Precision Medicine in Epithelial Ovarian Cancer

Iain McNeish

Professor of Oncology, Imperial College London
Disclosures

- I have sat on Advisory Boards for Clovis Oncology, Tesaro, AstraZeneca and Takeda.

- Co-chief investigator ARIEL2 (Clovis Oncology)

- Chief Investigator OCTAVE (PsiOxus Therapeutics)

- My institution receives grant support from AstraZeneca
Ovarian cancer is not like a Mondrian painting

Line over form (1922) – Piet Mondrian
Ovarian cancer is more like this

Convergence (1952) – Jackson Pollock
Current view of ovarian cancer biology

- Mucinous invasive
  - KRas
- Endometrioid
  - PI3K
  - B-catenin
  - PTEN
- Clear cell
  - ARID1A
  - PI3K
  - IL-6/HIF1a
- High-grade serous
  - p53
  - HRD
  - CNA
- Low grade serous
  - Kras
  - Braf

Vaughan et al Nat Rev Cancer (2011) 11:719
Data on non-HGSC disease are very limited

### CALYPSO

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>700</td>
<td>71.9</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>73</td>
<td>7.5</td>
</tr>
<tr>
<td>Clear cell</td>
<td>27</td>
<td>2.8</td>
</tr>
<tr>
<td>Mucinous</td>
<td>17</td>
<td>1.7</td>
</tr>
<tr>
<td>Other</td>
<td>104</td>
<td>10.7</td>
</tr>
<tr>
<td>Unspecified</td>
<td>52</td>
<td>5.3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>973</td>
<td></td>
</tr>
</tbody>
</table>

### OCEANS

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>391</td>
<td>80.8</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>29</td>
<td>6.0</td>
</tr>
<tr>
<td>Clear cell</td>
<td>15</td>
<td>3.1</td>
</tr>
<tr>
<td>Mucinous</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Other</td>
<td>45</td>
<td>9.3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>484</td>
<td></td>
</tr>
</tbody>
</table>

Clear cell carcinoma - response rates are dismal

Table 2. Response to second-line chemotherapy in the patients with treatment-free period 6 months or more (group A) and with treatment-free period less than 6 months (group B)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Response rate(^a) (%)</th>
<th>Non-PD rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP, CP</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Platinum + etoposide</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paclitaxel + platinum</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Docetaxel + platinum</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CPT-11 + platinum</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>14</td>
<td>57</td>
</tr>
<tr>
<td>CPT-11 + mitomycin C</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>2</td>
<td>5</td>
<td>17</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>CAP, CP</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platinum + etoposide</td>
<td>2</td>
<td>0</td>
<td>9</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Paclitaxel + platinum</td>
<td>0</td>
<td>2</td>
<td>15</td>
<td>0</td>
<td>12</td>
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<tr>
<td>Docetaxel + platinum</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weekly paclitaxel</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CPT-11 + platinum</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>CPT-11 + mitomycin C</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>CPT-11 + docetaxel</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MEP</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>3</td>
<td>6</td>
<td>42</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5</td>
<td>11</td>
<td>59</td>
<td>6.7</td>
<td>21</td>
</tr>
</tbody>
</table>

\(^a\) Response rate calculated as the number of partial responses (PR) plus the number of stable diseases (SD) divided by the total number of patients in each group.
A Randomised Phase II study Of Nintedanib (BIBF1120) Compared To Chemotherapy in Patients With Recurrent Clear Cell Carcinoma Of The Ovary Or Endometrium

EudraCT Number:2013-002109-73

ISRCTN50772895
NiCCC Recruitment

G143 NiCCC - Target vs Actual Recruitment
Ovarian Patients Only

- Number of Patients Recruited
- Period (Apr-15 to Apr-19)
- UK Sites
- EORTC Sites
- GINECO Sites
- NSCO Sites
- Overall Recruitment
- UK Recruitment
- International Recruitment
- Target Recruitment

Number of Patients Recruited per Site
Low grade serous carcinoma

Array BioPharma Announces Decision To Discontinue MILO Study In Ovarian Cancer

1st April 2016

Case report
Binimetinib (MEK162) in recurrent low-grade serous ovarian cancer resistant to chemotherapy and hormonal treatment
Chanhee Han, Stefania Bellone, Luca Zammataro, Peter E. Schwartz, Alessandro D. Santin*  
Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520, USA


Case report
Dramatic clinical response following dabrafenib and trametinib therapy in a heavily pretreated low grade serous ovarian carcinoma patient with a BRAF V600E mutation
Alberto A. Mendevil*, Paul K. Tung*, Randy Bohart*, Karen Bechtol*, Bram H. Goldstein*+*
*Gynecologic Oncology Associates, Newport Beach, CA 92663, United States
+University of California, Irvine, Department of Radiological Sciences, 1001 Health Sciences Road, Irvine, CA 92697-3950, United States
*Onc Home Care, 17175 Gillette Avenue, Irvine, CA 92614, United States


Current view of ovarian cancer biology

- **Stomach**
- **Colon**
- **Appendix**
- **Retrograde menstruation**
- **Uterus**
- **Fallopian tube**
- **Ovary**

### Gene Expression

- **Mucinous invasive**
  - KRas
  - PI3K
  - B-catenin
  - PTEN

- **Endometrioid**
  - ARID1A
  - PI3K
  - IL-6/HIF1a

- **Clear cell**
  - p53
  - HRD
  - CNA

- **High-grade serous**
  - Kras
  - Braf

- **Low grade serous**

**References**
Ovarian high-grade serous carcinoma

• Mostly arises in distal fallopian tube

Journal of Pathology
J Pathol 2007; 211: 26–35
Published online 20 November 2006 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/path.2091

Original Paper

A candidate precursor to serous carcinoma that originates in the distal fallopian tube

Y Lee,† A Miron,‡ R Drapkin,† MR Nucci,† F Medeiros,† A Saleemuddin,† J Garber,‡ C Birch,† H Mou,‡
RW Gordon,‡ DW Cramer,§ FD McKeon¶ and CP Crum† *

†Division of Women’s and Perinatal Pathology, Department of Pathology, Brigham and Women’s Hospital, Boston, MA, USA
‡Department of Cancer Biology, Dana-Farber Cancer Institute, USA
§Department of Medical Oncology, Dana-Farber Cancer Institute, USA
¶Department of Cell Biology, Harvard Medical School, USA
§Obstetrical and Gynecologic Epidemiology, Department of Obstetrics and Gynecology, Brigham and Women’s Hospital, Boston, MA, USA

Lee et al, J Pathol (2007) 211:26

Ovarian high-grade serous carcinoma

• Ovarian surface epithelium may still contribute...

Both Fallopian Tube and Ovarian Surface Epithelium Can Act as Cell-of-Origin for High Grade Serous Ovarian Carcinoma

Shuang Zhang#, Tao Zhang, Igor Dolgalev, Hao Ran, Douglas A. Levine, Benjamin G. Neel#

Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, 10016, USA.

#Corresponding authors: Benjamin G. Neel, New York University School of Medicine, 522 First Avenue, Smilow Building 12th Floor, Suite 1201, New York, NY 10016. Phone: 212-263-3019; Fax: 212-263-9190; E-mail: Benjamin.Neel@nyumc.org; Shuang.Zhang@nyumc.org
Genomic aberrations in HGSC

Original design - Doug Levine, NYU

Germline BRCA1 mutation
Germline BRCA2 mutation
Somatic BRCA1 mutation
Somatic BRCA2 mutation
Epigenetic BRCA1 loss
FANC gene mutation
Core HR gene mutation
Core DDR gene mutation
CCNE1 amplification
NF1 loss
RB1 loss
PTEN loss

Etemad moghadam, D et al CCR (2009) 15:1417
HGSC is driven by copy number (CN) change

This is normal...!
Most progress has been in good-prognosis disease
PARP inhibitors in *BRCA1/2*-mutated disease

Genomic aberrations beyond BRCA1/2

- Germline BRCA1 mutation
- Germline BRCA2 mutation
- Somatic BRCA1 mutation
- Somatic BRCA2 mutation
- Epigenetic BRCA1 loss
- FANC gene mutation
- Core HR gene mutation
- Core DDR gene mutation
- CCNE1 amplification
- PTEN loss
- RB1 loss
- NF1 loss

Survival analysis showing BRCA mutated, BRCA1 epigenetically silenced, and BRCA wild type with a Log-rank test P = 0.0008602.

Original design - Doug Levine, NYU

Methylation states

Homozygous

Heterozygous

Hemizygous

Partial

Methylation and rucaparib - ARIEL2

Resistance to therapy caused by intragenic deletion in BRCA2

Stacey L. Edwards\textsuperscript{1}, Rachel Brough\textsuperscript{1}, Christopher J. Lord\textsuperscript{1}, Rachael Natrajan\textsuperscript{1}, Radost Vatcheva\textsuperscript{1}, Douglas A. Levine\textsuperscript{5}, Jeff Boyd\textsuperscript{1}, Jorge S. Reis-Filho\textsuperscript{1} & Alan Ashworth\textsuperscript{1}

Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers

Wataru Sakai\textsuperscript{1,2}, Elizabeth M. Swisher\textsuperscript{3,4}, Beth Y. Karlan\textsuperscript{3}, Mukesh K. Agarwal\textsuperscript{5}, Jake Higgins\textsuperscript{4,7}, Cynthia Friedman\textsuperscript{1}, Emily Villegas\textsuperscript{1,2}, Céline Jacquemont\textsuperscript{1,2}, Daniel J. Farrugia\textsuperscript{6}, Fergus J. Couch\textsuperscript{6}, Nicole Urban\textsuperscript{7} & Toshiyasu Taniguchi\textsuperscript{1,2}


Norquist et al (2011) JCO 29:3008
BRCA reversion mutations in pre-rucaparib treatment cfDNA and tumour biopsy

## BRCA reversion mutations in pre-rucaparib treatment cfDNA and tumour biopsy

<table>
<thead>
<tr>
<th>Platinum status</th>
<th>Cases with primary BRCA and TP53 mut detected</th>
<th>Cases with BRCA reversion mut detected</th>
<th>BRCA reversion mut frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive</td>
<td>48</td>
<td>1*</td>
<td>2.1%</td>
</tr>
<tr>
<td>Resistant</td>
<td>35</td>
<td>5</td>
<td>14.3%</td>
</tr>
<tr>
<td>Refractory</td>
<td>14</td>
<td>2</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

* Detected at MAF=0.42%

Overall reversion rate in cfDNA pre-rucaparib = 8/97 (8.2%)

ARIEL2 - PFS according to reversion vs non-reversion

As of clinical data cut-off of 4JAN2018

BRCA reversion mutations detected in post-progression cfDNA

<table>
<thead>
<tr>
<th>Platinum status</th>
<th>Cases with primary BRCA and TP53 mut detected</th>
<th>Cases with BRCA reversion mut detected</th>
<th>BRCA reversion mut frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive</td>
<td>27</td>
<td>3 (1 also found in pre-tx)</td>
<td>11.1%</td>
</tr>
<tr>
<td>Resistant</td>
<td>27</td>
<td>8 (5 also found in pre-tx)</td>
<td>29.6%</td>
</tr>
<tr>
<td>Refractory</td>
<td>11</td>
<td>4 (1 also found in pre-tx)</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

Overall reversion rate in cfDNA at progression = 15/65 (23.1%)

Can we identify meaningful patterns in apparent CN chaos?
Convergence (1952) – Jackson Pollock

Archæan (1981) – Bridget Riley
Mutational signatures

- Mutations are an *archaeological* record of exposure to mutational processes
- Signatures are the *patterns* of mutational processes
- Individual cancers have *multiple* mutational signatures

Can we do the same with copy number?

Copy-number profile
CN signature identification

a

Compute absolute CN from shallow WGS

Derive CN feature distributions

Fit optimal number of mixture model components

Are the CN signatures robust?

![Diagram showing CN signatures and their robustness across different metrics: Breakpoint count per 10MB (N=3), Copy number (N=8), Copy number changepoint (N=7), Breakpoint count per chromosome arm (N=5), Oscillating CN length (N=3), Segment size (N=10). The values range from 0.0 to 0.8.](image)

Are the CN signatures robust?

p < 0.005

BriTROC sWGS (N=117)  PCAWG-OV WGS (N=112)  TCGA SNP array (N=415)

Breakpoint count per 10MB (N=3)
Copy number (N=8)
Copy number changepoint (N=7)
Breakpoint count per chromosome arm (N=5)
Oscillating CN length (N=3)
Segment size (N=10)

CN signatures
Do CN signatures reflect the underlying mutational processes?

1. Oncogenic MAPK signalling

2. Tandem duplications, CDK12 mutation

3. BRCA1/2 HRD

4. WGD

5. Chromothripsis

6. Aberrant cell cycle (CCNE1)

7. Non-BRCA1/2 HRD

CN signatures predict survival

Risk of death
Tumors ordered by decreasing risk of death (n=575)

Stacked signature exposures
Smoothed signature exposures
Unsupervised clustering

Patients have multiple signatures

- MAPK signalling
- BRCA1/2 HRD N=130 (22%)
- WGD PI3K
- Chromothripsis

BRCA2 germline mutation carriers + somatic LOH (n=4)

Could CN signatures predict treatment?

BRCA2 germline mutation carriers + somatic LOH (n=4)

Signature
1
2
3
4
5
6
7

MAPK signalling - MEK inhibitor
BRCA1/2 HRD - PARP inhibitor
WGD PI3K - mTORC1/2 inhibitor
Chromothripsis

What about relapse?

Histology

- TP53: 94%
- KRAS: 5%
- PTEN: 2%
- PIK3CA: 2%

Anna Piskorz - unpublished
Comparison of diagnosis and relapse
Overall Similar Genomic LOH Levels Between Matched Archival Tumours and Screening Biopsies

Key challenges moving biology to the clinic
Conclusions

• Knowledge of tumour biology into our treatment strategies
• Trials in the rarer subtypes completely essential
• CN signatures suggest rational approaches for combination therapy
• Assessment of disease at relapse important - including methylation and cfDNA
• Functional assays required to assess what processes are active at any given time