A stratified clinical approach to uterine sarcoma

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Disclosure slide

- Spouse employed by Sanofi-Aventis
- One day advisory board participation (2011)-GSK
Uterine Sarcomas: histologic types

- Heterogenous group of tumors
- Natural history, prognosis, treatment vary by histology and grade
- Very few data regarding the rarest subtypes
# Uterine Sarcomas: prognostic strata

<table>
<thead>
<tr>
<th>Histology</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Stromal Sarcoma Adenosarcoma</td>
<td>Good</td>
</tr>
<tr>
<td>Leiomyosarcoma Carcinosarcoma</td>
<td>Bad</td>
</tr>
<tr>
<td>High grade undifferentiated sarcoma Adenosarcoma with Sarcomatous Overgrowth</td>
<td>Very, very bad</td>
</tr>
</tbody>
</table>
## Uterine Sarcomas

<table>
<thead>
<tr>
<th>Histology</th>
<th>Data-driven management?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Stromal Sarcoma Adenosarcoma</td>
<td>A little</td>
</tr>
<tr>
<td>Leiomyosarcoma Carcinosarcoma</td>
<td>Some more</td>
</tr>
<tr>
<td>High grade undifferentiated sarcoma</td>
<td>Almost none</td>
</tr>
<tr>
<td>Adenosarcoma with Sarcomatous Overgrowth</td>
<td></td>
</tr>
</tbody>
</table>
## Uterine Sarcomas—in 15 minutes

<table>
<thead>
<tr>
<th>Histology</th>
<th>What’s known?</th>
<th>What’s new?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS AS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMS CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGUS AS-SO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ESS: what do we know?

**Histologic Features**
- Low mitotic rate
- Lack of atypia and necrosis
- CD10 positive, h-caldesmon negative
- t(7;17)(p15;q21) present in 58%
- ER/PR positive 70-95%

**Clinical Features**
- Median age 48 years
- 15-30% have metastatic disease at diagnosis
- Lung is most common, others-pelvis, vagina
- Median 5-year survival, all stages 60-98%
- Recurrence risk for stage I disease is 25-35%
AS: what do we know?

- **Histologic Features**
  - Benign epithelial component
  - Sarcomatous portion typically low grade ESS
  - ER/PR positive 90%

- **Clinical Features**
  - 5-year OS 63-84% for stage I disease
  - Recurrence rate 14% if no sarcomatous overgrowth

Arend R, 2010
## ESS: BSO?

<table>
<thead>
<tr>
<th>Study</th>
<th>Recurrence rate with BSO</th>
<th>Recurrence rate without BSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck (Gyn Onc 2011)</td>
<td>8/23 (34.8%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>Amant (Br J Ca, 2007)</td>
<td>3/12 (25%)</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>Pautier (ASCO 2008)</td>
<td>9/42 (22.8%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Kim (Int J Gyn Ca 2008)</td>
<td>5/11 (45%)</td>
<td>5/11 (45%)</td>
</tr>
</tbody>
</table>
ESS: BSO?

- SEER data did not show worse outcomes among patients with BSO v. not
- but only 15% of pts did not have BSO
- endpoint was OS, not PFS

ESS: adjuvant RT?

- SEER data, n=1010

<table>
<thead>
<tr>
<th></th>
<th>Adjuvant WPRT</th>
<th>No adjuvant WPRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year cause-specific survival</td>
<td>80.1%</td>
<td>90.7%</td>
</tr>
<tr>
<td>5-year OS</td>
<td>72.2%</td>
<td>83.2%</td>
</tr>
</tbody>
</table>

ESS: treatment of metastatic disease

- hormone blockade
- Objective responses to:
  - megestrol
  - aromatase inhibitors

Consider resection of isolated mets

ESS: What’s new?

JAZF1/JJAZ1 gene fusion is a genetic hallmark of ESN and ESS

Chiang, Oliva. Human Pathology, 2011
ESS: what is the role of JAZF1/JJAZ1?

- Chimeric RNA
- Gene product affects cell survival and proliferation
- Found in 70-80% of ESS
- Specific for endometrial stromal tumors
- Not present in undifferentiated sarcomas

Chiang, Oliva. Human Pathology, 2011
ESS and AS: what do we need to know?

**ESS**
- Role of adjuvant hormone treatment for early-stage disease
- Role of adjuvant hormone treatment after resection of metastatic disease
- Whether ESS can “transform” into higher grade tumors
- Best hormone strategies for metastatic disease

**AS**
- Can they be treated like ESS?
- Can they “transform”?
- Why do some tumors have sarcomatous overgrowth?
Uterine LMS: what do we know?

**Histologic Features**
- high mitotic rate
- atypia and necrosis
- SMA positive, h-caldesmon positive
- ER/PR positive 7-71%
- Multiple, complex chromosomal abnormalities
- No single specific translocation

**Clinical Features**
- Median age 56 years
- 40-70% risk for recurrence in 2-5 years for uterus-limited disease
- Lung, liver, rarely bone
- Median survival after dx of metastatic disease is 1 year
LMS: adjuvant RT?
EORTC Phase III study: adjuvant pelvic RT v. observation in stage I and II uterine sarcomas

224 pts over 13 years: 103 LMS, 91 CS, 28 ESS

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>Observation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No event</td>
<td>55 (50%)</td>
<td>49 (45%)</td>
<td>104 (47.5%)</td>
</tr>
<tr>
<td>Relapse or death</td>
<td>55 (50%)</td>
<td>60 (55%)</td>
<td>115 (52.5%)</td>
</tr>
</tbody>
</table>

| Survival status       |              |             |          |
| Alive                 | 64 (58%)     | 61 (56%)    | 125 (57%) |
| Dead                  | 46 (42%)     | 48 (44%)    | 94 (43%) |

Adjuvant WPRT did not decrease relapse or increase survival

EORTC Phase III study: adjuvant pelvic RT v. observation in stage I and II uLMS

<table>
<thead>
<tr>
<th>uLMS pts:</th>
<th>Radiotherapy</th>
<th>Observation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
<td>49</td>
<td>99</td>
</tr>
</tbody>
</table>

**Recurrence Rates**

- No local: 22 (44%) vs. 26 (53%)
- Any local: 10 (20%) vs. 12 (24%)
- Any distant: 27 (54%) vs. 16 (33%)

Among LMS pts, RT did not decrease local recurrence or distant metastases

LMS: adjuvant chemo for uterus-limited disease?
SARC 005: Schema

- Gemcitabine 900 mg/m² over 90 minutes days 1, 8
- Docetaxel 75 mg/m² day 8
  q 3 wk x 4 cycles

Repeat CT scan—if disease free, then proceed:

- Doxorubicin 60 mg/m² q 3 w x 4

Repeat CT scan within 6 weeks after doxorubicin

CT c/a/p every 3 mo for 2 y, then every 6 mo

Hensley, ASCO 2010, CTOS 2011 (data updated 3/2012)
## Progression-Free Survival (n=47)

<table>
<thead>
<tr>
<th></th>
<th>% of patients progression-free at 2 years</th>
<th>78.4%</th>
<th>95% CI</th>
<th>67-91%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of patients progression-free at 3 years</td>
<td>57%</td>
<td>95% CI</td>
<td>44-74%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>&gt; 36 months (not yet reached)</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>Not yet reached</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Progression-Free Survival (n=47)

None of the following variables had significant association with PFS:
- age, mitotic rate, ER/PR status, FIGO stage

3 year PFS 57% (95% CI 44-74%)
LMS: treating recurrent disease
**GOG 87L: Gemcitabine-Docetaxel**

<table>
<thead>
<tr>
<th>Best response</th>
<th>39 pts evaluable for response</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2/39</td>
<td>4.8%</td>
</tr>
<tr>
<td>PR</td>
<td>13/39</td>
<td>31%</td>
</tr>
<tr>
<td>SD</td>
<td>11/39</td>
<td>26.2%</td>
</tr>
<tr>
<td>POD</td>
<td>12/39</td>
<td>32%</td>
</tr>
</tbody>
</table>

Clinical Benefit Rate: 62%
19/38 (50%) patients received ≥ 6 cycles

Hensley, Gyn Oncol 2008
### GOG 87L: response duration, PFS

<table>
<thead>
<tr>
<th>Best response</th>
<th>Median duration</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR duration</td>
<td>6+ months</td>
<td>2.1-33.4+ months</td>
</tr>
<tr>
<td>SD</td>
<td>4.3 months</td>
<td>2.1-17.2 months</td>
</tr>
<tr>
<td>PFS</td>
<td>4.4+ months</td>
<td>0.4 – 34.2+ months</td>
</tr>
</tbody>
</table>

% pts Progression-Free at **12 weeks**: 60%
% pts Progression-Free at **24 weeks**: 41%
## Uterine LMS: active agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response Rate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>25%</td>
<td>Omura, 1983</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>17%</td>
<td>Sutton, 1990</td>
</tr>
<tr>
<td>Doxorubicin + Ifos</td>
<td>33%</td>
<td>Sutton, 1996</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>20%</td>
<td>Look, 2004</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>15%</td>
<td>Sutton, 2005</td>
</tr>
<tr>
<td>Gem-Docetaxel</td>
<td>27% (2&lt;sup&gt;nd&lt;/sup&gt; line)</td>
<td>Hensley, 2008</td>
</tr>
<tr>
<td></td>
<td>36% (1&lt;sup&gt;st&lt;/sup&gt; line)</td>
<td>Hensley, 2008</td>
</tr>
</tbody>
</table>
## Response rates in GOG phase II trials in advanced uterine leiomyosarcoma

<table>
<thead>
<tr>
<th>GOG phase II PI, reference</th>
<th>Drug</th>
<th># prior regimens</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMeekin</td>
<td>thalidomide</td>
<td>1</td>
<td>0/29 (0%)</td>
</tr>
<tr>
<td><strong>Look</strong></td>
<td>gemcitabine</td>
<td>0-1</td>
<td>9/42 (20%)</td>
</tr>
<tr>
<td>Sutton</td>
<td>liposomal doxorubicin</td>
<td>0</td>
<td>5/32 (16%)</td>
</tr>
<tr>
<td>Gallup</td>
<td>paclitaxel</td>
<td>0-1</td>
<td>4/48 (8%)</td>
</tr>
<tr>
<td>Sutton</td>
<td>paclitaxel</td>
<td>0</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Thigpen</td>
<td>cisplatin</td>
<td>0</td>
<td>1/33 (3%)</td>
</tr>
<tr>
<td><strong>Sutton</strong></td>
<td>doxorubicin</td>
<td>0</td>
<td>7/28 (25%)</td>
</tr>
<tr>
<td>Sutton</td>
<td>ifosfamide</td>
<td>0</td>
<td>6/35 (17%)</td>
</tr>
<tr>
<td>Thigpen</td>
<td>etoposide IV</td>
<td>0</td>
<td>0/28 (0%)</td>
</tr>
<tr>
<td>Rose</td>
<td>etoposide PO</td>
<td>1</td>
<td>2/29 (7%)</td>
</tr>
<tr>
<td>Miller</td>
<td>topotecan</td>
<td>0</td>
<td>4/36 (11%)</td>
</tr>
<tr>
<td>Smith</td>
<td>trimetrexate</td>
<td>0-1</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td><strong>Hensley</strong></td>
<td>gemcitabine + docetaxel</td>
<td>0</td>
<td>15/42 (36%)</td>
</tr>
</tbody>
</table>
GOG 231C: sunitinib, 1-2 prior uterine LMS

Sunitinib
50 mg orally
Treatment daily x 4 weeks
followed by
Two week rest
One cycle = 6 weeks

Until progression of disease or adverse effects prohibit further therapy.

Closed after first stage accrual goal of 19 patients in 7 months
ORR 8%; PFS at 6 months = 17%

Hensley, ML, Gyn Oncol 2009
Trabectedin in STS

- Response rate 8% (3/36) in previously treated (2 liposarcomas, 1 LMS)
- 6/35 (17%) response first-line (3 lipo, 1 LMS, 1 fibrosarc, 1 synovial)
- Objective response STS 5.6% with 24h infusion
- Objective response 17% among 62 uLMS, median PFS 2.5 months
- GOG phase II ut LMS, 0 prior: RR 10%
  median PFS 5.8 months

Garcia-Carbonero, JCO 2004 and 2005
Keohane, ASCO 2005
Garcia del Muro, CTOS 2001
Demetri, J Clin Oncol 2009
Judson, ASCO 2010
Monk, Hensley, Gyn Onc 2011
Temozolomide in STS and LMS

- PRs in 2/6 patients and 2/12 in retrospective uLMS reports
- 2/18 in prospective STS study, both in LMS

Ferris, Int J Gyn Oncol 2010
Anderson, Gyn Oncol 2005
Talbot, 2003
Aromatase Inhibitors in LMS

O’Cearbhaill, Hensley Gyn Onc, 2010

PFS longer among pts with ER/PR + LMS, but not necessarily attributable to the aromatase inhibitor
After fixed dose-rate gem-docetaxel
LMS: what’s new?

- Phase III trial for metastatic disease
- Nomogram to predict overall survival
- International collaboration--phase III trial of adjuvant chemotherapy v. observation
GOG 0250: phase III gem-doce + placebo v. bevacizumab

Regimen I:
- Gemcitabine 900 mg/m² IV days 1 and 8
- Docetaxel 75 mg/m² IV day 8
- Placebo (for Bevacizumab) Day 1
- Every 3 weeks

Regimen II:
- Gemcitabine 900 mg/m² IV days 1 and 8
- Docetaxel 75 mg/m² IV day 8
- Bevacizumab 15 mg/kg IV day 1
- Every 3 weeks

* All patients will receive GCSF on day 9 of each cycle

* Until disease progression or adverse effects prohibit further therapy

- Uterine LMS
- Measurable disease
- No prior cytotoxic therapy

* All patients will receive GCSF
**Uterine LMS**

**Nomogram to predict 5 year OS**

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td>40</td>
<td>45</td>
<td>50</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td>Tumor Size (cm)</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Grade</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical Involvement</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loco-regional Metastases</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Points</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year Survival</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

**C-index = 0.683**

Zivanovic, Hensley. *Cancer* 2012
GOG 0277: phase III adjuvant gem-doce, followed by dox v. observation for uterus-limited LMS

A collaborative study from the International Rare Cancers Initiative (NCI-EORTC-CR-UK)-Gynecologic Sarcomas

M. L. Hensley, M.D. Principal Investigator
Isabelle Ray-Coquard, M.D., Ph.D. (PI, EORTC)
Helen Hatcher, M.D. (PI, NCRN)
Uterine Carcinosarcoma: what’s known

- **Histologic Features**
  - Bi-differentiated tumor from single malignant clone
  - LN dissection associated with improved outcomes
  - Sarcomatous component may be homologous or heterologous

- **Clinical Features**
  - 50% recurrence rate in uterus limited disease
  - Occult LN mets more common than in LMS
  - 2008 FIGO staging uses Endometrial Cancer staging system for uterine CS
CS: what drugs for advanced disease?
GOG 161: Ifos v. Ifos-Paclitaxel for CS

- 179 evaluable patients, measurable disease
- About 1/3 with prior pelvic RT
- Superior RR, PFS, and OS with Ifos-Pac

<table>
<thead>
<tr>
<th></th>
<th>Ifos</th>
<th>Ifos-Pac</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10%</td>
<td>22%</td>
</tr>
<tr>
<td>PR</td>
<td>19%</td>
<td>24%</td>
</tr>
<tr>
<td>G3/4 ANC</td>
<td>47%</td>
<td>38%</td>
</tr>
<tr>
<td>G1-4 neuro</td>
<td>8%</td>
<td>30%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>3.6 months</td>
<td>5.8 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>8.4 months</td>
<td>13.5 months</td>
</tr>
</tbody>
</table>

Homesley, J Clin Oncol 2007
GOG 232B: Paclitaxel-Carboplatin for CS

- 46 evaluable patients
- No prior chemotherapy
- All with measurable disease
- Objective RR = 54%

Powell, J Clin Oncol 2010
Uterine CS: adjuvant therapy?

- GOG phase III trial
- 206 evaluable patients
- 44% were stage I or II
- Benefit for stage I and II
- Vaginal-pelvic failures same in both arms
  WART 17% v. CIM 24%

<table>
<thead>
<tr>
<th></th>
<th>WART</th>
<th>Ifos-Cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse at 5 years</td>
<td>58%</td>
<td>52%</td>
</tr>
<tr>
<td>OS at 5 years</td>
<td>34%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Wolfson, Gyn Oncol 2007
Overall Survival: WART v. Ifos-cis

Wolfson, Gyn Oncol 2007
CS: what’s new?

- Phase III to determine best doublet
- Phase II trials to find active agents, targeted and otherwise
GOG 0261: stage I-IV CS

- Randomize, stratified for stage

Paclitaxel-Carboplatin every 3 weeks for 8 cycles

Ifosfamide daily x 3 d + Paclitaxel day 1 + GCSF day 4 – 10 or Neulasta every 3 weeks for 8 cycles

- Primary endpoint: overall survival

Powell, Hensley, Principal Investigators
GOG 230D: pazopanib

- Phase II with primary endpoint either objective response or 6-month PFS
- On accrual hold pending assessment of responses in first-stage

Campos, Principal Investigator
LMS and CS: what (else) do we need to know?

• **LMS**
  - Does “low grade” LMS exist and can it be reliably defined at diagnosis?
  - Is there a role of hormone therapy in advanced disease?
  - Role of targeted agents, i.e. pazopanib
  - Is there a role for vaccine or immunotherapy in minimal residual disease (post-metastatectomy)

• **CS**
  - Role of RT in adjuvant therapy—can it add to chemotherapy?
  - Role of targeted therapies
  - Molecular characteristics—are these bad “carcinomas” or “sarcomas”?- likely not all CS are alike
High Grade Undifferentiated Sarcoma: what’s known

- **Histologic Features**
  - Lack tissue-specific differentiation
  - High mitotic rate, significant cellular atypia
  - Areas of necrosis and hemorrhage
  - No endometrial stromal features
  - Nearly always ER/PR negative

- **Clinical Features**
  - Median age 58 y
  - Occult LN metastases are common
  - May have rapid POD post resection
HGUS: what’s known?

- No prospective trials
- Retrospective study at MSKCC: 22 patients in 10 years

Tanner, Hensley, *unpublished*, 2012
HGUS: what’s known?

• 14 patients received chemotherapy for measurable disease
• Gem-doce objective response: 6/8 pts
• Dox +/- ifos objective response: 3/6 pts

Tanner, Hensley, *unpublished*, 2012
HGUS: what’s known?

- For all 22 patients:
  - PFS: 7.3 months
  - OS: 11.8 months

Tanner, Hensley, *unpublished*, 2012
HGUS: what’s new?
High Grade Undifferentiated Sarcoma: what’s new?

- Newly described molecular marker:
  - $t\ (10;17)$ translocation
  - YWHAE + FAM22A or FAM22B
    - alters cell cycle control
    - likely to have diagnostic utility
    - potential for clinical treatment if the gene product could be targeted

Lee et al, PNAS, Jan 5, 2012
Low v. High Grade Uterine Sarcomas

Stage and Survival: ESS v. HGUS

C

D

Fig. 2: Comparison of disease status and stage distribution between JAZF1 ESS (N=17) and YWHAE ESS (N=11) cases.

Fig. 3: Comparison of disease status between JAZF1 ESS (n=17) and YWHAE ESS (n=10) cases.

HGUS and AS-SO: what do we need to know?

**HGUS**
- Active agents for advanced disease
- Role adjuvant therapy
- Can targets be identified? Can they be targeted?
- Molecular basis of *de novo* drug resistance
- Need international collaboration

**AS-SO**
- Can these be treated like the SO portion?
- Role adjuvant therapy
- Active agents for advanced disease
A randomized phase II study evaluating the role of maintenance therapy with pazopanib in High Grade Uterine Sarcoma (HGUS) after stabilization or response to chemotherapy following surgery or in metastatic first line treatment

PI: I. Ray-Coquard

Registration

1:1 Randomization
non-PD within 12 wks after CT

HGUS adjuvant setting

HGUS 1st line metastatic disease

Anthracycline based CT (mono or combination) 4-6 cycles

Pazopanib maintenance 1-2 year or PD

Observation or placebo 1-2 year or PD

1° endpoint: PFS at 4 months from randomization

→ 80%

2 x 27 patients = 54 randomized ≈ 78 registered

2° endpoints: PFS, OS, RR and duration of response (RECIST 1.1), QoL (QLQ-C30 + QLQ-EN24), Toxicity (CTCAE 4.0)
For all uterine sarcomas: Prognosis and treatment vary greatly by histology—REVIEW the PATH

Low grade ESS are hormone-sensitive, indolent tumors—probably no role for cytotoxics, use hormone blockade
Summary: LMS

- Adjuvant WPRT for uterus-limited LMS did not improve outcomes in a phase III trial
- An international phase III trial of adjuvant chemotherapy v. observation for LMS will open in 2012
- Active agents for metastatic LMS: gemcitabine, doxorubicin, ifosfamide, gem/docetaxel
- Phase II studies of aflibercept, sorafenib, sunitinib negative for ORR; role of bevacizumab to be determined in phase III trial
Adjuvant chemotherapy was better than RT for stage I-IV uterine CS

Best doublet therapy (chose 2 out of 3: ifosfamide, paclitaxel, platinum) to be determined

Active agents for advanced disease include ifosfamide, cisplatin, carboplatin, paclitaxel

Role of targeted therapies under investigation (pazopanib, TRC105, etc)
Summary: HGUS

- need prospective study—recommend enrollment in STS clinical trials
- International Collaboration needed to answer the histology-specific questions in uterine sarcoma

Thank you!