Targeted Therapy in Gynecological Cancer

CONCLUSIONS and CLINICAL PERSPECTIVES

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Disclosure slide

- Advisory board participation: Astra Zeneca, Roche, Pharmamar, MSD, Novartis.
2014 ESMO CONGRESS THEME

• “PRECISION MEDICINE IN CANCER CARE”:
  – High technologies now available allowing us to see the complexity of cancer /Gynecological Cancer
• To translate the tumor genomic data into more precision medical care for the patients
  – Better outcome for our patients
  – More cost effective drug development
  – Treating the right patients with the right drug
### The Biology of Ovarian Cancer: New Opportunities for Translation

<table>
<thead>
<tr>
<th>Type</th>
<th>Histology</th>
<th>Precursor</th>
<th>Molecular features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low-grade serous carcinoma</td>
<td>Cystadenoma–borderline tumour–carcinoma sequence</td>
<td>Mutations in KRAS and/or BRAF (≥60%)</td>
</tr>
<tr>
<td>I</td>
<td>Low-grade endometrioid carcinoma</td>
<td>Endometriosis and endometrial cell-like hyperplasia*</td>
<td>Mutations in CTNNB1, PTEN and PIK3CA with microsatellite instability</td>
</tr>
<tr>
<td>I</td>
<td>Mucinous carcinoma</td>
<td>Cystadenoma–borderline tumour–carcinoma sequence; metastases from bowel</td>
<td>Mutations in KRAS; TP53 mutation associated with transition from borderline tumour to carcinoma</td>
</tr>
<tr>
<td>I</td>
<td>Clear cell carcinoma</td>
<td>Endometriosis</td>
<td>PTEN mutation or loss of heterozygosity; PIK3CA mutation*</td>
</tr>
<tr>
<td>II</td>
<td>High-grade serous carcinoma</td>
<td>De novo in epithelial inclusion cysts; fallopian tube</td>
<td>TP53 mutation (up to 80%) and BRCA1 dysfunction</td>
</tr>
<tr>
<td>II</td>
<td>High-grade endometrioid carcinoma</td>
<td>Epithelial inclusion glands or cysts</td>
<td>TP53 mutation and BRCA1 dysfunction; PIK3CA mutation</td>
</tr>
</tbody>
</table>

*Endometriosis and adjacent low-grade endometrioid carcinoma share common genetic events such as loss of heterozygosity at the same loci involving the same allele (for example, PTEN). By contrast, high-grade and poorly differentiated endometrioid carcinomas are similar to high-grade serous carcinomas. † PIK3CA at 3q26 encodes the p110α catalytic subunit of PI3K.\(^\text{19}\)*

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**Bast R et al. Nature Reviews Cancer 9, 415-428 (June 2009)**
Three degrees of genomic complexity

- High complexity cancers
  - Example HGSOC
  - Pathognomonic mutations unlikely
  - Profound inter- and intra-tumoural heterogeneity

- Moderate complexity cancers
  - Clear cell cancer
  - Mutations in specific pathways important in other cancers
  - Extent of intratumoral heterogeneity unknown

- Minimal complexity—often with pathognomonic features
  - Examples - AGCT, SCCOHT
  - Pathognomonic mutations
  - Minimal inter- and intra-tumoural heterogeneity

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Therapeutic strategies

Personalize
- High complexity cancers
- Example HGSOC
- Pathognomonic mutations unlikely
- Profound inter- and intra-tumoral heterogeneity

Stratify
- Moderate complexity cancers
- Clear cell cancer
- Mutations in specific pathways important in other cancers
- Extent of intratumoral heterogeneity unknown

Generalize
- Minimal complexity—often with pathognomonic features
- Examples - AGCT, SCCOHT
- Pathognomonic mutations
- Minimal inter- and intra-tumoral heterogeneity

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Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations. *, CHK2, BARD1, BRIP1, PALB2, RAD50, RAD51C, ATM, ATR, EMSY, Fanconi anemia genes.

High-grade serous
- TP53
- BRCA1 and 2
- NF1
- RB1
- CDK12
  Homologous recombination repair genes*

Low-grade serous
- BRAF
- KRAS
- NRAS
- ERBB2

Mucinous
- KRAS
- HER2 amplification

Clear cell
- ARID1A
- PIK3CA
- PTEN
- CTNNB1
- PPP2R1α

Endometrioid
- ARID1A
- PIK3CA
- PTEN
- PPP2R1α

Sex cord-stromal
- Granulosa cell
  - FOXL2
- Sertoli-Leydig cell
  - DICER1

Others, including germ cell
- MMR deficiency

Pathway alterations:
- PI3K/RAS/NOTCH/FOXM1

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CCR New Strategies

Conclusions

- Real optimism surrounding targeted therapy for first time in 20 years
- Besides angiogenesis, homologous recombination deficiency is the second most promising target in high grade serous ovarian cancer: PARP inhibition has given positive results in randomized clinical trials for ovarian cancer.
- Phase III studies ongoing in both first line and II line
# Targeting Ovarian Cancer: Subtypes

<table>
<thead>
<tr>
<th>Genetic Risk</th>
<th>HGSC</th>
<th>CCC</th>
<th>EC</th>
<th>MC</th>
<th>LGSC</th>
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<tbody>
<tr>
<td>BRCA1/2</td>
<td></td>
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<tr>
<td>HNPCC</td>
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<tr>
<td>HNPCC</td>
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<table>
<thead>
<tr>
<th>Other Risk Factors</th>
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<th>EC</th>
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<tbody>
<tr>
<td>↓ Risk with OC, pregnancy</td>
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<tr>
<td>None known</td>
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<tr>
<td>↓ Risk with OC, ↑ Risk with HRT</td>
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<tr>
<td>None known</td>
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<table>
<thead>
<tr>
<th>Precursors</th>
<th>HGSC</th>
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<tbody>
<tr>
<td>STIC</td>
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<td></td>
<td>SBT</td>
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<tr>
<td>Endometriosis</td>
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<table>
<thead>
<tr>
<th>Presentation</th>
<th>HGSC</th>
<th>CCC</th>
<th>EC</th>
<th>MC</th>
<th>LGSC</th>
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<tbody>
<tr>
<td>Ascites, GI sxs</td>
<td></td>
<td>Adnexal mass</td>
<td>Adnexal mass</td>
<td>Adnexal mass</td>
<td>GI sxs</td>
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</table>

<table>
<thead>
<tr>
<th>Pattern of Spread</th>
<th>HGSC</th>
<th>CCC</th>
<th>EC</th>
<th>MC</th>
<th>LGSC</th>
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<tbody>
<tr>
<td>Peritoneal, nodal</td>
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<tr>
<td>Peritoneal, nodal, distal</td>
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<tr>
<td>Peritoneal, nodal, distal</td>
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<tr>
<td>Peritoneal +/- Pseudomyxoma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal, nodal</td>
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</table>

<table>
<thead>
<tr>
<th>Chemotherapy Response</th>
<th>HGSC</th>
<th>CCC</th>
<th>EC</th>
<th>MC</th>
<th>LGSC</th>
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<tbody>
<tr>
<td>Sensitive, then resistant</td>
<td></td>
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<td></td>
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<tr>
<td>Resistant</td>
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<tr>
<td>Sensitive</td>
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<tr>
<td>Resistant</td>
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<tr>
<td>Resistant</td>
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<table>
<thead>
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<th>Molecular Genetics</th>
<th>HGSC</th>
<th>CCC</th>
<th>EC</th>
<th>MC</th>
<th>LGSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53, BRCA1/2, PI3K, HRD</td>
<td></td>
<td>PI3K, ARID1A, MSI</td>
<td>PTEN, β catenin, ARID1A, MSI</td>
<td>KRAS, HER2</td>
<td>BRAF, KRAS, NRAS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targets</th>
<th>HGSC</th>
<th>CCC</th>
<th>EC</th>
<th>MC</th>
<th>LGSC</th>
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</thead>
<tbody>
<tr>
<td>PARP, Angiogenesis</td>
<td></td>
<td>Angiogenesis</td>
<td>ER, PR, mTOR</td>
<td>HER2/neu</td>
<td>BRAF, KRAS MEK/ERK</td>
</tr>
</tbody>
</table>

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Modified from: Bookman MA, et al., *J Natl Cancer Inst* 2014;106 PMID 24627272
Phase III Design

Initial Design Parameters
- Scientific-Clinical Hypothesis
- Superiority vs Non-Inferiority
- Selection of Primary Endpoint (PFS or OS)
- Historical reference data
- Targeted improvement and hazard ratio

Sample Size Determination
- Anticipated rate of accrual
- Anticipated event rate
- Proposed \( \alpha \) (0.05) and \( \beta \) (0.80)
- One-sided or two-sided analysis
- Interim analysis for futility
- Interim analysis for efficacy

Budgetary Considerations
- Regulatory vs non-regulatory
- Size and duration of study
- Monitoring requirements
- Independent DSMB
- Independent response evaluation
- Medication production and supply
- Coverage for tests/procedures
- Potential for Return on Investment

Secondary Endpoints
- Stratification and subset analysis
- Incorporation of biomarkers
- Cost effectiveness, QOL
• Should Ovarian Tumors be defined as Tubo-Ovarian instead?
• Should we avoid using the term according to its anatomical (ovary) location?

• “It is essential that researchers, pathologists, epidemiologists and clinicians understand that ovarian cancer is a general term for a series of molecularly and aetiologically distinct diseases that simply share an anatomical location".

(Vaughan S et al. 2011)
Cervical Cancer
Targeted Therapies underway

- **Targeting the PI3K/PTEN/AKT Pathway**
  - Link between mTOR and HPV (E6 interacts TSC2, 4E-BP1 and E7)
  - 36% (5/14) PIK3CA mutations squamous cell cervix. Response rate PIK3CA mutant 40% (2/5) (Janku JCO 2012)
  - **Phase II temsirolimus (mTOR) (Tinker Gyn Onc 2013)**
    - 3% PR; 58% stable (duration 6.5 m); 6m PFS 28% median PFS 3.5 months
    - No molecular markers for benefit identified

- **PARP inhibitors**
  - **GOG#0076¹**: Paclitaxel, Cisplatin, and Veliparib; **GOG#0127²** Topotecan+Veliparib

- **Immunotherapy**
  - **GOG phase II live-attenuated L. monocytogenes cancer vaccine** (against viral oncoprotein E7) (ADXS-001) in persistent/recurrent cervical cancer
  - **NCI phase II ipilimumab³** (HPV-related)

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1. ClinicalTrials.gov Identifier: NCT01281852
2. ClinicalTrials.gov Identifier: NCT01266447
3. ClinicalTrials.gov Identifier: NCT01711515
CONCLUSIONS

Endometrial Cancer

- Targeting the PI3KCA Pathways needs further investigation and clarification of relevant biomarkers.
- Metformin is an interesting drug, which is likely to be the subject to a number of upcoming trials.
- Antiangiogenesis agents seem to be an useful strategy.

Cervical Cancer

- Bevacizumab improved overall survival in recurrent/ metastatic disease.
- New agents including immunotherapy are under investigation.
# Targeting Cervical Cancer

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Risk Factors</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPV Exposure</td>
<td>• Vaccine (pre-exposure)</td>
</tr>
<tr>
<td>Additional Risks</td>
<td>HPV Chronic Infection</td>
<td>• Smoking (Immune Suppression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cervical Trauma and Inflammation (Basal Access)</td>
</tr>
<tr>
<td>Screening</td>
<td>Socioeconomic Status, Politics, and Culture</td>
<td>• HPV and/or Cytology (min x1)</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
<td>• Ablation of pre-invasive disease</td>
</tr>
<tr>
<td>Primary Therapy (regional)</td>
<td>Inadequate Screening</td>
<td>• Surgery and/or Chemoradiation +/- Adjuvant Chemotherapy</td>
</tr>
<tr>
<td>Primary Therapy (advanced/recurrent)</td>
<td>Platinum Resistance Tumor Angiogenesis Tumor Hypoxia</td>
<td>• Prevention (as above)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tailored Radiation, Surgery, and Chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Incorporation of Bevacizumab and Investigational Agents</td>
</tr>
</tbody>
</table>
Targeting Cervical Cancer

• **HPV Vaccination and Screening**
  – Strategies tailored for the developing world, and immigrant populations within the developed world
  – Collaboration among public health agencies, NGOs, and foundations (not always easy)
  – Focus on younger generation, social media, information resources
  – Attention to other risk-altering modifications (i.e., smoking)
  – Greatest reduction in mortality from ONE screening cycle

• **Therapy**
  – Emphasis on early interventions for non-invasive disease and monitoring for residual HPV infection
  – Availability of radiation facilities in low-resource settings
  – Targeting angiogenesis and hypoxia in high-resource settings
  – Pharmacologic inhibition of HPV-E6 function (or MDM2/4) to restore P53 function
Targeting Endometrial Cancer: TCGA Network.
CONCLUSIONS

Endometrial Cancer

• Targeting the PI3KCA Pathways needs further investigation and clarification of relevant biomarkers.
• Metformin is an interesting drug, which is likely to be the subject to a number of upcoming trials.
• Antiangiogenesis agents seem to be an useful strategy.

Cervical Cancer

• Bevacizumab improved overall survival in recurrent/metastatic disease.
• New agents including immunotherapy are under investigation.
Targeting Endometrial Cancer

• Screening and risk stratification, incorporating DNA-based cytology
• Recognize increasing incidence of high-grade advanced-stage cancers without bleeding (Type II)
• Emphasis on minimally-invasive surgery and sentinel LN Bx (Type I)
• Optimized multi-modality therapy for advanced disease
• Broaden MSI screening by tumor IHC and genomics for family risk management HNPCC (Type I > II)
• Incorporate screening of BRCA status (Type II)
• Obesity has become a targetable risk factor (Type I > II)
• Incorporation of metformin, targeting obesity-associated growth factors and signal transduction pathways
TARGETED THERAPY IN GYNAECOLOGICAL CANCER
SUMMARY

• Stop treating average gynecological cancer patients with empirical treatments is a priority.
• We need effective Biomarkers to predict response or lack of response.
• We need personalized therapy with more effective combinations of targeted agents, because a single target is not enough:
• Gynecological cancers, as most solid tumors, are not sufficient “addict” to a single oncogen.
Thank you!!