Molecular/genetic stratification for first line treatment of recurrent or metastatic endometrial cancer: Are we ready?

Karen Lu, MD
MD Anderson/G-GOC
GCIG Endometrial cancer session
June 1, 2017
• “It always seems impossible until its done”

Nelson Mandela
Living in the era of personalized cancer therapies

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
Current state: First line treatment of metastatic endometrial cancer

- Endometrial cancer is common, but metastatic and recurrent disease is less common
- Still no agreement to separate out non-endometrioid histology
- GOG 209: establishment of carboplatin and paclitaxel as standard of care for first line treatment
Outline

• Lessons learned from other cancers
• Historical context
• Molecular stratification in metastatic setting
• A possible way forward
Molecular stratification in first line recurrent/metastatic disease

• Lung
  • PDL-1 high expresser (>50%): pembrolizumab for first line metastatic disease (FDA approval Oct 2016)
  • EGFR mutation: first line EGFR tyrosine kinase inhibitor
  • ALK or ROS1 gene rearrangement: first line ALK tyrosine kinase inhibitor

• Colon
  • KRAS/NRAS wild type: cytotoxic regimen plus cetuximab/panitumumab (anti-EGFR)
Molecular stratification in first line recurrent/metastatic disease

Breast

• ER/PR +/HER2 - : first line for recurrent/metastatic disease is endocrine therapy
  • Aromatase inhibitors with CDK4,6 inhibitor (palbociclib, ribociclib)
  • Only time endocrine therapy not recommended is in patients with high tumor burden, symptomatic
• ER/PR +/HER2 +: Addition of pertuzumab plus trastuzumab to aromatase inhibitor
• ER/PR -/HER2 +: Pertuzumab plus trastuzumab in combination with taxane
• “Triple negative”: cytotoxic chemotherapy
Requisite for molecular stratification for first line metastatic disease

• Robust biomarkers that allow stratification

• Matched effective treatments

• Need for **predictive** biomarkers, not **prognostic** biomarkers
Outline

• Lessons learned from other cancers
• Historical context
• Molecular stratification in metastatic setting
• A possible way forward
Historical context: treatment of metastatic/recurrent disease

• 1950’s: first report of use of progestins for metastatic endometrial cancer
• 1980’s: Hormonal treatment
• 1990’s: Emergence of cytotoxic chemotherapy
• 2000’s: Definition of PTEN/PI3K defects; early targeted therapies
• 2010’s: TCGA and expansion of targeted therapies
Era of hormonal trials

### Table 1. Selected Trials of Hormonal Therapy for Recurrent/Metastatic Endometrial Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>RR (%)</th>
<th>Median OS (months)</th>
<th>Prior Chemotherapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestins, SERMs, and combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone acetate 200 mg per day</td>
<td>Thigpen et al</td>
<td>145</td>
<td>25</td>
<td>11.1</td>
<td>No</td>
<td>One arm of a randomized study</td>
</tr>
<tr>
<td>Tamoxifen 40 mg per day</td>
<td>Thigpen et al</td>
<td>68</td>
<td>10</td>
<td>8.8</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone acetate 100 mg twice per day every other week plus tamoxifen 20 mg twice per day</td>
<td>Whitney et al</td>
<td>61</td>
<td>33</td>
<td>13</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate 80 mg twice per day for 3 weeks alternating with tamoxifen 20 mg per day for 3 weeks</td>
<td>Florica et al</td>
<td>61</td>
<td>27</td>
<td>14</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Megestrol 80 mg twice per day concomitant with tamoxifen 10 mg twice per day</td>
<td>Panici et al</td>
<td>42</td>
<td>19</td>
<td>8.6</td>
<td>No</td>
<td>One arm of small randomized study; no superiority to megestrol alone</td>
</tr>
<tr>
<td>Arzoxifene 20 mg per day*</td>
<td>McMeekin et al</td>
<td>29</td>
<td>31</td>
<td>13.9</td>
<td>Adjuvant only (in 3 patients)</td>
<td>Required: ER-positive or PgR-positive or grade 1 or 2</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leuprolide 7.5 mg every 28 days</td>
<td>Covens et al</td>
<td>25</td>
<td>0</td>
<td>6</td>
<td>Yes (in 2 patients)</td>
<td></td>
</tr>
<tr>
<td>Triptorelin 3.75 mg every 28 days</td>
<td>Lhomme et al</td>
<td>28</td>
<td>8.7</td>
<td>7.2</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Goserelin 3.6 mg every 4 weeks</td>
<td>Astudillo</td>
<td>40</td>
<td>11</td>
<td>7.3</td>
<td>Yes (in 1 patient)</td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrazole 1 mg per day</td>
<td>Rose et al</td>
<td>23</td>
<td>0</td>
<td>6</td>
<td>No</td>
<td>One prior hormone regimen permitted</td>
</tr>
<tr>
<td>Letrozole 2.5 mg per day</td>
<td>Me et al</td>
<td>28</td>
<td>0.4</td>
<td>6.7</td>
<td>Adjuvant only</td>
<td></td>
</tr>
<tr>
<td>ER antagonists/downregulator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulvestrant 250 mg IM every 4 weeks</td>
<td>Covens et al</td>
<td>22</td>
<td>ER-negative; 31</td>
<td>0; 16</td>
<td>Adjuvant only (32%)</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant 250 mg IM every 4 weeks</td>
<td>Emons et al</td>
<td>35</td>
<td>14.4</td>
<td>13.2</td>
<td>Yes (40%)</td>
<td>80% ER-positive or PgR-positive</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; IM, intramuscularly; OS, overall survival; PgR, progesterone receptor; RR, response rate; SERM, selective estrogen-receptor modulator.

*Arzoxifene is a selective estrogen receptor modulator whose development was discontinued.
Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study

James V. Fiorica, a, *, Virginia L. Brunetto, b Parviz Hanjani, c Samuel S. Lentz, d, 1 Robert Mannel, e and Willie Andersen f

a Division of Gynecologic Oncology, H. Lee Moffitt Cancer Center, University of South Florida, Tampa, FL 33612, USA
b Gynecologic Oncology Group, Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY 14263, USA
c Section of Gynecologic Oncology, Abington Memorial Hospital, Abington, PA 19001, USA
d Section on Gynecologic Oncology, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA
e Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190, USA
f Department of Obstetrics and Gynecology, University of Virginia Medical School, Charlottesville, VA 22908, USA

- Grade 1 38% response rate, overall 27% response rate
- Previously untreated
- Remains standard for GOG hormonal treatment

This trial could provide the basis for a future randomized trial of hormonal therapy versus cytotoxic chemotherapy in patients with metastatic endometrial cancer.
Outline

• Lessons learned from other cancers
• Historical context
• Molecular stratification in metastatic setting
• A possible way forward
TCGA endometrial stratification

• Group 1 – POLE, ultramutated
• Group 2 – MSI, frequent MLH-1 hypermethylation, hypermutated,
• Group 3 – low copy number alterations, ER/PR positive
• Group 4 – serous-like, copy number high, frequent tp53, serous and grade 3 endometrioid,
Requisite for molecular stratification for first line metastatic disease

• Robust biomarkers that allow stratification

• Matched effective treatments

• Need for **predictive** biomarkers, not **prognostic** biomarkers
POLE

• Ultramutated
• TCGA excellent prognosis even in high grade/high stage: good response vs. less aggressiveness
• Elevated expression of several immune checkpoint genes
• Candidates for immune checkpoint inhibitor therapy?

Bakhsh et al. Histopathology 2015
Mehnert et al. JCI 2016
MSI

• 30% of newly diagnosed endometrial cancers; ? Percent of recurrent, metastatic disease
• Most are due to MLH1 hypermethylation; fewer due to Lynch syndrome
• FDA approved for MSI-H tumors “after prior treatment and no satisfactory alternative treatment options”
• Proposed pembro trial in MSI-H endometrial cancer
• Possible movement to front line study
PDL-1 positive

- KEYNOTE-028: Pembro in PDL-1 positive EC
- 24 pts
- PDL-1 IHC at least 1%
- 13% partial response; 13% stable disease
- Only 1 pt MSI-H: progressive disease

Ott et al. JCO 2017
Hormone receptor positive

- Better options for hormonal treatments
- Rad/let – Slomovitz JCO 2015 Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma
  - CBR 40%, RR 32% (11/35 pts, with 9 CRs, 2 PRs)
- Rad/let/met – Soliman, ASCO abstract 2016 –
  - CBR 67% (32/48 pts, with 14 PR 18 SD)
Hormone receptor positive: on-going randomized trials

• ENGOT: palbociclib + letrozole vs. letrozole (ER+)

• VICTORIA trial (France): dual mTORC1/2 + anastrazole vs. anastrazole (ER+)

• GOG partners: everolimus + letrozole vs. megace/tamoxifen
HRD in endometrial cancer: PARPi candidates?

- Hansen et al. (abst SGO 2015) – assessed BRCA1 and 2 mutation status for 335 endometrioid endometrial cancer patients
  - 52/225 (16%) had somatic mutations in either BRCA 1 or 2
- Hansen et al. (abst ASCO 2016) – assessed HRD score in endometrioid endometrial cancer patients
  - High HRD score
  - For mice injected with endometrial cancer cell lines, high HRD score cell line had increased response to olaparib treatment measured by tumor growth

- UPSC?

- Window trial pre-surgery (POLEN – Spain)
- Niraparib (Canada)
- Olaparib + mToRC1/2 (MDACC); Olaparib + AKTi (MDACC)
- Olaparib + MEKi for K-ras mutant EC (MDACC)
HER2

- GOG181B – Phase II of trastuzumab in women with advanced or recurrent HER2/neu+ endometrial cancer
  - Limited by heterogeneity of histologic subtypes
  - 15/33 treated did not demonstrate HER-2 amplification by FISH analysis
  - Underpowered for single agent activity in UPSC
- NCT01367002 Evaluation of Carboplatin/Paclitaxel with and without trastuzumab in Uterine Serous Cancer – randomized phase II study

Fleming et al. Gyn Oncology 2010
Santin Gyn Oncology 2010
### TCGA subtypes: predictive biomarkers

<table>
<thead>
<tr>
<th>TCGA subtype</th>
<th>Molecular characteristic/target</th>
<th>Potential Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>POLE</td>
<td>Checkpoint blockade</td>
</tr>
<tr>
<td>Group 2</td>
<td>MSI</td>
<td>Checkpoint blockade</td>
</tr>
<tr>
<td>Group 3</td>
<td>ER+/PR+</td>
<td>Aromatase inhibitors; everolimus +AI; CDK4,6 + Al</td>
</tr>
<tr>
<td>Group 2,3</td>
<td>PTEN/AKT/PIK3CA mutation</td>
<td>Temsirolimus, everolimus, AKTi, mTORC1/2i</td>
</tr>
<tr>
<td>Group 3 &amp; 4</td>
<td>HER-2/neu</td>
<td>Trastuzumab, pertuzumab</td>
</tr>
<tr>
<td>Group 4</td>
<td>HRD</td>
<td>PARP inhibitors</td>
</tr>
</tbody>
</table>
Outline

• Lessons learned from other cancers
• Historical context
• Molecular stratification in metastatic setting
• A possible way forward
Proposal 1

• Continue to advance ER/PR pos treatment as a separate cue:
  • everolimus plus AI
  • CDK4/6 plus AI

• Unlikely to ever have randomized trial of hormone vs. chemo
Feasibility of front line hormonal trial

• GOG 209 C/T vs TAP accrual
  • Activated 8/25/2003, closed 4/20/2009
  • Total of 1381 patients were accrued, with 76 found to be ineligible/inevaluable leaving 1305 evaluable patients on trial

GOG #209

Steroid Receptor Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Regimen I</th>
<th>Regimen II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Estrogen Receptor</td>
<td>Pending</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>175</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>145</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>Strongly Positive</td>
<td>309</td>
<td>332</td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Progesterone Receptor</td>
<td>Pending</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>234</td>
<td>205</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>140</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td>Strongly Positive</td>
<td>255</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>11</td>
<td>20</td>
</tr>
</tbody>
</table>
Proposal 2

- Await Phase 2 results or consider window of opportunity studies
  - MSI-H: pembrolizumab/checkpoint blockade
  - Group 4 tumors: HRD based treatment
- Plan now for a randomized study of chemo vs. biomarker-driven approach for non-hormonal recurrent EC patients
Are we ready?

• “It’s kind of fun to do the impossible”

Walt Disney