What I shall discuss

• Clinical behaviour
• Biology
• Future trials and treatments
Current view of ovarian cancer biology

Histologically Distinct

First described in 1939 as mesonephroma ovari.
Cells arranged in tubules, nests or cysts.
Clear, glycogen-rich cytoplasm.
Immunophenotype: ER and WT1 –ve, HNF-1β +ve*

*Kobel et al/ Am J Surg Pathol 2009
Clinical Behaviour

• Younger (median 55 v 64 yr)
• Endometriosis
• Venous thromboembolic complications
• Hypercalcaemia
• More likely to present at an early stage
  - (Stage 1: 50% v <20% in HGS)
  - EORTC-ACTION: 5Y DFS 71% in CCC v 61% in serous cancer
Real clinical experience (my own….)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. cases</th>
<th>%</th>
<th>No. deaths</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Grade Serous</td>
<td>294</td>
<td>74.1</td>
<td>99</td>
<td>79.8</td>
</tr>
<tr>
<td>Low Grade Serous</td>
<td>15</td>
<td>3.8</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>33</td>
<td>8.3</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>27</td>
<td>6.8</td>
<td>9</td>
<td>7.3</td>
</tr>
<tr>
<td>Mucinous</td>
<td>8</td>
<td>2.0</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>14</td>
<td>3.5</td>
<td>7</td>
<td>5.6</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4</td>
<td>1.0</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Adenocarcinoma NOS</td>
<td>2</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>397</td>
<td>124</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>HGS</th>
<th>%</th>
<th>Clear cell</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1A+1B</td>
<td>7</td>
<td>2.4</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Stage 1C</td>
<td>9</td>
<td>3.1</td>
<td>14</td>
<td>51.9</td>
</tr>
<tr>
<td>Stage 2</td>
<td>18</td>
<td>6.1</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Stage 3A+3B</td>
<td>12</td>
<td>4.1</td>
<td>4</td>
<td>14.8</td>
</tr>
<tr>
<td>Stage 3C</td>
<td>175</td>
<td>59.5</td>
<td>5</td>
<td>18.5</td>
</tr>
<tr>
<td>Stage 4</td>
<td>73</td>
<td>24.8</td>
<td>3</td>
<td>11.1</td>
</tr>
<tr>
<td>Total</td>
<td>294</td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McNeish/Glasspool Beatson Cancer Centre newly diagnosed patients 2013 – 2017
Prognostic Relevance of Uncommon Ovarian Histology in Women With Stage III/IV Epithelial Ovarian Cancer

Helen J. Mackay, MD,* Mark F. Brady,† Amit M. Oza,* Alexander Reuss,‡ Eric Pujade-Lauraine,§ Ann M. Swart,∥ Nadeem Siddiqui,¶ Nicoletta Colombo,** Michael A. Bookman,† Jacobus Pfisterer,‡ and Andreas du Bois,∥ and on behalf of the Gynecologic Cancer InterGroup

A

Progression Free Survival
Stage 3/4 Only

<table>
<thead>
<tr>
<th>Histology</th>
<th>Rel. Haz. Var([ln(HR)])</th>
<th>Better than Serous</th>
<th>Worse than Serous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid Adeno</td>
<td>0.888</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Mucinous Adenocarcinoma</td>
<td>2.106</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Clear Cell</td>
<td>1.644</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Transitional Cell</td>
<td>0.869</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>Mixed Epithelial</td>
<td>0.906</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Undiff. Adenocarcinoma</td>
<td>0.989</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>1.168</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.241</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

B

Overall Survival
Stage 3/4 Only

<table>
<thead>
<tr>
<th>Histology</th>
<th>Rel. Haz. Var([ln(HR)])</th>
<th>Better than Serous</th>
<th>Worse than Serous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid Adeno</td>
<td>0.952</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Mucinous Adenocarcinoma</td>
<td>2.657</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Clear Cell</td>
<td>2.176</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Transitional Cell</td>
<td>0.700</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>Mixed Epithelial</td>
<td>1.029</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Undiff. Adenocarcinoma</td>
<td>1.068</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>1.350</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.478</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>
PFS and OS in GCIG trials

Only phase III trial specifically in clear cell carcinoma

- N = 677
- Stage I – IV
- Carboplatin (AUC6) + paclitaxel (175mg/m²) q3/52 vs.
- Irinotecan (60mg/m² weekly) + cisplatin (60mg/m²) q3/52
- Primary endpoint = PFS
- Central pathology review following registration: 43/667 (6.4%) ineligible
- 32 (5.2%) had measureable disease – overall response rate 37.5%

Chemotherapy in early stage clear cell

Histologic cell type
- serous: 27/161, 33/139
- mucinous: 10/90, 22/90
- endometrioid: 13/94, 20/129
- clear: 16/68, 17/62
- undifferentiated: 3/9, 2/7
- other: 3/23, 3/19

Interaction $\chi^2(5) = 4.099$, $P = 0.55$


Does stage IA clear cell need chemotherapy?

Does stage IA clear cell need chemotherapy?

Table 2. Five-Year DFS in the Modern Era

<table>
<thead>
<tr>
<th>Study Characteristic and DFS</th>
<th>Chan et al&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Takano et al&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Suzuki et al&lt;sup&gt;26&lt;/sup&gt;</th>
<th>Sugiyama et al&lt;sup&gt;10&lt;/sup&gt;</th>
<th>Mizuno et al&lt;sup&gt;10&lt;/sup&gt;</th>
<th>Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1,411</td>
<td>254</td>
<td>143</td>
<td>49</td>
<td>82</td>
<td>241</td>
</tr>
<tr>
<td>Country</td>
<td>United States</td>
<td>Japan</td>
<td>Japan</td>
<td>Japan</td>
<td>Japan</td>
<td>Canada</td>
</tr>
<tr>
<td>Disease-free survival by stage, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>92</td>
<td>96</td>
<td>100</td>
<td>96</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>77</td>
<td>77</td>
<td>63</td>
<td>76</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>IC (rupture alone)</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC (other)*</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>66</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: DFS, disease-free survival.
*Stage IC (other): cytologic positivity and/or surface involvement.
Does radiotherapy play a role?

Stage IC2/II

B

Disease-Free Survival

0 0.2 0.4 0.6 0.8 1.0

Time (weeks)

RR, 0.54 (P = .02)
Relapsed ovarian clear cell carcinoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total</th>
<th>% clear cell</th>
<th>% clear cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALYPSO</td>
<td>973</td>
<td>27</td>
<td>2.8</td>
</tr>
<tr>
<td>OCEANS</td>
<td>484</td>
<td>13</td>
<td>2.7</td>
</tr>
<tr>
<td>AURELIA</td>
<td>361</td>
<td>16</td>
<td>4.4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1818</td>
<td>56</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study

M. TAKANO*, T. SUGIYAMA†, N. YAEGASHI‡, M. SAKUMA‡, M. SUZUKI§, Y. SAGA§, K. KUZUYA¶, J. KICAWA¶, M. SHIMADA¶, H. TSUDA¶, T. MORIYA**, A. YOSHIZAKI†, T. KITA* & Y. KIKUCHI*

*Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Saitama, Japan; †Department of Obstetrics and Gynecology, Jichi Medical College, Kusasenri-gun, Tochigi, Japan; ‡Department of Obstetrics and Gynecology, Nakamura-gun, Tochigi, Japan; §Department of Obstetrics and Gynecology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; ¶Department of Obstetrics and Gynecology, Tottori University, Yonago, Tottori, Japan; ¶¶Department of Pathology II, National Defense Medical College, Tokorozawa, Saitama, Japan; and **Pathology Laboratory of Central Clinical Facilities, Tohoku University, Sendai, Miyagi, Japan


SaPPROC

RR, N (%)

- HGS/G3 endometrioid: 25/76 (37.3%)
- LGS: 2/6 (33.3%)


What I shall discuss

- Clinical behaviour
- Biology
- Future trials and treatments
Different Biology

- TP53 wild type and BRCA mutations rare
- Some genomic instability but far less than HGSC
- Gene expression – angiogenesis and IL-6
- ARID1A (c.50%) mutation
- PIK3CA (c.33%) mutation
- MET amplification
Endometriosis

Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies

Endometriosis

Endometriosis

Endometriosis

• Sequenced CCC, endometriosis (atypical and typical)
• Up to 98% CCC mutations seen in endometriosis
• No unique mutations in CCC
• Atypical endometriosis ‘borderline CCC’
IL-6 in endometriosis

Interleukin 1β, interleukin-6, and tumor necrosis factor-α in endometriotic tissue and in endometrium

Agneta Bergqvist, M.D., Ph.D., Christine Bruse, M.D., Magdalena Carlberg, Ph.D., and Kjell Carlström, Ph.D.

Nuclear factor κB pathway and interleukin-6 are affected in eutopic endometrium of women with endometriosis

Carlos Ponce1, Marisa Torres1, Carolina Galleguillos1, Hugo Sovino1,2, M Angélica Boric1, Ariel Fuentes1,2 and M Cecilia Johnson1

1 School of Medicine, Institute of Maternal and Child Research and 2 San Borja Arriarán Clinical Hospital, University of Chile, PO Box 226-3, Santiago, Chile

Correspondence should be addressed to M C Johnson; Email: cjohnson@med.uchile.cl


Gene expression

Interleukin-6 signalling

Consequences of interleukin-6 signalling

Chemotherapy resistance

Proliferation

Migration and invasion

Th17 cell differentiation

MΦ differentiation

Jim Coward – PhD thesis, Barts Cancer Institute
IL-6 in Clear Cell Carcinoma

Gene expression and inflammatory cytokines

IL-6 in Clear Cell Carcinoma

Baseline data

- CAOV3
- SKOV-3
- TOV21G
- OVTOKO
- OVMANA
- JHOC-5
- JHOC-7
- JHOC-9

[Graph showing IL-6 levels in different cell lines]
Interleukin-6, platelets and ovarian cancer

Paraneoplastic Thrombocytosis in Ovarian Cancer

Plasma IL-6 and OS

Proportion Alive (%)

Plasma IL-6 levels (pg/mL)

Tumor IL-6 mRNA (normalized to control)

Proportion Alive (%)

IL-6 in Castleman’s Disease

Siltuximab for multicentric Castleman’s disease: a randomised, double-blind, placebo-controlled trial

Frits van Rhee, Raymond S Wong, Nikhil Munshi, Jean-Francois Rossi, Xiao-Yan Ke, Alexander Fossá, David Simpson, Marcelo Capra, Ting Liu, Ruey Kuen Hsieh, Yeow Tee Goh, Jun Zhu, Seok-Goo Cho, Hanyun Ren, James Cavet, Rajesh Bandekar, Margaret Rothman, Thomas A Puchalski, Manjula Reddy, Helgi van de Velde, Jessica Vermeulen, Corey Casper
• aCGH on 50 CCC samples
• Two copy number clusters
• Common amplicons 20q13, 17q23.2
• HER2 amplified in 14% cases

**ARID1A mutations**

**Frequent Mutations of Chromatin Remodeling Gene ARID1A in Ovarian Clear Cell Carcinoma**


**ARID1A Mutations in Endometriosis-Associated Ovarian Carcinomas**

SWI/SNF complex

ARID1A mutations and DNA damage

**Short Communication**

Frequent Activating Mutations of PIK3CA in Ovarian Clear Cell Carcinoma

**Table 2.** Sequence Mutation Rates in Ovarian Clear Cell Carcinomas

<table>
<thead>
<tr>
<th>Sample (n)</th>
<th>KRAS</th>
<th>BRAF</th>
<th>TP53</th>
<th>PIK3CA</th>
<th>CTNNB1</th>
<th>PTEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>JH (10)</td>
<td>20%</td>
<td>0%</td>
<td>10%</td>
<td>50%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>TW (8)</td>
<td>0%</td>
<td>0%</td>
<td>ND</td>
<td>50%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Cell line (10)</td>
<td>10%</td>
<td>10%</td>
<td>20%</td>
<td>40%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>TW-paraffin (44)</td>
<td>9%</td>
<td>0%</td>
<td>ND</td>
<td>25%</td>
<td>2%</td>
<td>ND</td>
</tr>
<tr>
<td>JP-paraffin (25)</td>
<td>0%</td>
<td>0%</td>
<td>ND</td>
<td>32%</td>
<td>8%</td>
<td>ND</td>
</tr>
<tr>
<td>Overall: non-paraffin (JH + TW + Cell line)</td>
<td>11%</td>
<td>3%</td>
<td>15%</td>
<td>46%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Overall (97)</td>
<td>7%</td>
<td>1%</td>
<td>15%</td>
<td>33%</td>
<td>1%</td>
<td>5%</td>
</tr>
</tbody>
</table>


Coexistent ARID1A–PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signalling


Transgenic mice (Arid1afl/fl;Gt(Rosa26Pik3caH1047R))

• Ovarian surface epithelium
  • Bi-allelic loss of Arid1a
  • Knock-in of mutant Pik3ca

• CCC-like tumours
  • IL-6
  • HIF1a

Angiogenesis

Vascular Endothelial Growth Factor Is a Promising Therapeutic Target for the Treatment of Clear Cell Carcinoma of the Ovary

Seiji Mabuchi1, Chiaki Kawase1, Deborah A. Altomare4, Kenichirou Morishige1, Masami Hayashi1, Kenjiro Sawai1, Kimitiko Ito6, Yoshito Tera7, Yukihito Nishio2, Andrés J. Klein-Szanto5, Robert A. Burger4, Masahide Ohmichi5, Joseph R. Testa4, and Tadashi Kimura1

Table 1. VEGF immunoreactivity by histology and clinical stage

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Immunoreactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero, n (%)</td>
<td>Weak (+0.5 or 1), n (%)</td>
</tr>
<tr>
<td>CCOs</td>
<td>Stage I-II</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Stage III-IV</td>
<td>25</td>
</tr>
</tbody>
</table>

But, ICON7 data...

<table>
<thead>
<tr>
<th></th>
<th>Standard therapy (n=77)</th>
<th>Bevacizumab (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration (months)</td>
<td>52.5 (29.0-57.5)</td>
<td>50.7 (28.2-57.9)</td>
</tr>
<tr>
<td>Deaths</td>
<td>20 (26%)</td>
<td>24 (29%)</td>
</tr>
<tr>
<td>Log-rank test p-value</td>
<td>p=0.74</td>
<td></td>
</tr>
<tr>
<td>Non-proportionality p-value†</td>
<td>p=0.58</td>
<td></td>
</tr>
<tr>
<td>(Restricted) mean survival time (months; 95% CI)</td>
<td>48.0 (43.9-52.2)</td>
<td>47.6 (43.6-51.6)</td>
</tr>
<tr>
<td>Restricted mean survival time difference (95% CI)</td>
<td>-0.4 (-6.1 to 5.3)</td>
<td></td>
</tr>
</tbody>
</table>

NICCC: Nintedanib in Clear Cell Cancer

Cl: Ros Glasspool, Glasgow
Translational lead: Iain McNeish

SGCTG/NCRI/NSGO
EORTC/GINECO
NICCC: Nintedanib in Clear Cell Cancer

90 pts with progressive or relapsed CCC of ovary within 6 months of previous platinum
Plus up to 30 women with endometrial CCC

Primary Endpoint: PFS
Secondary Endpoints: OS, Toxicity, RR, QoL, Q-Twist

Chemotherapy

Ovary:
- PLD (40mg/m² d1q28)
- Weekly Paclitaxel (80mg/m² d1, 8, 15 q28)
- Weekly Topotecan iv (4mg/m² d1, 8, 15 q28)

Endometrium:
- Carboplatin (AUC 5) /Paclitaxel 175 mg/m² q21
- Doxorubicin 60mg/m² q21

Nintedanib 200mg bd until progression
NICCC: Nintedanib in Clear Cell Cancer
Other potential therapeutic targets

• MET
• HNF1β
• ?HER2
Other clear cell-specific trials from clinicaltrials.gov

- A Study of ENMD-2076 in Ovarian Clear Cell Cancers (recruiting)
- Sunitinib Malate in Treating Patients With Persistent or Recurrent Clear Cell Ovarian Cancer (active not recruiting)
Summary and future directions

- Stage IA/B (and possibly) stage IC1 patients may not need chemotherapy
- Carboplatin and paclitaxel remains standard first-line therapy
- Radiotherapy may play a role in early stage disease
- In relapsed disease, platinum-free interval may not matter
- Current phase II trials target angiogenesis
- Future trials must target IL-6, MET [alone or combined with angiogenesis inhibitors]