The Challenge of Rare Subsets of Rare Cancers: A focus on \textit{ESR1} mutations in gynecologic malignancies

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Estrogen Receptor – a ligand-dependent regulator of transcription

AI: Aromatase inhibitor
SERD: selective estrogen receptor disruptor
SERM: selective estrogen receptor modulator
Estrogen Receptor (ESR1) Activating Mutations are Associated with Resistance to Endocrine Therapy

Rare Gynecologic Cancers

OVARY
- High-grade serous
- Endometrioid
- Low-grade serous
- Clear cell
- Mucinous
- Carcinosarcoma
- Adenosarcoma
- Germ Cell Tumors
- Sex Cord-Stromal Tumors (Granulosa Cell Tumors)
- Small Cell Carcinoma
- Carcinoid
- Wolffian Tumors

UTERUS
- Endometrioid
- High-grade serous
- Clear cell
- Carcinosarcoma
- Leiomyosarcoma
- Low-grade endometrial stromal sarcomas
- High-grade endometrial stromal sarcomas
- Undifferentiated uterine sarcomas

CERVIX
- Squamous cell carcinoma
- Adenocarcinoma
- Adenosquamous carcinoma
- Small cell carcinoma

VAGINA/VULVA
- Squamous cell carcinoma
Endocrine Therapy is Associated with Modest Response

Advanced Endometrial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>OBR (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethier et al 2017 Gyn Onc</td>
<td>Hormonal agents</td>
<td>21.6</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>ER+ + PR+</td>
<td>32.5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ER+</td>
<td>26.6</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>PR+</td>
<td>35.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Ethier et al 2017 Gyn Onc

Recurrent Low-Grade Serous Ovarian Cancer

9% response rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>OBR (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gershenson et al 2012 Gyn Onc</td>
<td>Everolimus + letrozole</td>
<td>32</td>
<td>3.8</td>
</tr>
<tr>
<td>Oza et al 2018 SGO Annual Mtg</td>
<td>Erlotinib</td>
<td>12.5</td>
<td>-</td>
</tr>
<tr>
<td>Oza et al 2018 SGO Annual Mtg</td>
<td>Temsirolimus</td>
<td>13.7</td>
<td>-</td>
</tr>
</tbody>
</table>

Gershenson et al 2012 Gyn Onc

AI use in adjuvant therapy has been associated with prolonged PFS

Gershenson et al. 2017 JCO
Fader et al. 2017 Gyn Onc
Frequency of *ESR1* alterations in gynecologic malignancies

<table>
<thead>
<tr>
<th>Type of alteration</th>
<th>Frequency N=9645</th>
<th>Ovary/FT N=5594</th>
<th>Uterus N=3101</th>
<th>Cervix N=720</th>
<th>Vulva/Vagina N=216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, N (%)</td>
<td>295 (3.1)*</td>
<td>120 (2.1)</td>
<td>160 (5.2)</td>
<td>9 (1.2)</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Amplification</td>
<td>80 (0.8)</td>
<td>45 (0.8)</td>
<td>34 (1.1)</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Deletion</td>
<td>1 (&lt;0.1)</td>
<td>-</td>
<td>1 (&lt;0.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fusion</td>
<td>2 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
<td>-</td>
<td>-</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Rearrangements</td>
<td>18 (0.2)</td>
<td>9 (0.2)</td>
<td>9 (0.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Substitution Variants</td>
<td>194 (2.0)</td>
<td>65 (1.2)</td>
<td>116 (3.7)</td>
<td>8 (1.1)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Codon 536-538</td>
<td>75 (0.8)</td>
<td>18* (0.3)</td>
<td>56* (1.8)</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Other Activating Mut</td>
<td>12 (0.1)</td>
<td>3 (&lt;0.1)</td>
<td>7 (0.2)</td>
<td>-</td>
<td>2 (0.9)</td>
</tr>
</tbody>
</table>

*Includes 10 cases with 2 alterations each, 1 ovarian case & 2 uterine cases w/ 2 codon 536-538 mutations each

"-": none present, FT: fallopian tube, Mut: mutation
### ESR1 mutations identified through public databases

<table>
<thead>
<tr>
<th></th>
<th>N in dataset</th>
<th>mutESR1 N (%)</th>
<th>Histology</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LGSOC</strong></td>
<td>26</td>
<td>1 (3.8)</td>
<td>Low-grade serous</td>
<td>1</td>
</tr>
<tr>
<td><strong>AACR GENIE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>271</td>
<td>1 (0.4)</td>
<td>Adenocarcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Ovary</td>
<td>1473</td>
<td>2 (0.1)</td>
<td>2 Endometrioid</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>1076</td>
<td>26 (2.4)</td>
<td>26 Endometrioid</td>
<td></td>
</tr>
<tr>
<td>Uterine Sarcoma</td>
<td>199</td>
<td>2 (1.0)</td>
<td>2 ESS</td>
<td></td>
</tr>
<tr>
<td><strong>TCGA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine Corpus</td>
<td>248</td>
<td>5 (2.0)</td>
<td>5 Endometrioid</td>
<td>3</td>
</tr>
<tr>
<td>Ovary</td>
<td>0</td>
<td>0</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>0</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td><strong>Uterine</strong></td>
<td>22</td>
<td>1 (4.5)</td>
<td>Carcinosarcoma</td>
<td>6</td>
</tr>
</tbody>
</table>

ESR1 mutations are enriched in hormone-responsive histologies

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Histology</th>
<th>N</th>
<th>mutESR1 N (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CGP analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>serous</td>
<td>3502</td>
<td>12 (0.3)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>endometrioid</td>
<td>144</td>
<td>5 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>serous</td>
<td>446</td>
<td>1 (0.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>endometrioid</td>
<td>548</td>
<td>24 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>LMS</td>
<td>421</td>
<td>3 (0.7)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>ESS</td>
<td>103</td>
<td>3 (3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>AACR GENIE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>high-grade serous</td>
<td>687</td>
<td>0</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>endometrioid</td>
<td>57</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>serous</td>
<td>203</td>
<td>0</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>endometrioid</td>
<td>518</td>
<td>25 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>LMS</td>
<td>113</td>
<td>0</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>ESS</td>
<td>16</td>
<td>2 (12.5)</td>
<td></td>
</tr>
</tbody>
</table>

P value calculated using Fisher’s exact test
One patient’s story:

- 58F diagnosed with low-grade serous papillary carcinoma of gyn origin
  - Neoadjuvant Carboplatin/Paclitaxel
    - 3 cycles
    - CT: No change in calcified peritoneal carcinomatosis, bilateral pulmonary nodules
    - Attempted cytoreductive surgery: tumor engulfing small & large bowel, extensive adhesions

![ERα](image)

![Graph](image)

**ERα**

- **Y537N**

**Graph**

- **Patient C: CA125**
  - Initiation of fulvestrant
  - Most recent CT showing stable disease
Clinical Relevance of ESR1 mutations in Gyn Cancers

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**Diagram:**

- **A**: No mutESR1
- **B**: ESR1 Y537S
- **C**: ESR1 Y537N
- **D**: ESR1 Y537S, 4%
- **E**: ESR1 Y537S, 37%
- **F**: No mutESR1
- **G**: No mutESR1
- **H**: 5 years

**Legend:**

- **Surgery**
- **Chemotherapy**
- **Fulvestrant**
- **Other targeted therapy**
- **CGP**
- **AI**
- **Tamoxifen**
- **Immunotherapy**

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**Key:**

- ESR1 Y537S
- ESR1 Y537N
- Other targeted therapy
- CGP
- AI
- Tamoxifen
- Immunotherapy
Key Points from Clinical Review

- Prior treatment with aromatase inhibitors in 5 cases
  - Suggests mutation as a mechanism of resistance

- Mutations present in absence of exposure to endocrine therapy

- *mutESR1* tumors may clinically benefit from anti-ER directed therapy
Potential Reasons for Differences in Benefit

1. the use of hormone therapy in a later phase of the disease course after the cancer has had the opportunity to develop multiple adaptive/resistance mechanisms

2. the influence of co-occurring mutations

3. the specific $m^u\text{tESR}1$ present within each tumor
Mutations Confer Partial Resistance

**A**

**B**

**C**
Inhibitory Blood Concentrations May Not Be Achievable for some Mutations
Summary

• *ESR1* mutations are rare findings in rare cancers
  • Prevalence may increase with increased use of aromatase inhibitors
  • May be present in the primary tumor
  • Hotspot sequencing may miss some cases of activating mutations
  • Heterogeneity and polyclonality

• Important Treatment implications
  • Resistance to aromatase inhibitors
  • May respond to anti-ER directed therapy (SERMs/SERDs)
  • Relative response may be affected by the mutation(s) present

• Needs
  • Determine the true prevalence and conditions under which they arise
  • Development of drugs that more effectively inhibit mutERα, esp Y537S and D538G
Clinical Trial Implications

• Challenge of recruitment given small numbers
  • Advantage of cooperative group/rare tumor committee

Hyman et al, NEJM 2015

Migden, NEJM 2018
Clinical Trial Implications

- Challenge of recruitment given small numbers
  - Advantage of cooperative group/rare tumor committee
- Modern Trial Designs

**Basket Trials**

Multiple tumor/histologic types are grouped by similar genomic alteration

- Lymphoma
- Pancreatic Cancer
- Neuroendocrine Tumors
- Gastric Cancer

**Umbrella Trials**

Single tumor type divided by individual genomic alterations
Clinical Trial Implications

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• Modern Trial Designs
  • Hybrid designs
  • Adaptive designs
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- Lessons from prior trials
  - Tumor context matters

[Graphs show data for colorectal cancer treatments.]
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  • Not all mutations are the same

D M Hyman et al. 2018 Nature
Clinical Trial Implications

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• Modern Trial Designs
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• Lessons from prior trials
  • Tumor context matters
  • Not all mutations are the same

• Endpoints need to be selected wisely
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