al, 2008</td>
<td>48</td>
<td>Phase II</td>
<td>Uterine leiomyosarcoma</td>
<td>2nd</td>
<td>6.7+</td>
<td>14.7</td>
</tr>
<tr>
<td>Pautier et al, 2012</td>
<td>90</td>
<td>Randomised phase II (GvG)</td>
<td>Leiomyosarcoma (Uterine/non-uterine)</td>
<td>2nd</td>
<td>GD: 4.7(U), 3.8(NU)</td>
<td>GD: 23(U), 13(NU)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G: 5.5(U), 6.3(NU)</td>
<td>G: 20(U), 15(NU)</td>
</tr>
<tr>
<td>Seddon et al, 2015</td>
<td>44</td>
<td>Phase II</td>
<td>Leiomyosarcoma</td>
<td>1st</td>
<td>7.1</td>
<td>17.9</td>
</tr>
</tbody>
</table>
Progression-free survival

- **Doxorubicin**
  - Unadjusted HR = 1.28
  - 95% CI: (0.98, 1.67)
  - p = 0.07

- **Gemcitabine + Docetaxel**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (months)</th>
<th>24 week PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dox</td>
<td>5.4</td>
<td>46.1%</td>
</tr>
<tr>
<td>GemDoc</td>
<td>5.5</td>
<td>46.0%</td>
</tr>
</tbody>
</table>

**Number at risk**
- **Doxorubicin**: 129, 93, 58, 39, 26, 18, 9, 5, 3, 0
- **Gemcitabine & Doc.**: 128, 82, 58, 33, 9, 5, 3, 1, 1, 0

Presented By Beatrice Seddon at 2015 ASCO Annual Meeting
Overall survival

**Overall survival**

Unadjusted HR=1.07
95% CI: (0.77, 1.49)

- **Doxorubicin**
- **Gemcitabine & Docetaxel**

**Number at risk**
- Doxorubicin: 129, 120, 105, 91, 70, 51, 37, 24, 14, 9
- Gemcitabine & Doc.: 128, 114, 102, 81, 65, 46, 30, 23, 16, 10

**Proportion alive**

- **Weeks since randomisation**
- **Median OS (mths)**: 16.4, 14.5
- **24 week OS**: 86.7%, 82.5%

Presented By Beatrice Seddon at 2015 ASCO Annual Meeting
Study design and objectives

Select eligibility criteria
- LMS or ADI of high or intermediate grade
- ≥2 prior regimens for advanced disease
- Measurable disease (RECIST 1.1)

Randomize

Eribulin
1.4 mg/m² IV
Days 1 and 8 every 21 days
n=228

Dacarbazine*
850, 1000, or 1200 mg/m² IV
Day 1 every 21 days
n=224

Primary endpoint
- Overall survival (OS)

Selected secondary endpoints
- Progression-free survival (PFS)
- Progression-free rate at 12 weeks (PFR_{12wks})
- Safety and tolerability (AE assessment based on CTCAE v4.02)

Selected exploratory endpoints
- Objective response rate (ORR; CR or PR)
- Health-related quality of life

*Starting dose selected by the local investigator at study initiation; \textsuperscript{1}PFR_{12wks} - proportion of patients who were still alive without disease progression at 12 weeks from randomization.

CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary endpoint: OS

- The primary endpoint of OS was met, indicating a 2-month improvement in median OS with eribulin.

<table>
<thead>
<tr>
<th></th>
<th>Eribulin</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>13.5</td>
<td>11.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.768 (0.618, 0.954)</td>
<td></td>
</tr>
<tr>
<td>Stratified p-value</td>
<td>0.0169</td>
<td></td>
</tr>
</tbody>
</table>
### Preplanned OS subgroups analysis (continued)

<table>
<thead>
<tr>
<th>Group/Subgroup</th>
<th>— Events/n —</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADI</td>
<td>52/71</td>
<td>63/72</td>
<td>0.511</td>
<td>0.346</td>
<td>0.753</td>
</tr>
<tr>
<td>LMS</td>
<td>124/157</td>
<td>118/152</td>
<td>0.927</td>
<td>0.714</td>
<td>1.203</td>
</tr>
<tr>
<td><strong>AJCC sarcoma tumor grade score at</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>the date of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>118/150</td>
<td>125/152</td>
<td>0.796</td>
<td>0.607</td>
<td>1.042</td>
</tr>
<tr>
<td>Intermediate</td>
<td>57/77</td>
<td>55/69</td>
<td>0.649</td>
<td>0.439</td>
<td>0.961</td>
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<tr>
<td><strong>Baseline ECOG PS</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>0</td>
<td>76/111</td>
<td>72/90</td>
<td>0.579</td>
<td>0.407</td>
<td>0.823</td>
</tr>
<tr>
<td>1</td>
<td>97/114</td>
<td>97/121</td>
<td>1.107</td>
<td>0.826</td>
<td>1.484</td>
</tr>
<tr>
<td>2</td>
<td>3/3</td>
<td>12/13</td>
<td>3.000</td>
<td>0.251</td>
<td>35.794</td>
</tr>
<tr>
<td><strong>Prior anticancer therapy type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline</td>
<td>174/225</td>
<td>177/219</td>
<td>0.770</td>
<td>0.619</td>
<td>0.958</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>101/129</td>
<td>111/138</td>
<td>0.803</td>
<td>0.600</td>
<td>1.074</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>108/141</td>
<td>115/137</td>
<td>0.701</td>
<td>0.529</td>
<td>0.930</td>
</tr>
<tr>
<td>Taxane</td>
<td>87/109</td>
<td>92/114</td>
<td>0.835</td>
<td>0.604</td>
<td>1.156</td>
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<tr>
<td>Trabectedine</td>
<td>80/108</td>
<td>98/116</td>
<td>0.643</td>
<td>0.469</td>
<td>0.884</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>23/29</td>
<td>19/26</td>
<td>1.067</td>
<td>0.527</td>
<td>2.161</td>
</tr>
<tr>
<td>Other</td>
<td>66/83</td>
<td>70/90</td>
<td>0.902</td>
<td>0.631</td>
<td>1.289</td>
</tr>
</tbody>
</table>

**AJCC, American Joint Committee on Cancer.**

**Favors eribulin** ← 0.25 1 4 16 → **Favors dacarbazine**

---

Presented By Patrick Schoffski at 2015 ASCO Annual Meeting
Secondary endpoint: PFS

<table>
<thead>
<tr>
<th></th>
<th>Eribulin</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.877 (0.710, 1.085)</td>
<td></td>
</tr>
<tr>
<td>Stratified P-value</td>
<td>0.2287</td>
<td></td>
</tr>
</tbody>
</table>

Patients at Risk:

- Eribulin: 228, 79, 41, 27, 16, 9, 5, 2, 1, 0
- Dacarbazine: 224, 63, 27, 14, 6, 4, 2, 1, 1, 0
Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study

- 113 pts with STS (2 previous lines of CT; adria & ifosfamide)
- Gem 1800mg/m² fixed + DTIC 500 mg/m² q2 weeks or DTIC 1200 mg/m² q3 weeks
- Primary endpoint, PFR @ 3 months (40% to 60%)

STS: Bevacizumab plus Temozolomide

**Bevacizumab in Angiosarcoma**

- Agulnik et al Proc ASCO 2009, #10522 n=29
- Bevacizumab 15mg/kg KG, alle 3 Wochen
- Ansprechen: 3/26 PR, 13 SD

**Bevacizumab plus Temozolomide in SFT**

- Park et al Cancer 2011, Epub ahead of print
- Temozolomide 150mg/m² d1-7, 15-21 plus Bevacizumab 5mg/kg KG, d8+22
- Ansprechen: 11/14 PR, 2 SD, PFS: 9.7 Monate
Cediranib for Metastatic Alveolar Soft Part Sarcoma

Shivaani Kummar, Deborah Allen, Anne Monks, Eric C. Polley, Curtis D. Hose, S. Percy Ivy, Ismail B. Turkbey, Scott Lawrence, Robert J. Kinders, Peter Choyke, Richard Simon, Seth M. Steinberg, James H. Doroshow, and Lee Helman
STS: Sunitinib/Cediranib

Sunitinib

• Alveolar Soft Part Sarcoma (5PR 3SD/9; PFS: 17Mos)

• Solitary Fibrous Tumor (4SD/5)

• Desmoplastic Small-Round-Cell Tumor

Cediranib

• Alveolar Soft Part Sarcoma (14PR 3MR/33)

STS: Paclitaxel

Paclitaxel in radiation induced/secondary Angiosarcoma

- Pink et al Proc ASCO 2009, #10578 n=17
- Paclitaxel (175/50-60; 1st or 2nd line)
- Ansprechen: 8 PR (median PFS 6 mo); 1 SD

NB: 3/11 only responded to Anthracycline-based CT
Metastatic Disease

First-line treatment of metastatic or locally advanced unresectable soft tissue sarcomas with conatumumab in combination with doxorubicin or doxorubicin alone: a phase I/II open-label and double-blind study*

Doxorubicin Standard Arm:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>6,4 Monate</td>
</tr>
<tr>
<td>OS</td>
<td>21,6 Monate</td>
</tr>
</tbody>
</table>
## Metastatic Disease

### Table 3  Secondary efficacy outcomes

<table>
<thead>
<tr>
<th>Description</th>
<th>Overall survival (months) [median (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of M1 until death (n=60)</td>
<td>35.8 (28.7–42.9)</td>
</tr>
<tr>
<td>Start of trabectedin until death (n=60)</td>
<td>11.8 (10.7–13)</td>
</tr>
<tr>
<td>Subgroup analysis (start of trabectedin until death)</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma (n=20)</td>
<td>15.6 (0–32.6)</td>
</tr>
<tr>
<td>Liposarcoma (n=7)</td>
<td>15.8 (6.4–25.3)</td>
</tr>
<tr>
<td>Leiomyosarcoma and liposarcoma (n=27)</td>
<td>15.9 (9.4–22.3)</td>
</tr>
<tr>
<td>Synovial sarcoma (n=6)</td>
<td>7.6 (0–15.9)</td>
</tr>
<tr>
<td>Other (MFH like, chondrosarcoma, fibrosarcoma, angiosarcoma, rhabdomyosarcoma, schwannoma, NOS, other; n=27)</td>
<td>11.3 (4.5–18.2)</td>
</tr>
</tbody>
</table>

CI, confidence interval; MFH, malignant fibrous histiocytoma; NOS, not otherwise specified.

Pulmonary metastasectomy for soft tissue sarcoma
Report from a dual institution experience at the Medical University of Vienna


<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up time (mFU)</td>
<td>31.8 months (range 3.7–127.4)</td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td>Months, median (95% confidence interval (CI))</td>
</tr>
<tr>
<td>First diagnosis M1 (pulmonary metastasis)</td>
<td>47.1 (36.2–58.1)</td>
</tr>
<tr>
<td>until death</td>
<td></td>
</tr>
<tr>
<td>Calculated from first PM until death</td>
<td>45.3 (33.3–57.4)</td>
</tr>
<tr>
<td>Calculated from last PM until death</td>
<td>36.8 (29.3–44.3)</td>
</tr>
<tr>
<td>Median relapse-free survival (RFS)</td>
<td>13.4 (3–23.8)</td>
</tr>
<tr>
<td>Five-years OS calculated from first PM</td>
<td>32%</td>
</tr>
</tbody>
</table>
Activity of regorafenib (RE) in leiomyosarcomas (LMS) and other types of soft-tissue sarcomas (OTS): results of a double-blind, randomized placebo (PL) controlled phase II trial

MIR Olivier, BRODOWICZ Thomas, WALLET Jennifer, ITALIANO Antoine, LE CESNE Axel, BLAY Jean-Yves, RYCKEWAERT Thomas, BERTUCCI François, PIPERNO-NEUMANN Sophie, PLONER Ferdinand, TOULMONDE Maud, DOMONT Julien, SAADA-BOUZID Esma, DELCAMBRE Corinne, ISAMBERT Nicolas, CLISANT Stéphanie, TAIEB Sophie, LINDNER Elisabeth, LIEGL-ATZAWAGER Bernadette, PENEL Nicolas

On behalf of the French Sarcoma Group and Sarcoma Platform Austria
Patients and methods (1/2)

- 4 parallel randomized, double-blind, placebo-controlled, multi-center phase II studies in pts with refractory STS
- Regorafenib (160 mg once daily, three weeks on/one week off) plus BSC versus placebo plus BSC
- Stratification: prior exposure to pazopanib and country

**Advanced Liposarcomas**
- N=50
- Regorafenib (RE) + BSC versus Placebo (PBO) + BSC

**Advanced Leiomyosarcomas**
- N=50
- Regorafenib (RE) + BSC versus Placebo (PBO) + BSC

**Advanced Synovial Sarcomas**
- N=25
- Regorafenib (RE) + BSC versus Placebo (PBO) + BSC

**Advanced Other Sarcomas**
- N=50
- Regorafenib (RE) + BSC versus Placebo (PBO) + BSC

Until unacceptable toxicity or progression. Patients receiving PBO who experience disease progression were offered open-label RE.
Median PFS
3.7 months (2.0 – 7.9) vs 1.9 months (1.1 – 2.9) P=0.07
OS - Leiomyosarcoma

P = 0.01

Median not reached

Cross-over in Placebo arm: 20/28
PFS – other sarcomas

Median PFS

3.7 months (1.0 – 8.4) vs 1.0 months (0.9 – 1.9)

P=0.008
OS – other sarcomas

P = 0.06
Median not reached
Cross-over in Placebo arm 17/27
STS: palliative chemotherapy

2015: Standard of care? → YES!

- Anthrazyklin
- Ifosfamide
- Trabectedin
- Gemcitabine
- DTIC
- Docetaxel
- Paclitaxel
STS: palliative „biologic“ therapy

2015: Standard of care? → Yes

- Pazopanib
- Ridaforolimus
- Brivanib
- Cediranib
- Sorafenib
- Sunitinib
- Bevacizumab (plus Temozolamide)
Interuniversitäre Empfehlung

Ein Weichteilsarkom sollte unbedingt interdisziplinär behandelt werden*

*Konsensus Diagnose und Therapie von Weichteilsarkomen

T. Brodowicz, G. Amann, A. Leithner, A. Sztankay, F. Kainberger, W. Eisterer, B. Liegl-Atzwanger, F. Rachbauer, T. Rath, M. Bergmann, P. Funovics, F. Ploner, R. Windhager

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dediff. Liposarcoma</td>
<td>Doxo +/- Ifo</td>
</tr>
<tr>
<td>Myxoid Liposarcoma</td>
<td>Trabectedine +/- Doxo</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Uterine LMS</td>
<td>Gem/Doce; Doxo/Trab</td>
</tr>
<tr>
<td>LMS</td>
<td>Doxo/DTIC; Doxo/Trab</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>DFSP</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Giant Cell Tumor</td>
<td>Denosumab</td>
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</table>
GIST: Current Landscape and Emerging Data
## Morphologie

<table>
<thead>
<tr>
<th>H&amp;E</th>
<th>CD117 (c-kit)</th>
<th>CD34</th>
<th>Smooth muscle actin</th>
<th>S100 protein</th>
<th>Desmin</th>
<th>Pan-keratin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95%</td>
<td>70%</td>
<td>30%</td>
<td>5%</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**Spindelzellig 70%**  
**Gemischtzellig 10%**  
**Epitheloidzellig 10%**

## Risk of Recurrence – Patient Stratification (2006 AFIP criteria) – “Miettinen”

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>% Patients with Disease Recurrence or Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stomach</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 2, ≤ 5 cm</td>
<td>1.9</td>
</tr>
<tr>
<td>&gt; 5, ≤ 10 cm</td>
<td>3.6</td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>12</td>
</tr>
<tr>
<td><strong>Mitotic Count</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 5 per 50 HPFs</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 per 50 HPF</td>
<td></td>
</tr>
<tr>
<td>* Too few cases *</td>
<td></td>
</tr>
</tbody>
</table>

Prognostic factors

The best documented prognostic factors are tumour size, mitotic activity, and anatomical site [1885]. It should be noted that mitotic counts have been defined with a small-field microscope with a total area of 5 mm² per 50 HPFs. Therefore, one should generally count a smaller number of wide fields to reach a comparable total area (usually about 25 fields). In the TNM classification, grading is based on mitotic rate (5 mitoses per 50 HPFs is considered to
Klinik - Relapsrisiko

Joensuu H et al., Lancet Oncol 2012
Mutational Subtype Has Prognostic Importance

Relapse-free survival in 127 patients with completely resected localized GIST

- **KIT exon 11 PM/INS** (n = 32)
- **Other KIT exon 11 deletion** (n = 17)
- **PDGFRA mutation** (n = 8)
- **No mutation** (n = 29)
- **KIT exon 11 DEL557/8** (n = 35)
- **KIT exon 9 mutation** (n = 4)

Mutational analysis should be considered standard practice (with the possible exception of small \(<2\) cm non-rectal GISTs, which are very rarely to be candidates for medical treatment).

ESMO 2014

Suggested Panel:

KIT Exons 8,9,11,13,17
PDGFRA Exons 12,14,18
BRAF
HRAS
NRAS
NF-1
SDHA,B,C,D

Optional
KRAS, p53, Rb1, p16\(^{INK4a}\)
**Recurrence-free Survival (RFS)**

**Median follow-up:** 19.7 months

**Estimated 1-year RFS (95% CI):**

- **Imatinib:** 98% (96-100)
- **Placebo:** 83% (78-88)

**HR = 0.35 (0.22-0.53)**

**P < 0.0001**

**Events experienced:**

- **Imatinib:** 8.0% (30)
- **Placebo:** 20.0% (70)

*All randomized patients were included in the analysis; recurrence-free survival was defined as the time from patient registration to the development of tumor recurrence or death from any cause. Intention-to-treat analyses were done for recurrence-free survival (ie, analyzed patients by randomized group).*

DeMatteo R et al. Lancet 2009;373:1097-104
Recurrence-free Survival

Intention-To-Treat Population

Alive without recurrence (%)

HR 0.60, 95% CI 0.44-0.81

P < .001

3 years of imatinib

52.3%

1 year of imatinib

71.1%

Years since randomisation

Presented By Heikki Joensuu at 2015 ASCO Annual Meeting
Overall Survival

Intention-To-Treat Population

- 91.9% after 3 years of imatinib
- 85.3% after 1 year of imatinib

HR 0.60, 95% CI 0.37-0.97

P = .036

Years since randomisation

Alive (%)
Imatinib in Metastatic GIST

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Months: 0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>Median Time (months)</th>
<th>95% CL LL</th>
<th>95% CL UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR</td>
<td>100</td>
<td>98</td>
<td>87</td>
<td>69</td>
<td>57</td>
<td>44</td>
<td>63</td>
<td>52</td>
<td>N/A</td>
</tr>
<tr>
<td>SD</td>
<td>23</td>
<td>22</td>
<td>18</td>
<td>15</td>
<td>13</td>
<td>10</td>
<td>N/A</td>
<td>34</td>
<td>N/A</td>
</tr>
<tr>
<td>PD</td>
<td>17</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response; LL, lower limit; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; UL, upper limit


→ OS-benefit due to imatinib is comparable in SD + PR
Ad 3: Secondline treatment with Sunitinib: PHIII (n=312)

Demetri et al. *Lancet* 2006;368:1329-38
GIST – Regorafenib In Progressive Disease (GRID): Study Design

- Multicenter, randomized, double-blind, placebo-controlled phase III study
  - Global trial: 17 countries across Europe, North America, and Asia-Pacific
  - Stratification: treatment line (2 vs >2 prior lines), geographical location (Asia vs “Rest of World”)

Regorafenib + best supportive care (BSC)
160 mg once daily
3 weeks on, 1 week off (n=133)

Placebo + BSC
3 weeks on, 1 week off (n=66)

Disease progression
per independent blinded central review

Unblinding
Crossover offered for placebo arm or continued regorafenib for treatment arm

Regorafenib (unblinded) until next progression

Demetri et al. ASCO 2012
GRID Study: Progression-Free Survival (primary endpoint per blinded central review)

Regorafenib significantly improved PFS vs placebo (p<0.0001); primary endpoint met

Demetri et al. ASCO 2012
GRID Study: Overall Survival
(following 85% cross-over of patients on placebo arm)

Because of the crossover design, lack of statistical significance between regorafenib and placebo was not unexpected

Demetri et al. ASCO 2012
OSTEOSARCOMA & EWING Family
DISCUSSION
DISCUSSION