Best of ASCO 2014
Sarcoma

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Presentation Outline

• Overview progress made in sarcoma

• Highlight 2 trials in metastatic GIST

• Highlight efforts to molecularly characterize sarcoma for personalized therapy

• Other abstracts of interest
Sarcomas

- Rare
- Heterogeneous
- Wide anatomic distribution
  - Challenging to treat

- Multi disciplinary Team
ASCO 2014

• 50 years of Advances in Sarcoma

• Robert Henshaw – Surgical Oncology
• Dian Wang – Radiation Oncology
• Shryeas Patel – Medical Oncology
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
Sarcoma: Issues

• Adjuvant chemotherapy in resected soft tissue sarcoma?

• Limited options for metastatic disease
  – Outcome poor

• Systemic therapy
  – Previously: “One size fits all” approach
Different drugs for different diseases

• Localized
  – Osteosarcoma
  – Ewing
  – Rhabdomyosarcoma
  – GIST

• Metastatic
  – Dermato fibrosarcoma protuberans
  – Giant cell tumor of bone
  – Alveolar soft part sarcoma
  – Inflammatory myofibroblastic tumor
  – PEComas
  – Endometrial stromal sarcoma
  – Chordoma
  – Ewing/ Rhabdomyosarcoma
  – Ewing/ Rhabdomyosarcoma
  – Solitary fibrous tumor

MAP
VDC/ IE
VAC
Imatinib
Denosumab
Cediranib/ sunitinib
ALK inhibitors
mTOR inhibitors
Letrozole
Imatinib / mTOR Inhibitors
Cyclo/ topotecan
Irinotecn / temozolamide
Anti angiogenic agents
<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>135 (18%)</td>
</tr>
<tr>
<td>Pleomorphic/unclassified</td>
<td>117 (16%)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>112 (15%)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>85 (11%)</td>
</tr>
<tr>
<td>Dermatofibrosarcoma</td>
<td>38 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>261 (35%)</td>
</tr>
</tbody>
</table>

Ducimetiere F, Lurkin A et al, Plos One, 6; 2011
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)
S0033 trial: Randomized Phase III trial of Imatinib at 400 vs. 800 mg/d for Advanced KIT-expressing GIST

- Multicenter, randomized, phase III Intergroup study
- FULLY ACCRUED between December 2000 – September 2001
- 746 patients entered, 695 fully eligible

Demetri G et al. ASCO 2014
S0033 Overall Survival by GIST Genotype – 2014 data

Significantly worse OS for KIT exon 9 mutant vs. KIT exon 11 mutant
P = 0.001
vs. No Mutation (WT)
P = 0.047

- **KIT exon 11**
  - NO MUTATION
  - KIT exon 9

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT exon 11</strong></td>
<td>262</td>
<td>201</td>
</tr>
<tr>
<td><strong>NO MUTATION</strong></td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td><strong>KIT exon 9</strong></td>
<td>32</td>
<td>30</td>
</tr>
</tbody>
</table>

Median OS (months)
- KIT exon 11: 66
- KIT exon 9: 40
- NO MUTATION: 38
Prognostic factors significantly associated with Overall Survival in S0033 GIST patients on imatinib

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analyses</th>
<th>Multivariate Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>Age (by decade)</td>
<td>&lt;0.0001</td>
<td>1.23</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.03</td>
<td>1.21</td>
</tr>
<tr>
<td>Performance Status (0-1 vs. 2-3)</td>
<td>&lt;0.0001</td>
<td>2.53</td>
</tr>
<tr>
<td>Maximum Tumor Diameter</td>
<td>&lt;0.0001</td>
<td>1.05</td>
</tr>
<tr>
<td>Albumin (≤3.5 gm/dl vs. &gt;3.5 gm/dl)</td>
<td>&lt;0.0001</td>
<td>0.49</td>
</tr>
</tbody>
</table>
GIST: S0033 Long-term follow-up

• 746 patients with metastatic GIST
  – entered trial

• 180 long-term survivors (≥ 8 years OS)

• Additional therapy data
  – 137 of 180 patients (76%)

• Imatinib administered continuously as only therapy in 67 (49%) of patients

Demetri G et al. ASCO 2014
GIST: S0033 Long-term follow-up

• Standard of care
  – Imatinib 1st line therapy

• Long-term follow-up
  – Continued benefit of imatinib in metastatic GIST

• Trial population had bulky metastatic disease
  – The situation now is different

• Further analysis
  – Comparing patients on long-term imatinib to the others
GIST: Ponatinib Phase II trial

- Ponatinib
- Oral TKI – potent activity against BCR-ABL
- Potent activity against mutated forms of
  - KIT
  - PDGFRA
  - Including mutations that confer resistance to imatinib

Heinrich M et al. ASCO 2014
## GIST: Ponatinib Phase II Trial

<table>
<thead>
<tr>
<th></th>
<th>KIT e11+ve (N=24)</th>
<th>KIT e11-ve (N=11)</th>
<th>Total (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>15 (63)</td>
<td>5 (45)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>2 prior GIST-approved TKIs, n (%)</td>
<td>10 (42)</td>
<td>6 (55)</td>
<td>16 (46)</td>
</tr>
<tr>
<td>3 prior GIST-approved TKIs, n (%)</td>
<td>12 (50)</td>
<td>4 (36)</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Median number of prior cancer regimens [range]*</td>
<td>4 [1 - 10]</td>
<td>5 [2 - 7]</td>
<td>4 [1 - 10]</td>
</tr>
</tbody>
</table>

*Includes investigational TKIs

Heinrich M et al. ASCO 2014
# GIST: Ponatinib Phase II trial

<table>
<thead>
<tr>
<th></th>
<th>KIT e11+ve (N=22&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>KIT e11-ve (N=11)</th>
<th>Total (N=33&lt;sup&gt;a&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBR at 16 weeks</strong></td>
<td>11 (50)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (27)</td>
<td>14 (42)</td>
</tr>
<tr>
<td><strong>ORR&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>2 (6)</td>
</tr>
<tr>
<td><strong>Best Response&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CR</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- PR</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>- SD</td>
<td>14 (64)</td>
<td>6 (55)</td>
<td>20 (61)</td>
</tr>
<tr>
<td>- PD</td>
<td>3 (14)</td>
<td>4 (36)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>- NE</td>
<td>3 (14)</td>
<td>1 (9)</td>
<td>4 (12)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Excludes 2 patients who were discontinued per FDA request

<sup>b</sup>CBR in KIT e11+ve patients with 2 and 3 prior TKIs was 56% and 50%, respectively

<sup>c</sup>Based on patients with at least 1 scan or discontinued without a scan

Heinrich M et al. ASCO 2014
GIST: Ponatinib Phase II
Treatment-emergent AE (≥20%)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Any Grade n (%)</th>
<th>Grade 3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>20 (57)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (49)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (46)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>15 (43)</td>
<td>1 (3)</td>
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<tr>
<td>Headache</td>
<td>15 (43)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (37)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (34)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>11 (31)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>9 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>9 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>7 (20)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>7 (20)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (20)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- No Grade 4 TEAEs
- 1 death (pneumonia) possibly ponatinib-related

Heinrich M et al. ASCO 2014
GIST: Ponatinib Phase II trial

• No standard of care for patients with
  – Imatinib, sunitinib and regorafenib resistant disease

• Phase II: Ponatinib
  – Clinical benefit in heavily pre-treated GIST
  – Well tolerated in this group of patients

• Ponatinib
  – Requires further evaluation in metastatic GIST

• Randomized Phase III trial
Predictive biomarker profiling

- Multiplatform profiling CARIS Life Sciences

- Immunohistochemistry
  - 21 protein panel
  - Standard thresholds specific for each antibody

- Fluorescence/ chromogenic in situ hybridization
  - Detect gene amplifications
  - 7 gene panel

- Next generation DNA sequencing
  - Somatic mutations
  - 45 genes

Movva et al. ASCO 2014
Results

Alveolar soft part sarcoma (ASPS)
Angiosarcoma (11=breast)
Chondrosarcoma
Chordoma
Clear cell sarcoma
Desmoplastic small round cell tumor (DSRCT)
Epithelioid hemangioendothelioma (EHE)
Epithelioid sarcoma
Endometrial stromal sarcoma (ESS)
Ewing sarcoma
Fibromatosis
Fibrosarcoma
Giant cell tumour
Leiomyosarcoma (355=uterine)
Liposarcoma
Malignant fibrous histiocytoma (MFH/UPS)
Malignant peripheral nerve sheath tumor (MPNST)
Osteosarcoma
Perivascular epithelioid cell tumor (PEComa)
Rhabdomyosarcoma
Solitary fibrous tumor (SFT)
Synovial sarcoma
Other

Movva et al. ASCO 2014
Predictive biomarker profiling

- IHC: N=1968
- FISH/ CISH: N=1048
- Sequencing: N=261
- All 3 platforms: N=256

Movva et al. ASCO 2014
Predictive biomarker profiling

- PD-L1 expression
  - 100% of liposarcomas

- EGFR
  - >20% amplification
  - Leiomyosarcoma, MPNST, osteosarcoma, pleomorphic sarcoma

Movva et al. ASCO 2014
Predictive biomarker profiling

• TOPO2A
  – Overexpressed approximately 50% sarcomas
  – Without associated gene amplification

• SPARC overexpressed
  – Angio, chondrosarcoma, osteosarcoma, EHE

• PTEN
  – Loss 80%
  – Without high frequency PTEN mutations

Movva et al. ASCO 2014
Results (Sequencing)

N = 261

- 0 Mutations: 156
- 1 Mutation: 78
- 2 Mutations: 2
- 3 Mutations: 1
- 5 Mutations: 2
## Results (Sequencing)

<table>
<thead>
<tr>
<th>Gene</th>
<th>APC</th>
<th>ATM</th>
<th>BRAF</th>
<th>cKIT</th>
<th>cMET</th>
<th>CTNNB1</th>
<th>IDH1</th>
<th>JAK3</th>
<th>KRAS</th>
<th>NRAS</th>
<th>PIK3CA</th>
<th>PTEN</th>
<th>RB1</th>
<th>STK11</th>
<th>TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Tested</td>
<td>261</td>
<td>258</td>
<td>542</td>
<td>394</td>
<td>260</td>
<td>261</td>
<td>261</td>
<td>260</td>
<td>1473</td>
<td>365</td>
<td>333</td>
<td>249</td>
<td>258</td>
<td>247</td>
<td>254</td>
</tr>
<tr>
<td>WildType</td>
<td>254</td>
<td>252</td>
<td>534</td>
<td>389</td>
<td>254</td>
<td>255</td>
<td>257</td>
<td>257</td>
<td>1454</td>
<td>362</td>
<td>323</td>
<td>241</td>
<td>252</td>
<td>243</td>
<td>197</td>
</tr>
<tr>
<td>Mutated</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>19</td>
<td>3</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>% Mutated</td>
<td>2.7</td>
<td>2.3</td>
<td>1.5</td>
<td>1.3</td>
<td>2.3</td>
<td>2.3</td>
<td>1.5</td>
<td>1.2</td>
<td>1.3</td>
<td>0.8</td>
<td>3.0</td>
<td>3.2</td>
<td>2.3</td>
<td>1.6</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Only 1 mutant found: ABL1, AKT1, AKT1, FGFR2, FLT3, GNA11, KDR, MLH1, SMARCB1, SMO
No mutations found: ALK, CDH1, CSF1R, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, GNAQ, GNAS, HRAS, JAK2, MPL, NOTCH1, NPM1, PDGFRA, PTPN11, SMAD4, VHL
# Results, % mutated by histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>N, NGS</th>
<th>APC</th>
<th>ATM</th>
<th>BRAF</th>
<th>cKIT</th>
<th>cMET</th>
<th>CTNNB1</th>
<th>IDH1</th>
<th>JAK3</th>
<th>KRAS</th>
<th>NRAS</th>
<th>PIK3CA</th>
<th>PTEN</th>
<th>RB1</th>
<th>STK11</th>
<th>TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angio (all)</td>
<td>15</td>
<td>13.3</td>
<td>6.7</td>
<td>10.0</td>
<td>0.0</td>
<td>6.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>5.8</td>
<td>13.3</td>
<td>0.0</td>
<td>6.7</td>
<td>0.0</td>
<td>0.0</td>
<td>26.7</td>
</tr>
<tr>
<td>Chondro</td>
<td>12</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>25.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>16.7</td>
<td>0.0</td>
<td>0.0</td>
<td>25.0</td>
</tr>
<tr>
<td>LMS (all)</td>
<td>44</td>
<td>2.3</td>
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<td>0.0</td>
<td>0.0</td>
<td>4.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.6</td>
<td>7.1</td>
<td>7.0</td>
<td>2.5</td>
<td>41.5</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>30</td>
<td>0.0</td>
<td>3.3</td>
<td>2.1</td>
<td>0.0</td>
<td>3.3</td>
<td>0.0</td>
<td>0.0</td>
<td>3.3</td>
<td>0.0</td>
<td>0.0</td>
<td>5.6</td>
<td>3.6</td>
<td>0.0</td>
<td>3.7</td>
<td>13.3</td>
</tr>
<tr>
<td>UPS</td>
<td>24</td>
<td>0.0</td>
<td>0.0</td>
<td>2.4</td>
<td>3.1</td>
<td>0.0</td>
<td>4.2</td>
<td>0.0</td>
<td>2.7</td>
<td>0.0</td>
<td>3.8</td>
<td>0.0</td>
<td>4.2</td>
<td>0.0</td>
<td>0.0</td>
<td>34.8</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>10</td>
<td>0.0</td>
<td>10.0</td>
<td>0.0</td>
<td>11.8</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

BRAF, KIT, KRAS, NRAS, PIK3CA include Sanger and NGS test results
## Results, % mutated, by histology, rare sarcomas

<table>
<thead>
<tr>
<th>Histology</th>
<th>N, NGS</th>
<th>APC</th>
<th>ATM</th>
<th>BRAF</th>
<th>cKIT</th>
<th>cMET</th>
<th>CTNNB1</th>
<th>IDH1</th>
<th>JAK3</th>
<th>KRAS</th>
<th>NRAS</th>
<th>PIK3CA</th>
<th>PTEN</th>
<th>RB1</th>
<th>STK11</th>
<th>TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>4</td>
<td>NT</td>
<td>NT</td>
<td>0.0</td>
<td>0.0</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>6.1</td>
<td>0.0</td>
<td>0.0</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>7</td>
<td>14.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>85.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>14.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>7</td>
<td>0.0</td>
<td>14.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>6.1</td>
<td>0.0</td>
<td>0.0</td>
<td>6.7</td>
<td>16.7</td>
<td>0.0</td>
<td>28.6</td>
</tr>
<tr>
<td>MPNST</td>
<td>9</td>
<td>0.0</td>
<td>0.0</td>
<td>7.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>3.8</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>3</td>
<td>33.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>20.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rhabdo</td>
<td>9</td>
<td>0.0</td>
<td>0.0</td>
<td>4.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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</tbody>
</table>

BRAF, KIT, KRAS, NRAS, PIK3CA include Sanger and NGS test results
NT=not tested
Predictive Biomarker Profiling

• No standard predictive biomarker available in sarcoma

• Largest series sarcomas tested by CLIA therapeutic platforms

• Assays not specifically developed for sarcoma

• Retrospective study
  – Limited clinical information
    • Tumor site
    • Treatment administered
  – Pathology was not centrally reviewed

• Prospective evaluation
Other Abstracts

• 2 promising studies of anti CSF-1 inhibitors in pigmented villonodular synovitis (PVNS)
  • Tap W et al. ASCO 2014. Abstract 10503
  • Cassier PA et al. ASCO 2014. Abstract 10504

• Phase II trial of lisitinib in “wild type” GIST
  • Von Mehren M et al. ASCO 2014. Abstract 10507

• Randomized Phase II trial of aldoxorubicin versus doxorubicin in soft tissue sarcoma
  • Chawla S et al. ASCO 2014. Abstract 10502
Conclusions

• 50 years of advances in sarcoma
  – Randomized data
  – Despite huge challenges

• Continued benefit of long-term imatinib in GIST

• Ponatinib clinical activity in resistant GIST

• Exploratory biomarker study – prospective evaluation

• Other promising trials – niche studies
  – CSF-1 inhibition in PVNS
  – IGF1-R inhibitor in “wild type” GIST
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