Principles of Systemic Therapy for Sarcomas

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Plan

• Adjuvant/ Neoadjuvant
  – Rhabdomyo, osteo, Ewing, GIST

• ? Role for adjuvant chemotherapy
  – Large, high grade extremity tumours

• Palliative
  – Locally advanced/ metastatic
Sarcoma: Progress

• Limb salvage surgery

• Multi-agent chemotherapy
  – Ewing
  – Osteosarcoma
  – Embryonal rhabdomyosarcoma

• Radiation
  – Extremity and trunk soft tissue sarcomas

• “Targeted therapy”
  – GIST
  – Dermatofibrosarcoma protuberans
  – Inflammatory myofibroblastic tumor
Adult Sarcoma: Issues

• Adjuvant chemotherapy in resected soft tissue sarcoma?

• Soft tissue sarcoma staging

• Limited options for metastatic disease
  – Outcome poor

• Systemic therapy
  – Previously: “One size fits all” approach
Differential Sensitivity

• Sensitive:
  – Synovial sarcoma
  – Myxoid liposarcoma
  – Uterine leiomyosarcoma

• Resistant:
  – Alveolar soft part sarcoma
  – Clear cell sarcoma
  – Low grade fibromyxoid sarcoma
  – Extraskeletal myxoid chondrosarcoma

• NB: Retrospective data
Sarcomas – biological groups

- **COMPLEX**
  - Multiple complex genetic alterations

- **SIMPLE**
  - Specific translocations generating fusion oncogenes
  - Specific kinase mutations (GIST)
  - Gene inactivation (NF1 in MPNST, INI1 in rhabdoid tumours, APC in desmoid)
  - Simple genetic alterations (amplifications – *mdm2+/ cdk4* in well- / dedifferentiated liposarcoma)
Different drugs for different diseases

• Localized
  – Osteosarcoma       MAP
  – Ewing             VDC/ IE
  – Rhabdomyosarcoma  VAC
  – GIST              Imatinib

• Metastatic
  – Dermato fibrosarcoma protuberans Imatinib
  – Giant cell tumor of bone       Denosumab
  – Alveolar soft part sarcoma     Cediranib/ sunitinib
  – Inflammatory myofibroblastic tumor ALK inhibitors
  – PEComas                      mTOR inhibitors
  – Endometrial stromal sarcoma    Aromatase inhibitors
  – Chordoma                     Imatinib/ mTOR Inhibitors
  – Ewing/ Rhabdomyosarcoma       Cyclo/ topotecan
  – Ewing/ Rhabdomyosarcoma       Irinotecan/ temozolamide
  – Solitary fibrous tumor         Anti angiogenic agents
Adjuvant / Neoadjuvant
Systemic Therapy: Benefit

- Embryonal rhabdomyosarcoma
  - VAC (vincristine, actinomycin-D, cyclophosphamide)

- Ewing’s sarcoma
  - Vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide

- Osteosarcoma
  - MAP (Methotrexate, doxorubicin, cisplatin)

- Gastro intestinal stromal tumor (GIST)
  - Imatinib
Adjuvant Chemotherapy

- 1997 Meta-analysis of 14 randomized trials using an anthracycline-based regimen
  - Surgical resection followed by chemotherapy or observation
  - n=1568
  - 80% extremity/ trunk STS
  - Grade: 67% high; 5% low; 28% unknown
  - Size: 18% <5cm; 45% >5cm; 37% unknown
  - 18% subtype not known

## Adjuvant Chemotherapy

1997 Meta-analysis results:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Overall DFS 10 yr</th>
<th>p</th>
<th>Local DFS 10 yr</th>
<th>p</th>
<th>Distant DFS 10 yr</th>
<th>p</th>
<th>Overall Survival 10 yr</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>55%</td>
<td>.0001</td>
<td>81%</td>
<td>.016</td>
<td>70%</td>
<td>.0003</td>
<td>54%</td>
<td>0.12</td>
</tr>
<tr>
<td>Control</td>
<td>45%</td>
<td></td>
<td>75%</td>
<td></td>
<td>60%</td>
<td></td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

Extremity sarcoma subgroup had a 7% absolute improvement in overall survival (p=0.029)

Overall Recurrence-free Survival probability

Years from Randomisation

Events Total

Surgery (± RT) + CT
Surgery (± RT)

1997 Meta-analysis: RFS
Overall survival benefit

HR 0.89; p=0.12
absolute benefit 4%

1997 Meta-analysis: Survival
<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Regimen</th>
<th>F/U</th>
<th>OS</th>
<th>p</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frustaci 2001</td>
<td>104</td>
<td>EPI+IFOS x 5 No chemo</td>
<td>59 mos</td>
<td>66%</td>
<td>0.04</td>
<td>Update @90 mos, ITT analysis OS benefit not significant p=0.07; 7% pts did not get planned chemo</td>
</tr>
<tr>
<td>Petrioli 2002</td>
<td>88</td>
<td>EPI or EPI+IFOS x 4 No chemo</td>
<td>94 mos</td>
<td>72%</td>
<td>0.06</td>
<td>Also randomized pts to groups with or without post operative RT EPI+IFOS better than EPI</td>
</tr>
<tr>
<td>Brodowicz 2000</td>
<td>59</td>
<td>DOXO+DTIC +IFO x 6 No chemo</td>
<td>41 mos</td>
<td>Not reported</td>
<td>0.4</td>
<td>Small trial; low dose ifos; underpowered for survival</td>
</tr>
<tr>
<td>Wolf EORTC 2007</td>
<td>351</td>
<td>DOXO+IFOS x 5 No chemo</td>
<td>NR</td>
<td>64%</td>
<td>---</td>
<td>low dose ifos; low grade small tumors included</td>
</tr>
</tbody>
</table>
Adjuvant / Neoadjuvant Chemotherapy Soft Tissue Sarcomas

- Limited evidence base

- NO clear evidence of survival benefit

- Conflicting opinions

- Long-term complications of chemotherapy
Contrast with:

“A landmark in osteosarcoma care”

- A revolution in treatment with 36 patients randomised!

“………36 patients were randomly allocated to adjuvant chemotherapy or to observation without adjuvant treatment. At two years the actuarial relapse-free survival was 17% in the control group, similar to that found in studies before 1970, and 66% in the adjuvant-chemotherapy group (P<0.001)……… and that it should be given to all such patients”

Link et al N Eng J Med 1986; 314: 1600-6
Locally advanced/ metastatic

• First-line chemotherapy
NCCN Guidelines for Metastatic Soft Tissue Sarcoma

Disseminated metastases or unresectable

Options:
Observation, if asymptomatic.
Chemotherapy
Radiation
Palliative surgery
Best supportive care
Ablation procedures
RFA
Cryotherapy
Embolization procedures

NCCN Practice Guidelines 2013
First-line metastatic disease

• Retrospective data: Improvement OS

• PICASSO trial
  – Doxorubicin + placebo vs
  – Doxorubicin + palifosfamide

• European (EORTC) trial
  – Doxorubicin vs doxorubicin + ifosfamide

• British (GEDDIS) trial
  – Doxorubicin vs gemcitabine + docetaxel
Metastatic soft tissue sarcoma: an analysis of systemic therapy and impact on survival

*OS has improved over last 20 years to ca. 18 months*

**Figure 4: Trends in Survival with Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months Median Survival</th>
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<tbody>
<tr>
<td>T1</td>
<td>12.3</td>
</tr>
<tr>
<td>T2</td>
<td>13.6</td>
</tr>
<tr>
<td>T3</td>
<td>19.2</td>
</tr>
<tr>
<td>T4</td>
<td>23.8</td>
</tr>
</tbody>
</table>

**Figure 2: Systemic Therapy and Survival**

- **Systemic Therapy** median = 19.80 (17.2-22.4)
- **No systemic therapy** median = 12.53 (9.2-15.8)

HR 0.83 (95%CI 0.75-0.91)

Harris S et al ASCO 2015 Abs. 10545
Results of EORTC 62012

Median overall survival:
Doxorubicin: 12.8 months
Doxorubicin + ifosfamide: 14.3 months

Survival at 1 year:
Doxorubicin: 51%
Doxorubicin + ifosfamide: 60%

Median PFS
Doxorubicin: 4.6 months  Doxorubicin + ifosfamide: 7.4 months

Overall response rate:
Doxorubicin: 13.6%
Doxorubicin + ifosfamide: 26.5%

How to use this information?

• No survival benefit from combination therapy
• Single agent doxorubicin is still recommended for palliation and as a reference arm for RCTs

• *But*, combination therapy valuable if:
  – tumour shrinkage is required for symptom control
  – treatment is being given pre-operatively
  – disease is imminently life-threatening
  – treatment is in adjuvant setting

• One could argue that this is a discussion to be had with every patient
GeDDiS Trial Design

**Eligible patients (n=250)**

*Stratification factors:*
- age (≤18 years, >18 years)
- histological subtype:
  - Uterine leiomyosarcoma
  - Synovial sarcoma
  - Pleomorphic
  - Other types of eligible STS

**Control Arm:**
Doxorubicin 75 mg/m² day 1 every 21 days x 6 cycles

**Investigational Arm:**
- Gemcitabine 675 mg/m² days 1, 8
- Docetaxel 75 mg/m² day 8 every 21 days x 6 cycles, with GCSF

1:1 randomisation*

**Disease assessments (RECIST 1.1) at:**
- Baseline
- 12 weeks post randomisation
- 24 weeks post randomisation
- 12 weekly thereafter

**Quality of life assessments at:**
- Baseline
- 12 weeks post randomisation
- 18 weeks post randomisation
- 24 weeks post-randomisation

Seddon B et al. ASCO 2015
GeDDiS: Progression-free survival

Progression-free survival

Unadjusted HR = 1.28
95% CI: (0.98, 1.67)

p = 0.07

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (mths)</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>
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</table>

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Doxorubicin</th>
<th>Gemcitabine &amp; Doc.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>129</td>
<td>128</td>
</tr>
<tr>
<td>0-12</td>
<td>93</td>
<td>82</td>
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<td>13-24</td>
<td>58</td>
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<td>25-36</td>
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<td>37-48</td>
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<td>9</td>
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<td>49-60</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>61-72</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>73-84</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>85-96</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>97-108</td>
<td>3</td>
<td>0</td>
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</table>
GeDDiS: Overall survival

Overall survival

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

p = 0.67

<table>
<thead>
<tr>
<th></th>
<th>Median OS (mths)</th>
<th>24 week OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dox</td>
<td>16.4</td>
<td>86.7%</td>
</tr>
<tr>
<td>GemDoc</td>
<td>14.5</td>
<td>82.5%</td>
</tr>
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</table>

Seddon B et al. ASCO 2015
PICASSO/Palifosfamide – Negative Trial

Overall Survival

Why?
Trial design
Phase II
Inactive drug?
If so, how did we miss signal?
Victim of heterogeneity?

Ryan C et al. ESMO 2013
Evofofamide (TH-302)

- Phase II trial
- 91 patients
  - 6 cycles of doxorubicin + TH-302 (300 mg/m²)
    - Benefit from 6 cycles
    - Maintenance TH-302

- 6-month PFS: 58% (95% CI, 46-68%)

- 3-month PFS: 83% (95% CI, 74-89%)

- Median PFS: 6.5 months (95% CI, 5.8-7.7 months)

Evofofamide (TH-302)

• Median OS: 21.5 months (95%CI, 16-26.2 months)

• 1-year OS: 73% (95% CI, 63% to 81%)
• 2-year OS: 44% (95% CI, 33% to 54%)

• Multivariable analyses, patients with:
  – Leiomyosarcoma
  – Higher serum albumin
  – Locally advanced disease
  – Fewer sites of disease

• Had significantly longer survival

Evofofamide (TH-302)

- Combination common adverse events:
  - Fatigue \( n=64 \) (74.3%)
  - Nausea \( n=68 \) (74.7%)
  - Skin/ mucosal \( n=41 \) (45.1%)
  - Anemia, thrombocytopenia and neutropenia

- TH-302 alone: Less severe/ frequent

- Randomized trial (NCT01440088)

Open-label, Multicenter, Phase 1b/2 Trial

**Phase 2**

- Same entry criteria as Phase 1b
- Stratification:
  - PDGFRα (IHC)
  - Lines of prior treatment
  - ECOG PS
  - Histology (leiomyosarcoma, synovial sarcoma, other)

**Randomize**

- Olaratumab 15 mg/kg D1,8 + Dox 75 mg/m² D1 × 8 cycles (21 days)*
- Dox 75 mg/m² D1 × 8 cycles
- Olaratumab monotherapy until progression
- Optional olaratumab monotherapy after progression

**Primary endpoint:** Progression-free survival (PFS) (predefined statistical significance: 2-sided alpha = 0.2)

**Secondary end points:** Overall survival (OS), objective response rate, PFS at 3 months

**Biomarker:** PDGFRα (IHC) and related ligands

* During Cycles 5-8, patients receiving Dox could receive dexrazoxane, at the investigator’s discretion.

Tap W et al. ASCO 2015
Progression-Free Survival (ITT) (Phase 2)

- **Olaratumab + Dox**
  - Event: 55 (83.3)
  - Censored: 11 (16.7)
  - Median PFS (95% CI): 6.6 (4.1, 8.3)
  - Stratified p-value: 0.0615
  - Hazard ratio (95% CI): 0.670 (0.401, 1.117)

- **Dox**
  - Event: 48 (71.6)
  - Censored: 19 (28.4)
  - Median PFS (95% CI): 4.1 (2.8, 5.4)
  - Hazard ratio (95% CI): 0.672 (0.442, 1.021)

Independent radiology review
- Hazard ratio (95% CI): 0.670 (0.401, 1.117)

Tap W et al. ASCO 2015
Overall Survival (ITT) (Phase 2)

Overall Survival

0.0 0.2 0.4 0.6 0.8 1.0

Olaratumab + Dox
Dox

N
Event 66
Censored 34 (51.5)
32 (48.5)
Median OS (95% CI) 25.0 (20.9, 30.9)
14.7 (9.2, 18.0)
Stratified p-value 0.0004
Hazard ratio (95% CI) 0.441 (0.277, 0.702)

Tap W et al. ASCO 2015
Locally advanced/ metastatic

- $2^{\text{nd}}/3^{\text{rd}}$ line systemic therapy:
  - Ifosfamide
  - Gemcitabine/docetaxel
  - Pazopanib
  - Trabectedin
  - Eribulin
  - DTIC
Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas: Results of Sarcoma Alliance for Research Through Collaboration Study 002


Gem/Doce vs. Gem
ORR: 16% vs 8%
mPFS: 6.2 vs 4 months
mOS: 18 vs. 12 months
Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ovali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel Coens, George D Demetri, Christopher D Fletcher, Angelo Paolo Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group

Why: Right Mix of Biology and Biological Activity?
Study design: PFS v. Placebo
Powered Correctly
Subtypes and Pt Selection
(47% LMS, 10% SS, 47% other)

Lancet 379; 1879-1886: 2012
Randomized Phase 3 Study of Trabectedin vs Dacarbazine (ET743-SAR-3007): Study Design and Status at Interim Analysis

**Stratification:**
- Prior lines chemotherapy (1 vs 2+)
- ECOG PS (0 vs 1)
- Sarcoma subtype (LPS vs LMS)

**Key Criteria:**
- Histologically proven LPS or LMS
- Previous therapy with an anthracycline containing regimen and ≥ 1 additional cytotoxic chemotherapy regimen
- Adequate bone marrow, renal and liver function

**Randomization**
- 2:1

Trabectedin 1.5 mg/m²
24h q3wks
(N=345*)

Dexamethasone 20 mg IV pre-medicaiton

Dacarbazine 1g/m²
20-120 min q3wks
(N=173*)

* Numbers reflect randomizations at time of Interim Analysis

- Conducted at 85 sites in 4 different countries (94% of patients were enrolled at US sites)

**Primary Endpoint**

Overall Survival (OS)

**Secondary Endpoints**

Progression-free survival (PFS), Overall Response Rate (ORR), Duration of Response (DOR), Safety, Patient-Reported Outcomes (PRO)

Demetri G, et al. JCO 2015
Final Analysis of PFS (Investigator Assessed)

HR (95% CI) = 0.55 (0.436, 0.696)
p < 0.0001

PFS events: 329 (63.5% of 518 patients)
mPFS Trabectedin: 4.2 months
mPFS Dacarbazine: 1.5 months

No. Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>Subjects at Risk</th>
</tr>
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<tbody>
<tr>
<td>Dacarbazine</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>345</td>
</tr>
<tr>
<td></td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>71</td>
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<td>0</td>
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</tbody>
</table>

Demetri G, et al. JCO 2015
Final Analysis of Overall Survival

OS events: 381
median OS Trabectedin: 13.7 months
median OS Dacarbazine: 13.1 months

HR (95% CI)=0.927 (0.748, 1.150)
P=0.4920

No. Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Dacarbazine</th>
<th>Trabectedin</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>193 149 119 95 89 64 49 33 24 10 6 2 0</td>
<td>384 341 287 242 207 153 111 61 35 19 9 5 2 1 0</td>
</tr>
</tbody>
</table>

Patel SR, et al. ECCO 18/ESMO 40; 2015, Sep 25 - 29; Vienna, Austria. Abs. 3403
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)\(^1\)

**Randomize**

Eribulin
- 1.4 mg/m\(^2\) IV
- Days 1 and 8 every 21 days
- n=228

Dacarbazine*
- 850, 1000, or 1200 mg/m\(^2\) IV
- Day 1 every 21 days
- n=224

1:1

Primary endpoint
- Overall survival (OS)

Selected Secondary endpoints
- Progression-free survival (PFS)
- Progression-free rate at 12 weeks (PFR\(_{12\text{wks}}\))\(^{†}\)
- Safety and tolerability (AE assessment based on CTCAE v4.02\(^2\))

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; \(^{†}\)PFR\(_{12\text{wks}}\), 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.

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

<table>
<thead>
<tr>
<th>Group/Subgroup</th>
<th>Eribulin</th>
<th>Dacarbazine</th>
<th>HR (95% CI) Eribulin</th>
<th>Dacarbazine</th>
<th>Median (months) Eribulin</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>176/228</td>
<td>181/224</td>
<td>0.768 (0.618, 0.954)</td>
<td>13.5</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>138/178</td>
<td>148/178</td>
<td>0.728 (0.569, 0.931)</td>
<td>13.5</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>38/50</td>
<td>33/46</td>
<td>0.766 (0.445, 1.319)</td>
<td>13.5</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>124/161</td>
<td>110/142</td>
<td>0.896 (0.682, 1.175)</td>
<td>13.2</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52/67</td>
<td>71/82</td>
<td>0.591 (0.402, 0.868)</td>
<td>14.7</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Prior regimens for advanced STS</td>
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<td></td>
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</tr>
<tr>
<td>2</td>
<td>92/121</td>
<td>92/122</td>
<td>0.902 (0.671, 1.214)</td>
<td>13.9</td>
<td>12.3</td>
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<tr>
<td>&gt;2</td>
<td>84/107</td>
<td>89/102</td>
<td>0.640 (0.466, 0.879)</td>
<td>13.2</td>
<td>10.1</td>
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<td>Stratification region*</td>
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<tr>
<td>Region 1</td>
<td>63/87</td>
<td>69/86</td>
<td>0.669 (0.466, 0.958)</td>
<td>15.3</td>
<td>11.5</td>
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<tr>
<td>Region 2</td>
<td>85/106</td>
<td>84/105</td>
<td>0.890 (0.653, 1.214)</td>
<td>13.3</td>
<td>11.5</td>
<td></td>
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<tr>
<td>Region 3</td>
<td>28/35</td>
<td>28/33</td>
<td>0.667 (0.380, 1.171)</td>
<td>11.4</td>
<td>9.7</td>
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</tbody>
</table>

Favors eribulin ← 1 → Favors dacarbazine

*Region 1: USA, Canada; Region 2: Western Europe, Australia, Israel; Region 3: Eastern Europe, Latin America, Asia.
CI, confidence interval; HR, hazard ratio; STS, soft tissue sarcoma.

Schoffski P, et al. ASCO 2015
Preplanned OS subgroups analysis (continued)

<table>
<thead>
<tr>
<th>Group/Subgroup</th>
<th>— Events/n —</th>
<th>HR (95% CI)</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Eribulin</td>
<td>Dacarbazine</td>
<td>Eribulin</td>
</tr>
<tr>
<td>ADI</td>
<td>52/71</td>
<td>63/72</td>
<td>0.511 (0.346, 0.753)</td>
</tr>
<tr>
<td>LMS</td>
<td>124/157</td>
<td>118/152</td>
<td>0.927 (0.714, 1.203)</td>
</tr>
<tr>
<td><strong>AJCC sarcoma tumor grade score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>118/150</td>
<td>125/152</td>
<td>0.796 (0.607, 1.042)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>57/77</td>
<td>55/69</td>
<td>0.649 (0.439, 0.961)</td>
</tr>
<tr>
<td><strong>Baseline ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>76/111</td>
<td>72/90</td>
<td>0.579 (0.407, 0.823)</td>
</tr>
<tr>
<td>1</td>
<td>97/114</td>
<td>97/121</td>
<td>1.107 (0.826, 1.484)</td>
</tr>
<tr>
<td>2</td>
<td>3/3</td>
<td>12/13</td>
<td>3.000 (0.251, 35.794)</td>
</tr>
<tr>
<td><strong>Prior anticancer therapy type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthraclyline</td>
<td>174/225</td>
<td>177/219</td>
<td>0.770 (0.619, 0.958)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>101/129</td>
<td>111/138</td>
<td>0.803 (0.600, 1.074)</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>108/141</td>
<td>115/137</td>
<td>0.701 (0.529, 0.930)</td>
</tr>
<tr>
<td>Taxane</td>
<td>87/109</td>
<td>92/114</td>
<td>0.835 (0.604, 1.156)</td>
</tr>
<tr>
<td>Trabectedine</td>
<td>80/108</td>
<td>98/116</td>
<td>0.643 (0.469, 0.884)</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>23/29</td>
<td>19/26</td>
<td>1.067 (0.527, 2.161)</td>
</tr>
<tr>
<td>Other</td>
<td>66/83</td>
<td>70/90</td>
<td>0.902 (0.631, 1.289)</td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee on Cancer.

Schoffski P, et al. ASCO 2015
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>0.877 (0.710, 1.085)</td>
</tr>
<tr>
<td>Stratified P-value</td>
<td>0.2287</td>
<td>0.2287</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.

Schoffski P, et al. ASCO 2015
Before treatment you have to answer these questions:

1. What is the aim of giving chemotherapy?
   - Palliation – to prevent progression or to relieve specific symptoms?
   - Down-sizing, i.e. maximum possible tumour shrinkage
   - Prevention of recurrence – systemic, local

2. Does chemotherapy work in this subtype?

3. Are there specific agents that might be best?
Systemic therapy: Conclusion

• Localized Disease:
  – Clear benefit in certain subtypes
  – Unclear in majority soft tissue subtypes

• Advanced / metastatic disease:
  – Mainstay of management
  – Increasing number of agents
  – Clinical trial design
    • Biomarkers
    • Rationale
Thank you – any questions?

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