Influence of Molecular Pathology on Ovarian Cancer Treatment Now and in the Future

Charlie Gourley
Professor of Medical Oncology
University of Edinburgh Cancer Research Centre
Disclosures

• Personal interests:
  • Roche, PharmaMar, Boehringer Ingelheim, Caris Life Sciences, Almac Diagnostics

• Non-personal interests:
  • Roche, AstraZeneca, GlaxoSmithKline, Cyclacel
Ovarian cancer; standard first-line treatment

- Maximal debulking surgery
- 6 cycles of carboplatin and paclitaxel chemotherapy
- ‘One size fits all’ approach
- Histological subtypes differ in response to chemotherapy, survival, genetics and tissue of origin
Which predictive biomarkers have made it into ‘standard’ practice?
Which predictive biomarkers have made it into ‘standard’ practice?

1. Histological subtype

Kurman and Shih, Human Pathol 2011
Which predictive biomarkers have made it into ‘standard’ practice?

1. Histological subtype
2. ER expression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CA125 response</th>
<th>CA125 nonprogressor</th>
<th>CA125 progressor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER 250-300</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ER 200-249</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>ER 150-199</td>
<td>0</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Bowman et al, 2001
Smyth et al, 2007
Influence of molecular pathology on ovarian cancer clinical research

1) Biological agents in early development which have a defined target (patients selected on basis of molecular test)

2) Biological agents in later development which have a defined MOA but for whom the selection criteria remain unclear

3) Licensed agent(s) currently given to all patients but for whom the ability to select patients would be beneficial
Example 1

Low grade serous ovarian cancer
Low grade serous ovarian cancer

- Often presents early in association with serous borderline tumour
- Increased risk in patients with a history of endometriosis (HR 2.11, 1.39–3.20, p<0.0001)
- Median/mean age: 43/45 years
- Comprises 10–15% of serous carcinoma
- For stage II–IV disease – median PFS: 19 months median OS: 81 months
- Often calcified disease

Systemic treatment of low-grade serous ovarian cancer: Retrospective data

- Response to platinum-based chemotherapy: <5%
  - First line: 4% response, 88% disease stabilization
  - Second line: 3.7% response, 60% disease stabilization
- Response to hormonal therapy: around 10%
  - Response to endocrine therapy: 9% in retrospective analysis
  - ER+/PR+ had longer TTP than ER+/PR− (p=0.053, 64 patients)

ER = oestrogen receptor; PR = progesterone receptor; TTP = time to progression.

Mutation profile of low versus high grade serous ovarian cancer

SBT = serous borderline tumours; LG = low grade; HG = high grade.
KRAS    BRAF    MEK    MAPK (ERK)    cyclin D1    GLUT1

Progression    Survival    Proliferation

cadherin

β-catenin

RTK

ERRB2

PTEN

PI3K

AKT

mTOR

TP53

ERRB2 mutations

KRAS mutations

BRAF mutations

cyclin E

β-catenin

LEF/TCF

MAPK (ERK)

cyclin D1    GLUT1
Low grade with KRAS/BRAF mut more sensitive to MEKi in vitro than high grade

Mutation status

<table>
<thead>
<tr>
<th>KRAS</th>
<th>BRAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>mut</td>
</tr>
<tr>
<td>mut</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>mut</td>
</tr>
<tr>
<td>mut</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>mut</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>wt</td>
<td>wt</td>
</tr>
</tbody>
</table>

Cell number (% of DMSO controls)

GOG 239 study

• Phase II study of MEK inhibitor AZD 6244, (selumetinib) 100 mg b.i.d.

• 52 patients

• Primary endpoint: response rate

• Heavily pretreated (58% at least 3 prior treatment regimens)

• 15% response rate, 65% stable disease

• Median PFS: 11 months

• 6% BRAF, 41% KRAS, 15% NRAS mutations

• No correlation of mutation status with response

Farley et al, Lancet Oncol 2013
LOGS study

- Randomized 2-arm Phase II/III of MEK inhibitor trametinib vs control in relapsed low-grade serous ovarian cancer
- Control arm nominated prior to randomization
  - Weekly paclitaxel
  - Pegylated liposomal doxorubicin
  - Weekly topotecan
  - Letrozole
  - Tamoxifen
- 80 centres across USA and UK
- 250 patients
- Translational plans include NGS, gene expression microarray analysis, proteomics and optional biopsies at relapse (investigation of MEKi and hormonal sensitivity/resistance)

CTAAC = Clinical Trials Advisory and Awards Committee
Example 2

PARP inhibition in the treatment of high grade serous ovarian cancer
Poly (ADP-Ribose) Polymerase (PARP)

DNA damage → PARP → PAR → PARP modifies itself and produces large branched chains of Poly(ADP-ribose) → DNA repair enzymes → repaired DNA → PARP binds to single strand breaks → NAD+ is required → nicotinamide + pADPr is involved.
PARP inhibition and tumour-selective synthetic lethality


Slide provided with permission by Andrew Tutt
PARP inhibition and tumour-selective synthetic synthetic lethality

BRCA1<sup>−/−</sup> and BRCA2<sup>−/−</sup> cells are extremely sensitive to PARP inhibition.

No difference in sensitivity between heterozygous and wild-type BRCA cells.

Targeted inhibition → selective and less toxic therapy.

Farmer et al. Nature 2005; 434:917-21
Poly(ADP)-Ribose Polymerase Inhibition: Frequent Durable Responses in BRCA Carrier Ovarian Cancer Correlating With Platinum-Free Interval

Peter G. Fong, Timothy A. Yap, David S. Boss, Craig P. Carden, Marja Mergui-Roelvink, Charlie Gourley, Jacques De Greve, Jan Lubinski, Susan Shanley, Christina Messiou, Roger A’Hern, Andrew Tutt, Alan Ashworth, John Stone, James Carmichael, Jan H.M. Schellens, Johann S. de Bono, and Stan B. Kaye

- Non-toxic, oral therapy
- Specifically active in BRCA1/2-deficient patients
- 70% response rate in platinum sensitive patients
- 44% response rate in platinum resistant patients
- 18% response rate in platinum refractory patients
- A number of patients remain in remission 36 months into treatment
Is it only BRCA1/2 germline mutation carriers who benefit from PARP inhibitors?
Is it only BRCA1/2 germline mutation carriers who benefit from PARP inhibitors?

TCGA, Levine et al, Nature 2011
Study aim and design

- To assess the efficacy of oral olaparib as a maintenance treatment in patients with platinum-sensitive high-grade serous ovarian cancer
- Randomized, double-blind, placebo-controlled Phase II study
- Multinational study; 82 sites in 16 countries

Patient eligibility:
- Platinum-sensitive high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy: platinum-based with a maintained response
- Stable CA125 at trial entry
- Randomization stratification factors:
  - Time to disease progression on penultimate platinum therapy
  - Objective response to last platinum therapy
  - Ethnic descent

Treatment until disease progression

Olaparib 400 mg po bid
Randomized 1:1
Placebo po bid

Ledermann et al, ASCO 2011
Progression-free survival

- **Olaparib** vs **Placebo**
- **No. of events: Total patients (%)**
  - Olaparib: 60:136 (44.1)
  - Placebo: 93:129 (72.1)

- **Median PFS (months)**
  - Olaparib: 8.4
  - Placebo: 4.8

- **Hazard ratio 0.35 (95% CI, 0.25–0.49)**
  - *P* < 0.00001

- **Randomized treatment**
  - Placebo
  - Olaparib 400 mg bid

- **At risk (n)**
  - **Olaparib**: 136, 104, 51, 23, 6, 0, 0
  - **Placebo**: 129, 72, 23, 7, 1, 0, 0

Ledermann et al, NEJM, 2012
Results: BRCA testing

<table>
<thead>
<tr>
<th>gBRCA</th>
<th>tBRCA</th>
<th>Mutated</th>
<th>Wild type*</th>
<th>Not available</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutated</td>
<td></td>
<td>71</td>
<td>3</td>
<td>22</td>
<td>96</td>
</tr>
<tr>
<td>Wild type*</td>
<td></td>
<td>20</td>
<td>79</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td></td>
<td>20</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

- 136 (51.3%) patients had a known deleterious BRCAm (BRCAm dataset)
- 118 (44.5%) patients were defined as BRCA1/2 wild type for this analysis
- 11 (4.2%) patients had neither a tumour nor a germline result available

• The number of patients with a known BRCAm status increased from 97 (36.6%) to 254 (95.8%) out of 265

*Wild-type group includes patients with no known BRCAm or a mutation of unknown significance (a non-deleterious mutation)
PFS by BRCAm status

- 82% reduction in risk of disease progression or death with olaparib

<table>
<thead>
<tr>
<th>BRCAm (n=136)</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events: total pts (%)</td>
<td>26:74 (35.1)</td>
<td>46:62 (74.2)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>11.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

HR=0.18
95% CI (0.11, 0.31); P<0.00001
PFS by BRCAm status

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>BRCAm (n=136)</th>
<th>BRCAwt (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events: total pts (%)</td>
<td>Olaparib</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>26:74 (35.1)</td>
<td>46:62 (74.2)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>11.2</td>
<td>4.3</td>
</tr>
<tr>
<td>HR=0.18</td>
<td>95% CI (0.11, 0.31); P&lt;0.00001</td>
<td>HR=0.53</td>
</tr>
</tbody>
</table>

BRCAwt, wild type (includes patients with no known BRCAm or a mutation of unknown significance)
Example 3

Bevacizumab in the first or second line treatment of advanced ovarian cancer
A Phase 3 Trial of Bevacizumab in Ovarian Cancer

Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D., Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D., Mark S. Carey, M.D., Philip Beale, M.D., Andrés Cervantes, M.D., Christian Kurzeder, M.D., Andreas du Bois, M.D., Jalid Sehouli, M.D., Rainer Kimmig, M.D., Anne Stähle, M.D., Fiona Collinson, M.D., Sharadah Essapen, M.D., Charlie Gourley, M.D., Alain Lortholary, M.D., Frédéric Selle, M.D., Mansoor R. Mirza, M.D., Arto Leminen, M.D., Marie Plante, M.D., Dan Stark, M.D., Wendi Qian, Ph.D., Mahesh K.B. Parmar, Ph.D., and Amit M. Oza, M.D., for the ICON7 Investigators*

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D., for the Gynecologic Oncology Group*
Updated PFS

<table>
<thead>
<tr>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>464 (61)</td>
</tr>
<tr>
<td>Median, months</td>
<td>17.4</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.039</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.87 (0.77–0.99)</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>704</td>
<td>704</td>
</tr>
<tr>
<td>693</td>
<td>716</td>
</tr>
<tr>
<td>474</td>
<td>599</td>
</tr>
<tr>
<td>350</td>
<td>221</td>
</tr>
<tr>
<td>430</td>
<td>229</td>
</tr>
<tr>
<td>114</td>
<td>107</td>
</tr>
<tr>
<td>29</td>
<td>27</td>
</tr>
</tbody>
</table>

Time (months)

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>704</td>
<td>704</td>
<td></td>
</tr>
<tr>
<td>693</td>
<td>716</td>
<td></td>
</tr>
<tr>
<td>474</td>
<td>599</td>
<td></td>
</tr>
<tr>
<td>350</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>430</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

GOG-0218: Investigator-Assessed PFS

<table>
<thead>
<tr>
<th>Arm I</th>
<th>Arm II</th>
<th>Arm III</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP (n = 826)</td>
<td>CP + BEV (n = 826)</td>
<td>CP + BEV → BEV (n = 826)</td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td>423 (57.7)</td>
<td>418 (56.9)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.3</td>
<td>11.2</td>
</tr>
<tr>
<td>Stratified analysis HR (95% CI)</td>
<td>0.903 (0.755-1.046)</td>
<td>0.625 (0.826)</td>
</tr>
<tr>
<td>One-sided P value (log rank)</td>
<td>0.000*</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Proportion alive without progression

Burger RA et al. LBA1, ASCO 2010

Proportion Surviving Progression Free

Monthly Since Randomization

p-value boundary = 0.0115

ARTICLE

Bevacizumab in the Treatment of Ovarian Cancer

Kravitz, Michael A. Bookman, M.D., Charles W. Monk, M.D., Helen Huang, M.S., Emily Homesley, M.D., Jeffrey Fowler, M.D., Michael J. Birrer, M.D., Ph.D., and the Gynecologic Oncology Group*
Interim OS analysis (regulatory request)

Deaths, n (%) | Control: 200 (26) | Research: 178 (23)

Median, months | Control: Not yet reached | Research: p=0.11

Log-rank test | Control: HR (95% CI) 0.85 (0.69–1.04)

1-year OS rate (%) | Control: 92 | Research: 95
Ovarian cancer treatment rejected for Scots

A LIFE-EXTENDING ovarian cancer drug has been rejected for NHS use in Scotland after the medicines watchdog ruled it was not value for money.

The Scottish Medicines Consortium said it could not approve bevacizumab (Avastin) for routine use on the health service because the main case submitted by its manufacturer, Roche, was based on a 7.5mg unlicensed dose which was trialled in Scotland as part of a European study.
What about predictive biomarkers of bevacizumab efficacy?
Unsupervised clustering; all histologies
Unsupervised clustering; all histologies

Association with histology p=3.7x10^{-33}
Unsupervised clustering; all histologies

Survival - Sample.Group (Overall.Survival..Months)

% Survival

Survival time

Sample.Group
- A
- B
- C
- D
Unsupervised clustering; all histologies

Association with histology $p=3.7 \times 10^{-33}$
Gene expression analysis: 265 HGS ovarian cancers
Gene expression analysis: 265 HGS ovarian cancers

![Survival analysis graph](image)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune vs angioimmune</td>
<td>0.66</td>
<td>0.46-0.94</td>
<td>0.022</td>
</tr>
<tr>
<td>Immune vs angio</td>
<td>0.63</td>
<td>0.42-0.95</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Gene expression analysis: 265 HGS ovarian cancers
Signature generation

Classifier development
- Classification workflow
- Cross-validation
- Angiogenesis signature

Cross-validation performance

Biological relevance
OS of HGS as defined by immune-only signature

HR = 0.62; 95% CI 0.44-0.86; p = 0.004
OS of HGS in Tothill data as defined by immune-only signature

Survival - PLS63.Call (Overall.Survival..Months)

HR=0.40;
95% CI 0.26-0.60
p<0.00001
A Phase 3 Trial of Bevacizumab in Ovarian Cancer

Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D., Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D., Mark S. Carey, M.D., Philip Beale, M.D., Andrés Cervantes, M.D., Christian Kurzeder, M.D., Andreas du Bois, M.D., Jalid Sehouli, M.D., Rainer Kimmig, M.D., Anne Stähle, M.D., Fiona Collinson, M.D., Sharadah Essapen, M.D., Charlie Gourley, M.D., Alain Lortholary, M.D., Fréderic Selle, M.D., Mansoor R. Mirza, M.D., Arto Leminen, M.D., Marie Plante, M.D., Dan Stark, M.D., Wendi Qian, Ph.D., Mahesh K.B. Parmar, Ph.D., and Amit M. Oza, M.D., for the ICON7 Investigators*

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D., for the Gynecologic Oncology Group*
Which predictive biomarkers may be used in the future?

- Markers based on relapsed tissue biopsies/ct DNA (somatic mutation status)
- BRCA1/2 mutation status

Ledermann et al, NEJM 2012
Which predictive biomarkers may be used in the future?

- Markers based on relapsed tissue biopsies/ct DNA (somatic mutation status)
- BRCA1/2 mutation status
- ‘test for BRCAness’
Which predictive biomarkers may be used in the future?

- Markers based on relapsed tissue biopsies/ct DNA (somatic mutation status)
- BRCA1/2 mutation status
- ‘test for BRCAness’
- Gene expression signatures?
Which predictive biomarkers may be used in the future?

- Markers based on relapsed tissue biopsies/ct DNA (somatic mutation status)
- BRCA1/2 mutation status
- ‘test for BRCAness’
- Gene expression signatures?
- Biomarkers developed from pathways analysis/systems biology?
Which predictive biomarkers may be used in the future?

- Markers based on relapsed tissue biopsies/ct DNA (somatic mutation status)
- BRCA1/2 mutation status
- ‘test for BRCAness’
- Gene expression signatures?
- Biomarkers developed from pathways analysis/systems biology?
- Proteomics?
Acknowledgements

Molecular taxonomy study

• The patients and their families
  • John Smyth, Tzyvia Rye

• Biomarker Research Team and Bioinformaticians from Almac Diagnostics
  • Katherine Keating, Steve Deharo, Eamonn O’Brien, Andreas Winter, Fionnuala McDyer, Jude Mulligan, Tim Davison, Laura Hill, Max Byelsjo, Tom Halsey, Lisa McCoy, Claire Wilson, Paul Harkin, Richard Kennedy, Claire Wilson, Katie Styer, Michelle Gugger, Jenna Barrett, Kerry Lavery, Donna McIlwaine, Rachel Wheavil

• Scientists and clinicians from IGMM
  • Caroline Michie, Alistair Williams, David Harrison, Fiona Campbell, Brigid Orr, Mike Churchman, Andy MacLeod, Tammy Piper and John Bartlett

• Queens University, Belfast
  • Glenn McCluggage

Funding Sources

• Melville Trust for Care & Cure of Cancer
• NHS Lothian endowment funds
• Scottish Funding Council
• CSO
• ECMC
• Charon Fund
• Cancer Research UK
• Invest Northern Ireland

LOGS study

• Prof David Gershenson (USA)
• Prof S Kaye (UK)
• Mr J Paul (UK)
• Ms Karen Carty (UK)
• Dr K Connolly (UK)
• Dr John Farley (USA)
• Dr Bill Brady (USA)
• Dr Mark Brady (USA)
• Dr Mike Birrer (USA)
• Dr Lari Wenzel (USA)