GIST and Soft Tissue Sarcomas: Applying Recent Clinical Advances in Systemic Therapy to the Adjuvant and Metastatic Settings

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• Sarcomas are malignancies derived from cells of mesenchymal origin
• Generally quoted incidence: 16,000 new cases per year in the USA
  • 1% of cancers in adults
  • 15% of pediatric cancers

• True incidence is likely somewhat higher

• Gastrointestinal Stromal Tumor (GIST) alone has an estimated incidence of 5,000 to 15,000 new cases per year in the USA
Two Broad Clinical Groups of Sarcomas

Soft Tissue Sarcomas (90%)

Bone Sarcomas (10%)
“Soft Tissue Sarcoma” is not a single disease
Soft Tissue Sarcomas represent a very heterogeneous set of diseases

- GIST: 18%
- Liposarcomas: 15%
- Unclassifiable: 11%
- Leiomyosarcomas: 16%
- Other very rare subtypes: 5%
- Endometrial stromal sarcoma
- Synovial sarcoma
- Myxofibrosarcoma
- Angiosarcoma
- Rhabdomyosarcoma
- Unclassified sarcoma
- Dermatofibrosarcoma
- Kaposi sarcoma
- Soft-Tissue Ewing sarcoma/PNET

Another Way to Classify Soft Tissue Sarcomas [STS] (before 2016)

STS without any FDA-approved Targeted Rx (80%)

STS with FDA-approved Molecular-targeted Rx (20%)
- GIST (18%)
- DFSP (2%)
2017: New Way to Classify Soft Tissue Sarcomas

Soft Tissue Sarcomas with FDA-approved Molecular-targeted Rx (100%)
Overview of recent changes in therapy for Soft Tissue Sarcomas [STS]

• FDA Approvals of SUBTYPE-SPECIFIC therapy
  • GIST
  • Liposarcomas
  • Leiomyosarcomas and Liposarcomas

• FDA Approval of first-line targeted therapy to be given in combination with doxorubicin for any subtype of STS

• New molecularly-defined diagnostic tools to define patient subtypes with increased precision and to identify candidates for promising molecular-targeted therapeutics
Gastrointestinal Stromal Tumor (GIST)

Most common form of soft tissue sarcoma

- Stomach 60%
  - Eso / Duodenum 5%
- Small intestine 30%
  - Colon / rectum 5%

Mutated Receptor Tyrosine Kinases drive 90% of metastatic GISTs

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Percentage</th>
<th>Primary Mutational Hotspots</th>
<th>Resistance Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT</td>
<td>80%</td>
<td>Exons 9, 11, 12, 13, 17, 18</td>
<td>Exons 13, 17</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>10%</td>
<td>Extracellular Domain</td>
<td>D842V Exons 18, 12</td>
</tr>
</tbody>
</table>

- Malignant precursors of the GI pacemaker interstitial cells of Cajal
- Primary generally in stomach or small intestine
- Metastases in liver, abdomen, elsewhere
- Completely resistant to cytotoxic chemotherapy

Precision Cancer Medicine for GIST: Gene Mutations Matter

**GIST**

- **KIT mutation** (80%)
- **PDGFRA mutation** (10% in met, 25% in gastric primary)
- **SDH mutation or deficiency** (either SDHA, SDHB, or SDHC) (approx. 10%)
- **BRAF or NF1 mutations** (<2%)

**SPECIFIC MUTATIONS impact patient outcomes**

Long Term Survival in Metastatic GIST Patients with Imatinib

From: Correlation of Long-term Results of Imatinib in Advanced Gastrointestinal Stromal Tumors With Next-Generation Sequencing Results - Analysis of Phase 3 SWOG Intergroup Trial S0033

JAMA Oncol. Published online February 09, 2017. doi:10.1001/jamaoncol.2016.6728
Outcomes of metastatic GIST patients vary with type of PDGFRA mutations

Progression-Free Survival

- D842V
- PDGFRA non-D842V

Probability of PFS

$P < 0.0001$

Overall Survival

- D842V
- Non-D842V PDGFRA mutations

Probability of survival

$P < 0.0001$


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Improved Overall Survival with 3 yrs vs. 1 yr of Adjuvant Imatinib in GIST

Hazard ratio 0.45
(95% CI 0.22-0.89)

P = 0.019

Joensuu H, et al

[Graph showing survival rates: 3 Years IM vs 1 Year IM]
Mutation Type Impacts Recurrence-Free Survival with Adjuvant Imatinib

From: Effect of KIT and PDGFRA Mutations on Survival in Patients With Gastrointestinal Stromal Tumors Treated With Adjuvant Imatinib – An Exploratory Analysis of a Randomized Clinical Trial

JAMA Oncol.
Published online March 23, 2017.
NO IMATINIB BENEFIT IN RFS for GIST without KIT or PDGFRA Mutations ("Wild Type" GIST)

% Recurrence-Free and Alive

Time in Months

p=0.6126 at 24 months

Corless et al ASCO 2010
GIST Adjuvant Benefit Correlates with Tumor Genotype

NO IMATINIB BENEFIT IN RFS for GIST with PDGFRA D842V Mutation

% Recurrence-Free and Alive

Time in Months

Imatinib Rx

Imatinib (n=15)

Placebo (n=13)

p=0.9984

Corless et al ASCO 2010
## Understanding Resistance to Targeted Therapy in GIST

<table>
<thead>
<tr>
<th>Primary Resistance</th>
<th>Secondary Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L imatinib</td>
<td>ORR ~60%</td>
</tr>
</tbody>
</table>
New Developments in Overcoming TKI Resistance in GIST

• Several trials of new agents designed to overcome resistance
  • BLU-285
  • DCC-2618
  • PLX-9486
  • Crenolanib

• Combinations galore

• Clinical trial participation is encouraged
Challenges in Managing Metastatic Soft Tissue Sarcomas
Choices of Therapy by Line for Metastatic Soft Tissue Sarcoma Patients

Wagner et al. BMC Cancer (2015) 15:175
DOI 10.1186/s12885-015-1182-4
Does Combination Chemotherapy Improve Outcomes for Metastatic Soft Tissue Sarcomas? (EORTC 62012)

Eligibility:
- High grade STS (2-3)
- Age 18-60
- 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 continous 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

## Objective Response Rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Doxo (n=228)</th>
<th>Doxo-Ifos (n=227)</th>
<th>Total (n=455)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (0.4)</td>
<td>4 (1.8)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>30 (13.2)</td>
<td>56 (24.7)</td>
<td>86 (18.9)</td>
</tr>
<tr>
<td><strong>Overall RESPONSE RATE</strong></td>
<td><strong>13.6</strong></td>
<td><strong>26.5</strong></td>
<td>****</td>
</tr>
<tr>
<td>No Change</td>
<td>105 (46.1)</td>
<td>114 (50.2)</td>
<td>219 (48.1)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>74 (32.5)</td>
<td>30 (13.2)</td>
<td>104 (22.9)</td>
</tr>
<tr>
<td>Early Death - Progression</td>
<td>4 (1.8)</td>
<td>5 (2.2)</td>
<td>9 (2.0)</td>
</tr>
<tr>
<td>Early Death – Other cause</td>
<td>3 (1.3)</td>
<td>2 (0.9)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>11 (4.8)</td>
<td>16 (7.0)</td>
<td>27 (5.9)</td>
</tr>
</tbody>
</table>

** Significant difference between the two arms: p < 0.001

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

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

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

Overall survival

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

No difference statistically

New Approaches to FIRST LINE Therapy of Soft Tissue Sarcomas
Olaratumab – PDGFRA Targeting MoAb

- Fully human monoclonal antibody of immunoglobin G class 1 (IgG1) that selectively binds PDGFRα
- Blocks PDGF binding and PDGF-induced signalling
- Demonstrated activity in both in vitro and in vivo cancer models known to be driven by a PDGF-PDGFRα autocrine loop
- Demonstrated antitumor activity alone or in combination with doxorubicin in human sarcoma xenograft models

Doxorubicin +/- Olaratumab
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 STS)

Randomization

- Olaratumab
  15 mg/kg d 1, and 8 + Dox 75 mg/m² d 1 x 8 cycles (21 d)a
- Olaratumab monotherapy until progression
- Olaratumab monotherapy after progression (optional)

Primary endpoint: PFS (predefined statistical significance: 2-sided alpha = 0.2)
Secondary endpoints: OS, ORR, PFS at 3 mo
Biomarker: PDGFRα (IHC) and related ligands


a During cycles 5-8, patients receiving Dox could receive dexrazoxane, at the investigator’s discretion.
Doxorubicin +/- Olaratumab
Open-Label, Multicenter, Phase 1b/2 Trial

PFS Median 6.6 vs 4.1 months (N.S.)

OS Median 26.5 vs 14.7 months (p = 0.0003)

FDA and European Medicines Agency
Accelerated / Conditional Approvals in November 2016

Histology-Specific Management of Soft Tissue Sarcomas
Trabectedin Molecular Pharmacology

- Binds to DNA minor groove, bending the helix
- Interacts with transcription factors and other DNA binding proteins
- Major activity in myxoid/round cell liposarcoma with TLS/CHOP fusion oncoprotein (DNA binding protein)
Randomized Phase 3 Study of Trabectedin vs Dacarbazine:
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-medication

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

N=518*

*Numbers reflect randomizations at time of Interim Analysis

Conducted at 85 sites in 4 different countries (94% of patients were enrolled at US sites)
Trabectedin vs. Dacarbazine in Leiomyosarcoma and Liposarcoma: 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

HR (95% CI) = 0.55 (0.436, 0.696)

p < 0.0001
PFS Improved for both Leios and Lipos with Trabectedin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>HR 95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>ALL</td>
<td>0.55 (0.44, 0.70)</td>
</tr>
<tr>
<td>Lines of prior chemotherapy</td>
<td>1</td>
<td>0.49 (0.23, 1.04)</td>
</tr>
<tr>
<td></td>
<td>&gt;= 2</td>
<td>0.56 (0.43, 0.71)</td>
</tr>
<tr>
<td>ECOG</td>
<td>0</td>
<td>0.51 (0.36, 0.71)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.60 (0.43, 0.82)</td>
</tr>
<tr>
<td>Histological subtype</td>
<td>LEIOMYSARCOMA</td>
<td>0.55 (0.42, 0.73)</td>
</tr>
<tr>
<td></td>
<td>Nonuterine</td>
<td>0.58 (0.37, 0.92)</td>
</tr>
<tr>
<td></td>
<td>Uterine</td>
<td>0.58 (0.41, 0.81)</td>
</tr>
<tr>
<td></td>
<td>LIPOSARCOMA</td>
<td>0.55 (0.34, 0.87)</td>
</tr>
<tr>
<td></td>
<td>Decifferentiated</td>
<td>0.68 (0.37, 1.25)</td>
</tr>
<tr>
<td></td>
<td>Myxoid +/- round cell</td>
<td>0.41 (0.17, 0.98)</td>
</tr>
<tr>
<td></td>
<td>Pleomorphic</td>
<td>0.33 (0.07, 1.64)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 65</td>
<td>0.60 (0.46, 0.78)</td>
</tr>
<tr>
<td></td>
<td>&gt;= 65</td>
<td>0.40 (0.24, 0.67)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>0.56 (0.43, 0.74)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.53 (0.34, 0.82)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>0.52 (0.39, 0.68)</td>
</tr>
<tr>
<td></td>
<td>Non-White</td>
<td>0.65 (0.40, 1.03)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt; 30</td>
<td>0.56 (0.41, 0.75)</td>
</tr>
<tr>
<td></td>
<td>&gt;= 30</td>
<td>0.54 (0.37, 0.80)</td>
</tr>
</tbody>
</table>
Overall Survival: Final Analysis

- 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>
</thead>
<tbody>
<tr>
<td>19 months</td>
<td>193</td>
<td>384</td>
</tr>
<tr>
<td>24 months</td>
<td>149</td>
<td>341</td>
</tr>
<tr>
<td>36 months</td>
<td>119</td>
<td>287</td>
</tr>
<tr>
<td>45 months</td>
<td>95</td>
<td>242</td>
</tr>
<tr>
<td>54 months</td>
<td>89</td>
<td>207</td>
</tr>
<tr>
<td>63 months</td>
<td>64</td>
<td>153</td>
</tr>
<tr>
<td>72 months</td>
<td>49</td>
<td>111</td>
</tr>
<tr>
<td>81 months</td>
<td>33</td>
<td>61</td>
</tr>
<tr>
<td>90 months</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>99 months</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>108 months</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>117 months</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>126 months</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>135 months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>144 months</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Sensitivity Analysis: Overall Survival
With Censoring at Post-Protocol Therapy

HR (95% CI) = 0.70 (0.47, 1.06)

p = 0.0927

No. Patients at Risk
Dacarbazine 193 90 38 13 8 4 3 1 0
Trabectedin 384 267 168 110 61 35 15 8 7 5 4 2 0
Trabectedin is FDA approved only for leiomyosarcomas and liposarcomas after prior doxorubicin-based chemotherapy.
Eribulin vs. Dacarbazine Phase 3 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 1:1

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
- 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;
†PFR_{12wks}, proportion of patients who were still alive without disease progression at 12 weeks from randomization.

No Difference in 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>0.2287</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
Primary endpoint: OS

- 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

<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>LIPOSARCOMA</td>
<td>Eribulin: 52/71, Dacarb: 63/72</td>
<td>0.511 (0.346, 0.753)</td>
<td>15.6</td>
</tr>
<tr>
<td>LEIOMYOSARCOMA</td>
<td>Eribulin: 124/15, Dacarb: 118/15</td>
<td>0.927 (0.714, 1.203)</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Favors eribulin

Progression-free survival in Liposarcoma Pts

- PFS was improved with eribulin compared with dacarbazine (2.9 vs 1.7; HR: 0.521 [95% CI: 0.346–0.784]; nominal \( p = 0.0015 \)).
Overall survival in Liposarcoma Patients

- OS was longer with eribulin treatment compared with dacarbazine (15.6 vs 8.4 months; HR: 0.511; 95% CI: 0.346–0.753; nominal $p = 0.0006$).

**OS MEDIAN**

15.6 vs. 8.4 months
Eribulin: Histology-specific FDA approval

Eribulin is FDA approved only for liposarcomas after prior doxorubicin-based chemotherapy
Phase III Study Design in chemo-refractory STS
PAZOPANIB vs. PLACEBO

Primary Endpoint
PFS by Independent Review

Secondary Endpoints
• Overall Survival
• Overall Response Rate
• Quality of Life
• Safety

N= 369

Soft Tissue Sarcomas (Excluding LIPOSARCOMA and GIST) after chemo failure
Stratification Factors:
• Performance status
• # of Prior lines of systemic therapy for advanced disease

• NO cross-over of patients on placebo to pazopanib
Pazopanib Significantly Improves Progression-Free Survival in Metastatic Soft Tissue Sarcoma progressing after standard chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>4.60 months (4.12-4.90)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.61 months (1.01-1.86)</td>
</tr>
<tr>
<td>HR</td>
<td>0.35 (0.26-0.48)</td>
</tr>
<tr>
<td>p-value</td>
<td>≤ 0.001</td>
</tr>
</tbody>
</table>

No Significant Impact of Pazopanib on Overall Survival in Metastatic Soft Tissue Sarcoma progressing after standard chemotherapy

Median OS (95% CI)
12.6 months (10.9-14.9)  
10.7 months (9.0-13.1)  
HR=0.87 (95.57% CI: 0.67-1.13)  
p-value=0.256

Other New Molecular Targeted Approaches for Therapy of Metastatic Soft Tissue Sarcomas
INI1 Loss Creates an Oncogenic Dependency on EZH2 in Tumors

**Stem or Progenitor Cells**

*Highly dependent on EZH2 activity*

- SWI/SNF
- INI1
- SMARCA4
- PRC2
- EZH2

**INI1-negative tumors, e.g.:**
- Malignant rhabdoid tumor (MRT)
- Epithelioid sarcoma

**EZH2 knockout reverses oncogenesis induced by INI1 loss**

- Hyper-repression of PRC2 targets
- Potentiation of stem cell programs
- Oncogenic Transformation

Adapted from Wilson 2010

Italiano A et al. ECC presentation, Vienna Sept 2015
CR in Patient with INI1-Negative Malignant Rhabdoid Tumor

Baseline

Week 4

Week 8: CR

Week 20

55 y.o. male
800 mg BID

INI1 IHC

Diagnosis: Surgery + XRT

Tazemetostat: ongoing response week 65+

2013 CR

2014 PD

2015 Week 8: CR

Week 20: pathologic CR
NY-ESO-1: A Target Antigen in Synovial Sarcoma

- **NY-ESO-1 is a Cancer-Testis Antigen** identified by Chen et al (1997)
- **Highly Expressed in synovial sarcomas**
  - 76% of synovial sarcomas express strong staining
- **A T cell receptor (TCR)** recognizing **NY-ESO-1** in the context of **HLA:A0201** was cloned from a patient with cancer, then modified for higher affinity
  
  Zhao, J Immunol, 2007

Modified from slide courtesy of Crystal McKall, NCI (now Stanford)
Efficacy of Genetically Engineered Autologous T-cells with TCR Targeting NY-ESO1: 60% Response Rate

Modified from slide courtesy of Crystal McKall, NCI (now Stanford)
• There are recent therapeutic advances for patients with sarcomas
• First monoclonal antibody, Olaratumab, with doxorubicin may improve survival, but needs phase III data to confirm
• Other agents have evidence of benefit
• New drugs for TKI-resistant GIST subsets in development
• Translational research works to improve the outcomes of patients with defined sarcoma subsets
Thank you for your attention