Biomarkers in Ovarian Cancer: To be or not to be

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Conflict of Interest Disclosure

________________________________________________________________________

Michael J. Birrer

Roche, GSK, Clovis, Tesaro, Merrimack, Immunogen
Ovarian Cancer: The Clinical Problem

- 250,000 women diagnosed yearly worldwide
- 75% patients present with advanced stage disease.
- 80% respond to chemotherapy.
- Vast majority of patients relapse and eventually develop drug resistant disease.
- Minimal increase in overall survival over last 30 years.
- 140,000 deaths yearly.
- Highest case fatality rate for gynecologic cancers in the world
- All ovarian cancers treated with surgery/chemotherapy
Ovarian Carcinoma: Natural History

Symptoms

Diagnosis

Chemotherapy #1*

Interval* Cytoreduction

Second-Look

Progression

Cure?

Consolidation Maintenance

Chemo #2

Chemo #3+

Secondary Cytoreduction

Death

Supportive Care

Staging*

Primary cytoreduction

Primary cytoreduction
Early Stage High Grade Ovarian Cancer
What can we do to personalize their therapy?

• Standard of care for early stage high grade epithelial ovarian cancer (ESHGOC) is the same as its advanced counterpart.
• 10-20% will have a recurrence despite complete resection and adjuvant chemotherapy.
• 50-60% of patients with ESHGOC will not suffer recurrent disease even in the absence of adjuvant chemotherapy.
• Many women over treated!
The Consortium for Early Stage High Grade Ovarian Cancer
The Consortium for Early Stage High Grade Ovarian Cancer: Aims and Impact

Aims

• Identify a predictive signature for recurrence
• Identify early genomic changes and pathway activations
• Characterize potential early detection biomarkers

Methods

• 350 samples
• FFPE material
• Pathologically confirmed
• Macrodissected
• RNAseq
• microRNA
• CNV
• Immune infiltration
## Early Stage RNA-Seq

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Median AUC</th>
<th>Model</th>
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</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>41 NR, 18 R</td>
<td>0.81 Plus-minus, 20 genes</td>
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<tr>
<td>Serous</td>
<td>64 NR, 48 R</td>
<td>0.67 Random Forest, 200 genes</td>
</tr>
<tr>
<td>Serous &lt; 62, stage II</td>
<td>7 NR, 9 R</td>
<td>0.83 Random Forest, 10 genes</td>
</tr>
</tbody>
</table>

### 20 genes in the model for endometrioid

<table>
<thead>
<tr>
<th>Gene</th>
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<td>ADRB3</td>
<td>ARX</td>
<td>CDH19</td>
<td>CHGB</td>
<td>DLK1</td>
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<td>EDN3</td>
<td>FSHR</td>
<td>GPR12</td>
<td>LHFPL4</td>
<td>NELL1</td>
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<td>NR1H4</td>
<td>PLA2G2A</td>
<td>POU3F3</td>
<td>PTPN5</td>
<td>RALYL</td>
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<td>SCG3</td>
<td>SFTA3</td>
<td>SPHKAP</td>
<td>SPRR2F</td>
<td>ST8SIA3</td>
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### Pathway

<table>
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<tr>
<th>Pathway</th>
<th>Adjusted p-value</th>
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<tr>
<td>PKCA_DN.V1_DN</td>
<td>0.10</td>
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<tr>
<td>KRAS.50_UP.V1_UP</td>
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<tr>
<td>OSADA_ASCL1_TARGETS_UP</td>
<td>0.036</td>
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<tr>
<td>NAKAYAMA_SOFT_TISSUE_TUMORS_PCA1_DN</td>
<td>0.080</td>
</tr>
<tr>
<td>MIKKELEN_MEF_HCP_WITH_H3K27ME3</td>
<td>0.036</td>
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# Early Stage MicroRNA

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<th>Class</th>
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<th>Model</th>
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<tr>
<td>Endometrioid</td>
<td>46 NR, 20 R</td>
<td>0.63, Random LASSO, 20 mirs</td>
</tr>
<tr>
<td>Serous</td>
<td>69 NR, 49 R</td>
<td>0.62, Random Forest, 2 mirs</td>
</tr>
<tr>
<td>Serous &lt; 62, stage II</td>
<td>8 NR, 10 R</td>
<td>0.90, Random Forest, 50 mirs</td>
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</tbody>
</table>

![Graph showing predicted recurrence probability](image)

**Graph Details:**
- **Predicted Non-Recurrence:** 1 recurrence/8 cases
- **Predicted Recurrence:** 9 recurrences/10 cases
- **Years:** 0 to 8
- **Recurrence Probability:** 0.0 to 1.0

*Note: The graph illustrates the predicted recurrence probability over time, with a focus on early stage microRNA prediction.*
Early Stage Copy Number

TCGA  Serous recur  Serous non-recur
Early Stage Ovarian cancer

• Predictive signatures for recurrence have been developed.
• Identification of important therapeutic targets for recurrent early stage ovarian cancer is underway.
• Role of immune reaction to early stage ovarian cancer being defined
Advanced stage Disease

Can we improve on surgery?
Greater Success at Cytoreduction is Associated with Greater Median Survival

75% Max. CytoRS corresponds to a 34 mo. median survival

25% Max. CytoRS corresponds to a 25 mo. median survival

Bristow RE, et al.
J Clin Oncol 2002 20:1248-1259
Pathway analysis of a “suboptimal debulking” signature derived from 1,525 suboptimally debulked patients revealed hyperactivation of TGF-β pathway.
Expression of Three Proteins Provides 93% Accuracy for Determining Sub-optimal Debulking Status

A) POSTN tissue array staining

B) pSmad2/3 tissue array staining

C) CXCL14 tissue array staining

D) POSTN IHC

E) pSmad2/3 IHC

F) CXCL14 IHC

G) IHC multivariate

J Natl Cancer Inst. 2014 Apr 3;106(5)
Hypothesis

Hyperactivation of TGF-β pathway renders an **intrinsically more malignant phenotype** that contributes to the **difficulty for optimal debulking** as well as the **chemoresistance** in suboptimally debulked ovarian tumors.

Potential clinical benefits of TGF-β signaling inhibition

**Post-surgical management of suboptimally debulked tumors**

- Increase the chance of complete response
- Reduction of tumor recurrence and increase PFS
- Reduction of secondary tumor dissemination

**In neo-adjuvant setting (with first-line platinum/taxol):**

- Kill tumors posing anatomical hindrance to optimal debulking
- Reducing tumor dissemination during the “window period” between adjuvant-chemo and surgery
TGF-β signaling inhibition by TGFBR1 inhibitor LY2157299 (Eli Lilly)

1. CAGA12-Luciferase assay (SMAD4 transactivation activity):

   - **SKOV3:**
     - 1 hour: - + - +
     - 3.5 hours: - + - +
   - **OVCAR5:**
     - DMSO: 0.5
     - 1μM LY: 1
     - 5μM LY: 2
     - 10μM LY: 3
   - **OVCAR8:**
     - DMSO: 0
     - 0.5μM LY: 10
     - 1μM LY: 20
     - 5μM LY: 30

2. Western blot of pSmad2:

   - **SKOV3:**
     - TGF-β: - + - +
     - LY2157299: - - + +
   - **OVCAR8:**
     - TGF-β: - + - +
     - LY (5μM): - - + +

   ![Western blot images for SKOV3 and OVCAR8](image_url)
LY2157299 inhibits the migration and invasion of SKOV3 cells.
LY2157299 inhibits the migration of OVCAR4 and OVCAR8 cells
LY2157299 reduces the adhesive activities of ovarian cancer cells to confluent mesothelial layer

* Fluorescence labeled SKOV3 and OVCAR8 pretreated with TGF-β and LY2157299 for 24h before subjected to adhesion assay
LY2157299 treated mesothelial cells exhibits reduced activity to ovarian cancer cells

Confluent monolayer of HM-3 mesothelial cells pretreated with TGF-β and LY2157299 for 24h before the addition of fluorescence labeled ovarian cancer cells
The inhibitory effects on cell migration, invasion and adhesion to methothelial cells suggest LY2157299 is a potent reagent to suppress the dissemination of ovarian cancer cells.

- Ongoing *in vivo* work using intrabursal xenograft model to monitor tumor dissemination
Potential of LY2157299 to sensitize ovarian cancer cells to chemotherapeutic agent

No significant effect on cisplatin IC$_{50}$ \textit{in vitro}

OVCA1063

OVCA4

OVCA8

SKOV3

% Survival

Cisplatin (Log M)

Cisplatin (Log M)

Cisplatin (Log M)

Cisplatin (Log M)

% Survival

% Survival

% Survival

% Survival

• Untreated + DMSO

• 2ng/mL TGF- + DMSO

• 5 M LY2157299

• TGF- + LY2157299
TGF-β signaling inhibition sensitize the SKOV3 xenograft to cisplatin

**Tumor weight:**

![Graph showing tumor weight comparison between different treatments](image)

**pSmad2 staining:**

![Image of pSmad2 staining](image)

Partially inhibition may associate with the ineffectiveness of single agent.

**Potential mechanism underlying the difference in vitro and in vivo**

- Tumor-Stromal interaction as potential mechanism??
- Clonal selection which is hard to be detected by the IC50 assay
TGF-β signaling in stromal cells

**Tumor-associated fibroblasts (IHFOT208):**

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<th>1 hour</th>
<th>24 hours</th>
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<tbody>
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<td>- + - +</td>
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<td>- - + +</td>
<td>- - + +</td>
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</tbody>
</table>

TGF-β1 (2ng/mL)
LY2157299 (5 μM)
p-Smad2 (S465)
Smad2

**Mesothelial cells**

**HM3**

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<td>- + - +</td>
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<td>- - + +</td>
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2 ng/mL TGF-β1
5 μM LY2157299
pSmad2 (S465)
Smad2

**LP9**

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<td>- - + +</td>
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2 ng/mL TGF-β1
5 μM LY2157299
pSmad2 (S465)
pSmad2 (S245)
What about optimally debulked tumors?
Can we do better?
Single-walled carbon nanotubes (SWNTs)

Graphene

(n,m)-SWNT

A chiral vector, (n,m), defines a chirality of SWNT: if (n-m)=3 \times \text{integer}: metallic, if not, semiconducting
Probe targeting SPARC-expressing ovarian tumors

SPARC expression in OVCAR8 tumors

SPARC-binding peptide (SBP)

Targeting ligands

SWNT

M13 Phage

SWNTs Binding Motif

880 nm

6 nm
First-generation NIR-II imager

- 808 nm laser
- 2-D InGaAs detector
- NIR focusing lens
- Emission filter
- Excitation filter
- Phantom
- Stage controller
- Collimator
- X-axis
- Z-axis
Improved signal-to-noise performance and imaging using M13-SWNTs in the NIRII regime

- OVCAR8 xenograft tumors seeded in peritoneal cavity
NIR-II image-guided pre-surgical planning

SWNT NIR-II image guidance (pre-surgical planning): helps in better excision of sub-mm tumors

Randomize tumor cohort

Image-guided surgery

measure tumor nodules

Unguided surgery

PNAS, Ghosh et al 2014
Comparison of Non-guided v. Image-guided Surgery

Non-guided Surgery (visible eye only)

Real-time NIR-II Fluorescence image-guided Surgery

2 days pre-surgery | 10 days post-surgery | 3 weeks post-surgery | 5 weeks post-surgery

Dead
Guided Surgery Improves Survival in an Orthotopic Mouse Model

+40% survival

Accepted ACS Nano
Biologics: Angiogenesis Targeting

GOG218 (1150 cases)
PFS by CD31 (median cut-off)

Time (months)

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<th></th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
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<th>42</th>
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<td>168</td>
<td>79</td>
<td>32</td>
<td>14</td>
<td>5</td>
<td>3</td>
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<td>CPB15+ low CD31</td>
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<tr>
<td>CPP low CD31</td>
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<td>171</td>
<td>81</td>
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Interaction p=0.0025
### GOG218 (1150 cases)
#### OS by CD31 (median cut-off)

<table>
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<tr>
<th>Time (months)</th>
<th>CPB15+ high CD31</th>
<th>CPB15+ low CD31</th>
<th>CPP high CD31</th>
<th>CPP low CD31</th>
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<td>232</td>
<td>228</td>
<td>238</td>
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<tr>
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<td>12</td>
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<td>217</td>
<td>190</td>
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<td>198</td>
<td>167</td>
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<tr>
<td>66</td>
<td>12</td>
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Interaction p=0.0155

GOG218 (1150 cases)
GOG218 (1120 cases)

Predictive Associations

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<tr>
<th>Marker</th>
<th>PFS p-value</th>
<th>OS p-value</th>
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<tbody>
<tr>
<td>IL6</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td>OPN</td>
<td>0.09</td>
<td>0.15</td>
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<tr>
<td>VEGFD</td>
<td>0.6</td>
<td>0.7</td>
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<tr>
<td>ANG2</td>
<td>0.6</td>
<td>0.2</td>
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<tr>
<td>SDF1</td>
<td>0.8</td>
<td>0.5</td>
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Prognostic Associations

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<tr>
<th>Marker</th>
<th>PFS p-value</th>
<th>OS p-value</th>
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<tr>
<td>IL6</td>
<td>4.15^{-5}</td>
<td>4.18^{-6}</td>
</tr>
<tr>
<td>OPN</td>
<td>4.84^{-8}</td>
<td>1.28^{-9}</td>
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<tr>
<td>VEGFD</td>
<td>0.7</td>
<td>0.4</td>
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<tr>
<td>ANG2</td>
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<td>0.01</td>
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<tr>
<td>SDF1</td>
<td>0.1</td>
<td>0.2</td>
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</table>

p-value for interaction with bevacizumab treatment (predictive efficacy)
Explored based on continuous values; multivariate adjusted for cofounders – age, stage, debulking, and performance status. Prognostic associations using a threshold of p=0.01 to correct for multiple testing.
Association between IL6 and Survival Outcomes  
median cut off

### PFS

<table>
<thead>
<tr>
<th>IL6</th>
<th>PFS (months)</th>
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<td>Control</td>
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<tr>
<td>&lt; median</td>
<td>12.6</td>
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<tr>
<td>&gt; median</td>
<td>8.7</td>
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### OS

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<th>IL6</th>
<th>OS (months)</th>
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<td>Control</td>
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<tr>
<td>&lt; median</td>
<td>50.8</td>
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<tr>
<td>&gt; median</td>
<td>33.1</td>
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</table>
Association between IL6 and Survival Outcomes
Optimized cut points

A PFS Optimized Cut-point

B PFS Optimized Cut-point

C OS Optimized Cut-point

D OS Optimized Cut-point

Probability

Progression-Free Survival Time (Months)

Probability

Overall Survival Time (Months)

Probability

Progression-Free Survival Time (Months)

Probability

Overall Survival Time (Months)
PARP Inhibitors
Who benefits?
# PARP Inhibitor Summary

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
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<tbody>
<tr>
<td><strong>Current Label</strong></td>
<td>1. gBRCA\text{mut} 3+ prior lines of therapy</td>
<td>1. 1. somatic or germline BRCA\text{mut} patients with ≥2 prior 2. Maintenance for platinum sensitive</td>
<td>1. Maintenance for platinum sensitive</td>
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<tr>
<td><strong>Trial Name</strong></td>
<td>SOLO-2 (Study 19)</td>
<td>ARIEL3 (ARIEL 2)</td>
<td>NOVA</td>
</tr>
<tr>
<td><strong>Study Design, Population</strong></td>
<td>Maintenance olaparib vs placebo, BRCA\text{mut} (all had germline, some also somatic)</td>
<td>Maintenance rucaparib vs placebo; patients stratified according to tumor HRD status (3 groups)</td>
<td>Maintenance niraparib vs placebo, BRCA\text{mut} (germline 36.7%, somatic 8.5%) or BRCA\text{WT}</td>
</tr>
<tr>
<td><strong>Median PFS, Months</strong></td>
<td>BRCA\text{mut}: 19.1 vs 5.5, HR=0.3</td>
<td>BRCA\text{mut}: 16.6 vs 5.4, HR=0.23</td>
<td>gBRCA\text{mut}: 21.0 vs 5.5, HR=0.27</td>
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<tr>
<td></td>
<td></td>
<td>HRD: 13.6 vs 5.4, HR=0.32</td>
<td>Non-gBRCA: 9.3 vs 3.9, HR=0.45</td>
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<tr>
<td></td>
<td></td>
<td>ITT: 10.8 vs 5.4, HR=0.37</td>
<td></td>
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SOLO 1

Study design

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic BRCAm
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

2:1 randomization

- Stratified by response to platinum-based chemotherapy
- Olaparib 300 mg bd (N=260)

- Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease. BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TOI, Trial Outcome Index
SOLO 1

PFS by investigator assessment

- **Olaparib (N=260)**
  - Median PFS, months: NR
  - Events (%): 102 (39.2)
  - 60.4% progression free at 3 years

- **Placebo (N=131)**
  - Median PFS, months: 13.8
  - Events (%): 96 (73.3)
  - 26.9% progression free at 3 years

**HR 0.30**

95% CI 0.23, 0.41; P<0.0001

CI, confidence interval; NR, not reached
There Is More To DNA-Repair Than \textit{BRCA1/2}

Meindl et al, Nat Genetics 2010
Loveday et al, Nat Genetics 2011
Rafnar et al, Nat Genetics 2011
Casadei et al, Cancer Res 2011
BRCA1; 44,2%
BRCA2; 26,0%
BRIP1; 7,5%
PALB2; 3,4%
ATM; 3,0%
NBN; 2,6%
RAD51C; 2,3%
CHEK2; 2,6%
RAD51D; 2,6%
LYNCH; 1,9%
ATR; 0,8%
XRCC2; 0,4%
FAM175A; 0,4%
SLX4; 0,4%
MRE11A; 0,4%
TP53; 0,8%
BARD1; 0,8%
N = 117
N = 69
N = 20
Lynch; 1,9%
Summary of Cancer-Associated Mutations: GOG 218 and GOG 262
Response rates in patients with germline and somatic $BRCA^\text{mut}$ tumors are similar:

- $BRCA^\text{mut}$ ORR (RECIST) = 75%
- ORR (RECIST and/or CA-125) similar in germline (17/20; 85%) and somatic (17/20; 85%) patients
  - Germline $BRCA^\text{mut}$ group had 2 CRs
  - Somatic $BRCA^\text{mut}$ group had 4 CRs
- Median duration of response = 9.5 months
Genome-Wide LOH Profiles in Ovarian Cancer

- Principle of HRD assay
- LOH-based clustering of tumors reveals 2 cohorts (High vs. Low LOH)
- Fraction of LOH (% of the genome affected) correlates with outcomes

New PARPi Opportunities: Genome-Wide Loss of Heterozygosity (LOH) Occurs With HRD

BRCA\textsuperscript{mut}

High genomic LOH $\Rightarrow$ BRCA signature $\Rightarrow$ Response to PARPi

BRCA\textsuperscript{wt}

High genomic LOH $\Rightarrow$ BRCA-like signature $\Rightarrow$ Response to PARPi

BRCA\textsuperscript{wt}

Low genomic LOH $\Rightarrow$ Biomarker neg $\Rightarrow$ NO Response to PARPi

HRD Testing: MyChoice

NtAI: Number of telomeric allelic imbalances
LST: Large-scale state transition

LOH + TAI + LST = myChoice HRD Score

High-Grade Ovarian Carcinoma Patients Can Be Classified Into 3 Molecular Subgroups: BRCA$^{\text{mut}}$, BRCA-like, Biomarker-negative

But do they Work?
Duration of Response in *BRCA*mut, *BRCA*-like (Tumor), and Biomarker-negative Patients in ARIEL2 Part 1: ECCO/ESMO 2015

<table>
<thead>
<tr>
<th>HRD molecular subgroup</th>
<th>Objective RECIST response rate, % (N)</th>
<th>Median duration of response, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA</em>mut</td>
<td>75 (30/40)</td>
<td>9.5 (7.4, 12.9)</td>
</tr>
<tr>
<td><em>BRCA</em>-like</td>
<td>36 (28/77)</td>
<td>8.2 (5.6, 10.8)</td>
</tr>
<tr>
<td>Biomarker Negative</td>
<td>16 (11/68)</td>
<td>5.5 (2.1, 7.4)</td>
</tr>
</tbody>
</table>

HRD molecular subgroup

Objective RECIST response rate, % (N)

Median duration of response, mo (95% CI)

- CI, confidence interval.
Exploratory Analysis: PFS in Subgroups of Non-gBRCAmut Cohort

### HRD-positive

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Month(s))</th>
<th>Hazard Ratio (95% CI) p-value</th>
<th>% of Patients without Progression or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=71)</td>
<td>9.3 (5.8, 15.4)</td>
<td>0.38 (0.231, 0.628)</td>
<td>45% 27%</td>
</tr>
<tr>
<td>Placebo (N=44)</td>
<td>3.7 (3.3, 5.6)</td>
<td>p=0.0001</td>
<td>11% 6%</td>
</tr>
</tbody>
</table>

### BRCAwt

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Month(s))</th>
<th>Hazard Ratio (95% CI) p-value</th>
<th>% of Patients without Progression or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=92)</td>
<td>6.9 (5.6, 9.6)</td>
<td>0.58 (0.361, 0.922)</td>
<td>27% 19%</td>
</tr>
<tr>
<td>Placebo (N=42)</td>
<td>3.8 (3.7, 5.6)</td>
<td>p=0.0226</td>
<td>7% 7%</td>
</tr>
</tbody>
</table>

### HRD-negative

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Month(s))</th>
<th>Hazard Ratio (95% CI) p-value</th>
<th>% of Patients without Progression or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=35)</td>
<td>20.9 (9.7, NR)</td>
<td>0.27 (0.081, 0.903)</td>
<td>62% 52%</td>
</tr>
<tr>
<td>Placebo (N=12)</td>
<td>11.0 (2.0, NR)</td>
<td>p=0.0248</td>
<td>19% 19%</td>
</tr>
</tbody>
</table>

NR=Not reached

![Graphs showing progression-free survival for different treatments and subgroups](chart.png)
Advanced stage ovarian cancer

- TGF beta Activation
  - Neoadjuvant therapy
    - With TGF beta inhibition
  - Optimal debulking
    - HRD Pos
      - Parp inhibitor in maintenance
    - High CD31/IL6 Pos
      - Anti-angio inhibitor in maintenance
Are there other subsets of patients with ovarian cancer which can be targeted?

Multiple cell surface proteins are selectively expressed on ovarian cancer cells and are therapeutic targets
Folate Receptor Alpha Expression Distribution

Ventana Staining & Scoring

<table>
<thead>
<tr>
<th>Membrane Staining</th>
<th>Intensity Score</th>
<th>Percentage of Cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Weak</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

hscore=240/high expression
IMGN853 Mechanism of Action

AN INTEGRATED SYSTEM

**Linker**
- Cleavable linker stable in the blood stream
- Bystander killing of neighboring cancer cells

**Ultra-potent anticancer agent**
- DM4 – a potent tubulin-targeting agent

**Antibody (Ab)**
- A folate receptor α (FRα)-binding antibody

**Target**
- Highly expressed in ovarian and other cancers
Phase 3 Study Design

Patients with FRα-positive ovarian cancer

FRα Med/High
1-3 prior Tx

Mirvetuximab
6 mg/kg AIBW*
Q3W
n = ~222

Investigator’s choice
Pac, PLD* or Topo*
n = ~111

2:1 randomization

Co-PIs:
- Kathleen Moore
- Michael Birrer

Partnering with GOG Foundation

Design accepted by FDA and EMA

> 100 sites in US, Canada, W. Europe

Primary endpoint: PFS (Blinded Independent Central Review)
- Entire population
- Subset with high FRα (~2/3 of patients in study)

Secondary endpoints: ORR, DOR, QoL and OS

Interim analysis for futility at 80 events

* PLD: pegylated liposomal doxorubicin; Topo: topotecan; AIBW = adjusted ideal body weight
Conclusions

- Stratifying patients for up-front therapy will be important
  - TGF beta hyperactivity pathway maybe associated with sub-optimal debulking
  - Better optimal debulking with newer imaging technologies
- Personalizing adjuvant therapy for early stage patients
- Advanced stage patients will be stratifying based upon HRD or angiogenesis biomarkers
- Cell surface targets
Thanks!