Do we need Biomarkers in Gynecologic Oncology

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University of California Los Angeles
What are Biomarkers
Biomarkers tell you... 
...of an association 
...of the likelihood of an event
Estrogen Receptor as a Biomarker

*Single-agent Immunotherapy efficacy*

Myc, cyclinD1, BCL2, ...
Estrogen Receptor as a Biomarker **Prognostic Marker in Endometrial Cancer**
Estrogen Receptor as a Biomarker

**Predictive Marker for Response to Anti-Hormonal Therapy**

- Control 37.7%
- 26.1% at 5 years tamoxifen
- 24.8% at 5 years tamoxifen
- 15.4% at 5 years tamoxifen

ER-positive disease: 7378 women
(45% node positive, 55% chemotherapy)
Why do we need **Prognostic** or **Predictive** Markers?

- **Prognostic**
  - Who needs treatment?
- **Predictive**
  - Which treatment is best?

**Therapeutic Options**

- Avoid over & under treatment
- Individualize treatment
Predictive Markers help individualize Treatments

- Patients with a "type" of cancer (recognizing the molecular subtypes)
- Standard Therapy
- Few patients respond to therapy
- Most patients fail therapy
  - Inadequate response
  - No response
  - Develop resistance
How do we measure Biomarkers?

diagnostic

clinical and laboratory features
protein

prognostic

DNA
immune /stroma

predictive

metabolome
microbiome

drug A

month

probability of survival

drug B
How do we measure Biomarkers?

Diagram showing the relationship between DNA, RNA, and Protein.
Biomarkers in Endometrial Cancer
Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network®
4 Molecular Subtypes
Managing MSI-high disease
*Single-agent Immunotherapy efficacy*

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Patient Selection</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-158</td>
<td>Pembrolizumab</td>
<td>49</td>
<td>Advanced / metastatic dMMR</td>
<td>57%</td>
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<tr>
<td>GARNET</td>
<td>Dostarlimab</td>
<td>103</td>
<td>Previously treated Recurrent / advanced dMMR</td>
<td>45%</td>
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<tr>
<td>PHAEDRA</td>
<td>Durvalumab</td>
<td>35</td>
<td>Advanced / metastatic dMMR</td>
<td>43%</td>
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<tr>
<td>NCT02912572</td>
<td>Avelumab</td>
<td>15</td>
<td>Advanced / persistent dMMR</td>
<td>27%</td>
</tr>
</tbody>
</table>

# Managing MSS disease:
*Single Agent IO Efficacy in Biomarker Negative Endometrial Cancer*

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<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Patient Selection</th>
<th>ORR (%)</th>
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</thead>
<tbody>
<tr>
<td>KEYNOTE-28</td>
<td>Pembrolizumab</td>
<td>24</td>
<td>Advanced/metastatic PD-L1+</td>
<td>13%</td>
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<tr>
<td>Garnet</td>
<td>Dostarlimab</td>
<td>142</td>
<td>Previously treated Recurrent/advanced pMMR</td>
<td>13.4%</td>
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<tr>
<td>PHAEDRA</td>
<td>Durvalumab</td>
<td>36</td>
<td>Advanced/metastatic pMMR</td>
<td>3%</td>
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<tr>
<td>Konstantinopoulos</td>
<td>Avelumab</td>
<td>16</td>
<td>Advanced/metastatic pMMR</td>
<td>6%</td>
</tr>
</tbody>
</table>

Managing MSI-high disease
Mismatch Repair Deficiency or Microsatellite Instability
MSI-high ➔ TMB high ➔ Neo-Antigens
Biomarkers for MSI-high disease
Mismatch Repair Deficiency or Microsatellite Instability

- Immunohistochemistry
- qPCR-based MSI analysis
- Next-Generation Sequencing
4 Molecular Subtypes

- MSI
- CNL
- CNH
Estrogen Receptor as a Biomarker
Letrozole and Palbociclib in ER+ Endometrial cancer

HR=0.56
(95% CI 0.32-0.98)
P=0.0376
Median: 3.0 vs 8.3 mo

Number at risk
Palbociclib + letrozole  36  21  14
Placebo + letrozole  37  17  10
p53 as a Biomarker

Slenexor in **p53 wild-type** Endometrial Cancer
4 Molecular Subtypes
HER2 as a Biomarker in Endometrial or Ovarian Cancer
HER2 as a Biomarker

**Trastuzumab + Chemotherapy in HER2+ Endometrial Cancer**

<table>
<thead>
<tr>
<th>Survival Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab plus carboplatin and paclitaxel</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
</tr>
</tbody>
</table>

Santin et al, *Journal of Clinical Oncology*
Biomarkers in Ovarian Cancer
Homologous Recombination (HR) Deficiency
Homologous Recombination (HR) Deficiency

BRCA

BRCA-like

BRCA
t

Biomarker Negative

Chromosome No.
BRCA Mutations and HRD as a Biomarkers

PARPi synthetically lethal

![Diagram showing the interaction between PARP and PARP inhibitors in the context of BRCA mutations and HRD.](image_url)
Significant progress for BRCA associated cancers

SOLO1 - gBRCAm

NR mo vs 13 mo
HR 0.30 (95% CI: 0.23, 0.41)

NR vs. 14.1 mo
HR 0.28 (95% CI 0.2-0.39)

PRIMA

HR 0.40 (95% CI .27-0.62)

PAOLA-1

37.2 vs 17.7 mo
HR 0.33 (95% CI 0.25-0.45)

And for those women with HRD +/BRCAwt tumors - not perfect but good

HRP tumors are the big focus now

Cyclin E Amplification as a Biomarker

New Targets: WEE1, ATR, PKMYTH
Cyclin E Amplification as a Biomarker
Biomarkers of Angiogenesis

Hypoxia, acidosis activates hypoxia response genes (e.g., VEGFA)

Proteolytic processing:
- Plasminogen, Proactin, Procollagen XVIII, MMP-2

Integrins mediate ECM interactions

VEGFs A–D, placental growth factor (PIGF)

Local angiogenic stimulators:
- TGF-α, TGF-β, αFGF, βFGF, PDGF

Regulates sprouting and branching: Dll4

Proteolytic processing:
- Plasminogen, Proactin, Procollagen XVIII, MMP-2

ECM:
- MMPs, tPA, UPA, PAI, TIMPs

Thrombospondin

Integrins mediate ECM interactions

Ang-1, Ang-2

Biomarkers of Angiogenesis

Capillary organization mediated by cytokines and angiopoietins
Gene Expression Profiles as a Biomarkers
Gene Signatures and Bevacizumab Response

**ICON7/AGO-OVAR11**

- FIGO stage I–IIA (clear cell or grade 3) or FIGO stage IIB–IV
- Surgically debulked histologically confirmed OC

！1:1 R

- Carboplatin AUC 5 or 6
- Paclitaxel 175 mg/m²
- Carboplatin AUC 5 or 6
- Paclitaxel 175 mg/m²

Bevacizumab 7.5 mg/kg q3w
18 cycles (12 months)

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**PFS**

<table>
<thead>
<tr>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.4</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Log-rank test: \( p = 0.039 \)

HR (95% CI): \( 0.87 \) (0.77–0.99)

## Gene Signatures and Bevacizumab Response

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Δ PFS in Months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>6.5, p=0.004</td>
<td></td>
</tr>
<tr>
<td>Immunoreactive</td>
<td>3.8, p=0.080</td>
<td></td>
</tr>
<tr>
<td>Differentiated</td>
<td>3.7, p=0.610</td>
<td></td>
</tr>
<tr>
<td>Proliferative</td>
<td>10.1, p=0.015</td>
<td></td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>8.2, p=0.405</td>
<td></td>
</tr>
</tbody>
</table>

Winterhoff B, Kommoss S, Konecny GE. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5509)
Cell Surface Markers as Biomarkers
Tumor Specific Biomarker
Identify Proteins on the Cell Surface which can be targeted with Monoclonal Antibodies
Antibody Drug Conjugates

Antibody
Targets cancer cells

Linker
Joins antibody and drug

Cytotoxic drug
Destroys cancer cells
FOLR1 as a Biomarker in Ovarian Cancer

Based on their overall efficacy and adverse event profile ➔ paradigm shift.

Mirvetuximab Soravtansine
Novel Biomarker and ADC Target

CLAUDIN 6

Overall survival - Ovarian Cancer

HR = 1.53 (1.23 - 1.9)
logrank P = 9.1e-05
Novel Biomarker and ADC Target
CLAUDIN 6
Expression of Claudin 6 in Normal Tissues (GTEX)
Expression of HER2 in Normal Tissues (GTEX)
Claudin 6 a New Biomarker

- TORL-1-23 is an ADC with a fully humanized IgG1 (TORL-1-23-MAB) linked to MMAE through a cathepsin hydrolysable dipeptide VC linker (vc-MMAE).
The higher the CLDN6 positivity, the lower the likelihood that patients are FOLR1 positive.
ADC Landscape 2023
Immunotherapy Biomarkers
**PD-L1 is a Weak Biomarker for Immunotherapy**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
<th>Normalisation Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS (%)</td>
<td>Number of PD-L1-stained tumour cells / Total number of viable tumour cells</td>
<td>× 100% (for 22C3 or SP263)</td>
</tr>
<tr>
<td>TC (%)</td>
<td>Number of PD-L1-stained tumour cells / Total number of viable tumour cells</td>
<td>× 100% (for SP142)</td>
</tr>
<tr>
<td>IC (%)</td>
<td>Area of tumour infiltrated by PD-L1-stained immune cells / Total tumour area</td>
<td>× 100% (for SP142)</td>
</tr>
<tr>
<td>CPS</td>
<td>Number of PD-L1-stained cells (tumour cells, lymphocytes and macrophages) / Total number of viable tumour cells</td>
<td>× 100 (for 22C3)</td>
</tr>
</tbody>
</table>
Evolving Biomarkers for Immunotherapy Response
Redundancy of Immune-Checkpoints

Annual Survivor-Caregiver Summit
Biomarker Development with

Single Cell Sequencing

and

Multiplexed Immunohistochemistry
Single Cell RNAseq

Heterogeneous tissue → Dissociated cells → Single cells ready for scRNA-seq
Single Cell RNAseq for Biomarker Studies
Zoom in to the Single Cell Level
Muliplexed Immunohistochemistry
High Spacial Resolution of Biomarkers

IGCAN | ADVOCACY NETWORK
Annual Survivor-Caregiver Summit
Biomarker Testing
Germline Testing

Egg cell + Sperm cell → Embryo → Mutation → Somatic mutation

Somatic Testing

Egg cell + Sperm cell → Embryo → Mutation → Germline mutation
Biomarker Testing in circulating cell-free DNA (cfDNA)
Biomarker Testing will help us Understand Treatment Response and Failure
We need Biomarkers in Gynecologic Oncology

- ER
- BRCA1/2
- HRD
- MSI
- TMB
- FOLR1
- CLDN6

- HER2
- PDL1
- CCNE1
- P53
- KRAS
- NTRK
- B7H4