Emerging Opportunities in Rare Gynecologic Cancers

Anil K. Sood, M.D.
M.D. Anderson Cancer Center
Houston, TX
Disclosure

- SAB/consulting: Kiyatec, Tesaro
- Research funding: M-Trap
- Stockholder: Bio Path
Overview

- Rare cancers
- Molecular characteristics
- Therapeutic opportunities and trial development
What are rare cancers?

- NCI: <15 per 100,000 people per year
- ESMO: <6 per 100,000 people per year
Common cancers

- By NCI definition, only 11 cancer types are classified as common in US adults:
  - Prostate
  - Breast
  - Lung
  - Colon
  - Uterus (endometrial)
  - Bladder
  - Melanoma
  - Rectum
  - Ovary
  - Non-Hodgkin lymphoma
  - Kidney or renal pelvis
# Classification of “common cancers”

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Pathognomonic mutation</th>
<th>Post-genomics classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer</td>
<td><em>POLE</em></td>
<td>Molecularly defined subtype of common cancer</td>
</tr>
<tr>
<td>Breast cancer</td>
<td><em>ERBB2</em> amplification</td>
<td>Molecularly defined subtype of common cancer</td>
</tr>
<tr>
<td>High-grade serous ovarian cancer</td>
<td><em>BRCA1, BRCA2</em></td>
<td>Molecularly defined subtype of common cancer</td>
</tr>
<tr>
<td>Non-small-cell lung cancers</td>
<td><em>EML4–ALK</em> fusion</td>
<td>Molecularly defined subtype of common cancer</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td><em>TMPRSS2–ERG</em> fusion</td>
<td>Common cancer (prostate cancer)*</td>
</tr>
<tr>
<td>High-grade serous ovarian cancer</td>
<td><em>TP53</em></td>
<td>Common cancer (high-grade serous ovarian cancer)*</td>
</tr>
</tbody>
</table>

*Boyd et al., Lancet Oncol, 2016*
Ovarian Carcinomas – Origins

Cellular Origins of Ovarian Cancers

- Ovarian Surface Epithelium
- Fallopian Tube Epithelium
- Endometrium
- Retrograde Menstruation
- Endometriosis

Branches:
- High-Grade Serous Carcinoma
- Low-Grade Serous Carcinoma
- Clear Cell Carcinoma
- Endometrioid Carcinoma
- Mucinous Carcinoma
- Unknown

www.nas.edu/OvarianCancers
The Biology of Ovarian Cancer
Ovarian Carcinomas – Not one disease

www.nas.edu/OvarianCancers
Recommendation 2

• Reach consensus on diagnostic criteria, nomenclature, and classification schemes that reflect the morphological and molecular heterogeneity of ovarian cancers

• Promote universal adoption of standardized taxonomy
Molecular features of ovarian cancers

Mutations in major epithelial ovarian cancer subtypes

Epithelial Ovarian cancer

High-grade serous
- TP53 (95%)
- BRCA1/2 (12/11%)
- RB1 loss (20%)
- CCNE1 amp (14%)
- NF1 loss (17%)

Low-grade serous
- KRAS (19-54%)
- BRAF (2-33%)
- NRAS (5%)
- ERBB2 (6%)

Clear cell
- ARID1A (50%)
- PIK3CA (40%)
- PTEN (30%)
- MET amp (24%)

Endometrioid
- ARID1A (30%)
- PIK3CA (40%)
- PTEN (20%)
- CTNNB1 (50%)
- TP53 (64%)

Mucinous
- KRAS (60%)
- TP53 (56%)
- HER-2 amp (20%)

KK Wong
Low-grade serous carcinoma (LGSC): Impact of mutational status on survival

Median OS for women with KRAS or BRAF mutation was 106.8 months (95% CI, 50.6, 162.9) compared with 66.8 months (95% CI, 43.6, 90.0) for women whose tumors contained no KRAS or BRAF mutations (P = 0.018)

Gershenson, Sun and Wong. 2015 BJC
KRAS$^{G12D}$ and KRAS$^{G12V}$ have different cell signaling

Ihle et al., 2012. JNCI 104:228-39
An Extreme Responder with a 15–base pair deletion in $\text{MAP2K1}$ gene, an activating mutation in the GOG0239 (selumetinib) study

Complete radiographic response after 17 months of therapy, which was durable at 4 and 5 years

Grisham, Gershenson et al. JCO, 2015
Ovarian clear cell adenocarcinoma (OCCC)

- A distinct histological type of cancer in the WHO-classification
- Most patients present with early stage disease (FIGO I and II)
- Incidence: 5-10% of epithelial ovarian cancers
- OCCC occurs more frequently in Japan and Taiwan (15-25%)
- More resistant to systemic chemotherapy than other types; late stage associated with poorer prognosis than other types
Molecular abnormalities in ovarian clear cell carcinoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>Overall genomic alteration frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>52.8%</td>
</tr>
<tr>
<td>ARID1A</td>
<td>51.2%</td>
</tr>
<tr>
<td>TP53</td>
<td>21.6%</td>
</tr>
<tr>
<td>ZNF217</td>
<td>17.6%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>12.8%</td>
</tr>
<tr>
<td>KRAS</td>
<td>8%</td>
</tr>
<tr>
<td>CCNE1</td>
<td>7.2%</td>
</tr>
<tr>
<td>CRKL</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

- **N = 125 advanced/recurrent OCCCs**
- **FoundationOne® genomic profiling**
- **Genomic alterations:** base pair substitutions, insertions/deletions, copy number, rearrangements

**Therapeutic opportunities:**
- Everolimus
- HDACi
- EZH2i
- VEGF/VEGF-R blockers
- Trastuzumab
- MMR deficiency: ~6% (check-point blockers)

Elvin et al., Gyn Onc Rep, 2017
Stewart et al., Histopathol, 2017
Activated pathways in ovarian clear cell carcinoma

- Microdissected clear cell cancers
- Activated pathways:
  - Angiogenesis
  - Coagulation
  - Glucose metabolism

Stany et al., PLoS One, 2011
Targeted pathways implicated in the tumor suppressor activity of SWI/SNF complexes

Wilson and Roberts (2011), Nature Reviews Cancer
Broad spectrum of SWI/SNF mutations in human cancers

High frequency of co-occurring PIK3CA and ARID1A mutations in Ovarian clear cell carcinomas (OCCCs)

Chandler et al., (2014), Nature Communications
Mucinous ovarian carcinoma

Molecular features:
• Her2 amplification
• Kras mutation
• Src activation
• MSI-H
• No BRCA mutations; low rate of p53 mutations

Therapeutic opportunities:
• Ras-targeted drugs
• VEGF/VEGF-R inhibition
• Trastuzumab
• Src inhibitors
• PI3K/Akt inhibitors
• Immune therapies

Frumovitz et al., Gyn Oncol 2010
Matsuo et al., Clin Cancer Res 2011
Small cell carcinomas of the gynecologic tract

Small cell carcinoma of the ovary:

- Pulmonary type (SCCOPT)
  - Alterations in TP53, BRCA2
- Hypercalcemic type (SCCOHT)
  - Inactivating mutations in SMARCA4; loss of SMARCA2 expression

Conventional therapy:

- Chemotherapy
- Radiation

Emerging options:

- Immune therapy (PD-1/PD-L1 blockade)
- EZH2i, HDACi

*Patibandla et al., Gyn Oncol 2018*
Clinical trial considerations: Rare Cancers

- Create national and international networks
- Accepting greater type I and type II error
- Select trial population to minimize sample size
- Balancing scientific value and feasibility
- Incorporating Bayesian elements to quantify the resulting level of information
- N-of-1 trials; basket trials
Thank you!