Ovarian Cancer: Epidemiology

- 200,000 women diagnosed worldwide
- 125,000 die annually
- 21,550 US women will be diagnosed in 2013
- 14,600 US women are expected to die from ovarian cancer in 2013
- 75% present with advanced stage disease
  - Standard treatment is radical debulking surgery followed by adjuvant chemotherapy
  - Platinum agent and paclitaxel

ALL PATIENTS TREATED THE SAME!

The Problem
Cancer Death Rates: (US 1930-2006)*

*Cisplatin
Paclitaxel
Cytoreduction

*Age-adjusted to the 2000 US standard population.
## Five-Year Relative Survival Rates by Stage at Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ovary</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>93%</td>
<td>97%</td>
</tr>
<tr>
<td>Regional</td>
<td>55%</td>
<td>76%</td>
</tr>
<tr>
<td>Distant</td>
<td>25%</td>
<td>21%</td>
</tr>
<tr>
<td>All Stages</td>
<td>46%</td>
<td>84%</td>
</tr>
</tbody>
</table>
OVARIAN CANCER DETECTION

• Survival will be improved if detected in early stages
• Clinical exam/medical history
  – None of these assessments are specific or sensitive for ovarian cancer
• There are no FDA approved biomarkers for ovarian cancer screening.
• Two markers have been FDA approved to monitor the disease recurrence and therapeutic response
  – Cancer antigen 125 (CA-125) in 1987
  – Human epididymis protein-4 (HE4) in 2008
• Poor sensitivity (elevated in only 50% of women with Stage I disease)
• Poor specificity (elevated in many gynecologic and non-gynecologic malignancies as well as benign conditions)
OVARIAN CANCER DETECTION

• Development of new biomarker algorithms
  – Serial collections
  – Risk Of ovarian Cancer Algorithm (ROCA)

• Critical need to identify serum based biomarkers
  – Proteomic analysis
Measure candidate proteins in blood from screening trials to determine which detect ovarian cancer early!
Workflow for candidate biomarker discovery in ovarian cancer

**OCF samples**
- Extract OCF, aliquot, snap freeze
- BCA protein content

**IgY14 abundant protein depletion**
- Denature, Prepare for digestion

**Basic reversed-phase chromatography**
- Q-Exactive MS/MS
- Top 12 method

**Data analysis with Spectrum Mill**
- Quantification
- Identification

95 - 98% iTRAQ labeling efficiency; 100 ug total protein per label
New Hypothesis of the Origin of Ovarian Cancer Provides Source for Heterogeneity
Small Invasive Cancers Detected in Fallopian Tubes of Women At High Risk for Ovarian Cancer
<table>
<thead>
<tr>
<th></th>
<th>Fallopian Tube Epithelium</th>
<th>p53 Signature</th>
<th>Intraepithelial Carcinoma</th>
<th>Serous Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H&amp;E</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>p53</strong></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>γ-H2AX</strong></td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>MIB1</strong></td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Karst and Drapkin
J Oncol 2009
Integrated Model of OVCA Pathogenesis

Levanon et al, JCO 2008
Papillary Serous Ovarian Cancer

(40x Magnification)
Low-Malignant Potential (LMP)

(40x Magnification)
Invasive Carcinoma
Unsupervised Hierarchical Clustering of Serous Ovarian Cancers
Ovarian Cancer

Papillary Serous Ovarian Tumors

Normal Cells

P53-

P53+

High Grade

LMP/Low Grade

B-raf, ras

Bonome et al. Cancer Research 2005
KRAS/BRAF

- BRAF mutation rate
  - 25% low grade/borderline
- K-RAS mutation rate
  - 15% of low grade/borderline
- AZD6244 (ARRY-142886) orally-available, small molecule inhibitor of MEK-1/2

Mayr, Gynecol Oncol, 103:2006.
Martin, JCO, 25:2007
The Mitogen-activated Protein Kinase (MAPK) Cascades

- Low grade serous ovarian cancer
  - Ras mutations 20%
  - B-raf mutations 20%
  - Mutually exclusive
  - GOG 239 trial

- High grade serous ovarian cancer
  - 2% B-raf mutation
  - 2% ras mutation
  - ? Ras pathway activation?
A PHASE II TRIAL OF AZD6244 IN WOMEN WITH RECURRENT LOW-GRADE SEROUS CARCINOMA OF THE OVARY OR PERITONEUM: A Gynecologic Oncology Group Study

- Open label Phase II study
- Women with recurrent low-grade serous (invasive micropapillary) carcinoma of ovary or peritoneum
- Biopsy proven
- Prospective pathologic evaluation
- Treatment: AZD6244 50 mg BID
- Four weeks = 1 cycle
- 52 patients accrued between 17 Dec 2007 – 23 Nov 2009
MAPK pathway Inhibition is effective for Low grade tumors

<table>
<thead>
<tr>
<th></th>
<th>% 1 prior ChTx</th>
<th>% &gt; 3 prior ChTx</th>
<th>SD (%)</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC¹</td>
<td>28</td>
<td>14</td>
<td>60</td>
<td>7.25</td>
</tr>
<tr>
<td>GOG239</td>
<td>19</td>
<td>57</td>
<td>65</td>
<td>11</td>
</tr>
</tbody>
</table>

• exhibits considerable activity with minimal toxicity in recurrent low-grade serous tumors.
  – The 15% RR is 5X that observed for cytotoxic chemotherapy in the setting of recurrent low-grade serous tumors.
• These results warrant further evaluation of inhibitors of the MAPK pathway in low-grade serous ovarian cancers

1. Gershenson, Gynecol Oncol 2009;114:48
Ovarian Cancers
A heterogeneous disease

- Serous
- Mucinous
- Endometrioid
- Clear Cell

- A disease of genomic instability
- A disease of aberrant Ras pathway signaling
- Multiple diseases. True endometrioid a disease of aberrant PTEN, PI-3K, AKT signaling
- A disease of ARID1A
CLEAR CELL CANCER

- OVARIAN
- ENDOMETRIAL
- RENAL

Zorn et al. Clinical Cancer Research 2005
Clear Cell Ovarian Cancer HIF1 alpha Pathway

Cell Migration

HIF1alpha degradation

Cell Cycle Progression

Glycolysis

Angiogenesis
Clinical Impact of Genomic Characterization of Clear Cell Cancers

• Remove clear cell tumors from ovarian cancer phase III trials.
• Create clear cell specific phase II trials.
• Targeting angiogenesis or metabolic pathways strongly suggested.
• Phase II trials:
  – Sunitinib for recurrent clear cell GOG254
  – Temsirolimus + carbo/taxol up front GOG268
What about High Grade Cancers?

Are there evolving personalized algorithms? What do we know?
TCGA Overview

- Large amounts of genomic/epigenomic abnormalities
  - Few high frequent mutations except p53 and BRCA
  - Multiple areas of chromosomal gain
    - Containing 100s of genes
  - Multiple areas of relatively common chromosomal loss
    - Containing 100s of gene
  - Many hyper-methylated genes
  - 4 transcriptional cluster patterns
    - Transcriptional subtypes not linked strongly to survival
  - 3 microRNA subtypes
    - Loosely linked to transcriptional cluster
New Therapeutic Targets

Can we exploit the DNA repair deficiency and genomic instability?
PARP inhibition and tumor-selective synthetic lethality

DNA damage (SSBs)

DNA replication (accumulation of DNA DSBs)

PARP inhibition

Normal cell with functional HR pathway

HR-mediated DNA repair

Cell survival

Tumor-selective cytotoxicity

HR-deficient tumor cell (e.g. BRCA 1/2-/-)

No HR-mediated DNA repair

Cell death

DSB, double-strand break; HR, homologous recombination
SSB, single-strand break

Olaparib monotherapy is active in gBRCA tumours

<table>
<thead>
<tr>
<th></th>
<th>gBRCA ovarian cancer</th>
<th>gBRCA breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td>33% (11/33) 400mg bd</td>
<td>41% (11/27) 400mg bd</td>
</tr>
<tr>
<td></td>
<td>28% (13/46) 200mg bd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13% (3/24) 100mg bd</td>
<td>22% (6/27) 100mg bd</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>5.8 months (400mg bd)</td>
<td>6.2 months (400mg bd)</td>
</tr>
<tr>
<td></td>
<td>1.9 months (100mg bd)</td>
<td>3.8 months (100mg bd)</td>
</tr>
</tbody>
</table>

400 patients treated with olaparib monotherapy

Generally well tolerated, with GI toxicity and fatigue most common toxicities, which can be controlled with dose reductions

Randomised phase II versus liposomal doxorubicin*
Best % change from baseline in target lesions

Olaparib 400 mg bid cohort

- BRCA1
- BRCA2

*Platinum-sensitive patients. Figure includes 3 unconfirmed responses
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

Olaparib 400 mg po bid
Randomized 1:1
Treatment until disease progression
Placebo po bid
Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk (n)</td>
<td>136</td>
<td>129</td>
</tr>
<tr>
<td>Time from randomization (months)</td>
<td>104 51 23 6 0 0</td>
<td>72 23 7 1 0 0</td>
</tr>
<tr>
<td>No. of events: Total patients (%)</td>
<td>60:136 (44.1)</td>
<td>93:129 (72.1)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>8.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.35 (95% CI, 0.25–0.49)</td>
<td>P&lt;0.00001</td>
</tr>
</tbody>
</table>

Randomized treatment
- Placebo
- Olaparib 400 mg bid
Preplanned subgroup analysis of PFS

Overall
BRCA mutation
BRCA status known
BRCA unknown
Age <50
Age ≤50 to <65
Age ≥65
Race, white
Non-Jewish descent
CR at baseline
PR at baseline
TTP penultimate platinum regimen 6–12 mo
TTP penultimate platinum regimen >12 mo

Global interaction test showed no evidence of inconsistency across the subgroups (P=0.282)

Size of circle is proportional to number of events; grey band represents 95% confidence intervals (CIs) in overall population
Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities

Press et al BMC Cancer

Approximately 40% sporadic ovarian cancers have dysfunctional BRCA pathway
New Therapeutic Targets

Can we target the stroma of the tumor?
Therapeutic Targeting of Angiogenesis

• One of the most prolific arenas of drug development
• More than 360 agents in various phases of development
  – Compounds: modeled for direct and/or indirect AA properties
  – Approaches: ligand, receptor, signal, and regulators
  – Targets: endothelial cells, tumor cells, pericytes
• Approved: 9 (2 others with indirect effects)
  – Most recent Everolimus (3/30/09) in RCC
# Single-agent anti-VEGF therapy in EOC/PPC: Phase II efficacy

A trial terminated prematurely. The trial failed to meet the primary endpoint.

### Preliminary analysis


<table>
<thead>
<tr>
<th>Agent</th>
<th>GOG 170-D¹</th>
<th>Cannistra et al²</th>
<th>Tew et al³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>62</td>
<td>44a</td>
<td>162c</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>36</td>
<td>84</td>
<td>47</td>
</tr>
<tr>
<td>VEGF Trap</td>
<td>34/66/0/0</td>
<td>0/52/48/0</td>
<td>0/0/46/46</td>
</tr>
<tr>
<td>73/27/0</td>
<td>59/41/0</td>
<td>60/33/7</td>
<td></td>
</tr>
<tr>
<td>13 (21)</td>
<td>7 (16)</td>
<td>13 (8)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>27</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

- a Trial terminated prematurely
- b Trial failed to meet primary endpoint
- c Preliminary analysis

DFI = disease-free interval
GOG 0170 response and 6-month PFS

Response Rate (%) vs Progression-Free at 6 m (%)

- Enzastaurin
- Vorinostat
- Lapatinib
- Mifepristone
- Gefitinib
- Imatinib
- Temsirolimus
- Sorafenib
- Bevacizumab

Area proportional to number of patients

GOG Phase II Database 2009
GOG 218

Randomize

EOC Primary Peritoneal Stage III/IV Suboptimal

Bevacizumab 15 mg/kg IV

Paclitaxel (3 hour)
175 mg/m² q 21 d x 6
Carboplatin
AUC = 6 q 21 d x 6
Placebo d1 X 5, start cycle 2

Placebo
d1 q 21d
X 15 months

Paclitaxel (3 hour)
175 mg/m² q 21 d x 6
Carboplatin
AUC = 6 q 21 d x 6
Bev d1 X 5, start cycle 2

Placebo
d1 q 21d
X 15 months

Paclitaxel (3 hour)
175 mg/m² q 21 d x 6
Carboplatin
AUC = 6 q 21 d x 6
Bev d1 X 5, start cycle 2

Bevacizumab
d1 q 21d
X 15 months
Investigators assessed PFS

**Median follow-up: 17.4 months**

<table>
<thead>
<tr>
<th></th>
<th>Arm I CP + PLA → PLA (n=625)</th>
<th>Arm III CP + BEV → BEV (n=623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>423 (68)</td>
<td>360 (58)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.3</td>
<td>14.1</td>
</tr>
<tr>
<td>HR (stratified)</td>
<td>0.908 (0.759–1.040)</td>
<td>0.717 (0.625–0.824)</td>
</tr>
<tr>
<td>One-sided log-rank p-value</td>
<td>&lt;0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>p-value boundary = 0.0116

Proportion surviving progression free

Months since randomization

Median follow-up: 17.4 months
ICON 7 (Front-line European Trial)

Stages I-IV ovarian and peritoneal cancer
- Stratified according to stage, optimal status region or country

Carboplatin AUC 6 plus Paclitaxel 175 mg/m² (3 hr) q 21d x 6

Carboplatin AUC 6 plus Paclitaxel 175 mg/m² (3 hr) q 21d x 6 plus bevacizumab at 7.5 mg/kg followed by bevacizumab at 7.5 mg/kg q 21 d x 12 months

Translational Research
- Tissue and serum markers of angiogenesis
- Genomics
- DCE-MRI
- Quality of life
- Health economics

Accrual goal: 1,444 patients
Primary endpoint: PFS
Other endpoints: OS (10 mo), RR, Toxicity
Progression-free survival

Academic analysis

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>392 (51)</td>
<td>367 (48)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median, months</th>
<th>Control</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.3</td>
<td>19.0</td>
<td></td>
</tr>
</tbody>
</table>

Log-rank test: p = 0.0041

HR (95% CI): 0.81 (0.70–0.94)
Bevacizumab is active in ovarian cancer

When is it best used?
Conclusions

• Histology/grade specific trials and treatments are here!
• Identifying subsets in serous high grade tumors will be difficult!
• HRD can be exploited!
• Tumor stroma may an excellent target!
Conclusions (cont.)

• Most effective way of reducing deaths due to ovarian cancer - early detection!
• If the detection of early stage ovarian cancer can be increased from 25% to 50% - mortality will drop from 80% to 50%
• Decrease of 5000 deaths (US) and 62,000 worldwide!