Treatment of Recurrent Ovarian Cancer

Mihaela Cristea, MD
Associate Professor
Medical Oncology, City of Hope
Financial Disclosure

• No disclosures
Epithelial Ovarian Cancer Subtypes and Associated Mutations and Molecular Aberrations

**Ovarian cancer**
- Epithelial
  - High-grade serous: TP53, BRCA1 and 2, NF1, RB1, CDK12
  - Low-grade serous: BRAF, KRAS, NRAS, ERBB2
  - Mucinous: KRAS, HER2 amplification
  - Clear cell: ARID1A, PIK3CA, PTEN, CTNNB1, PPP2R1α
- Endometrioid: ARID1A, PIK3CA, PTEN, PPP2R1α
- Sex cord-stromal: Granulosa cell: FOXL2
- Others, including germ cell: Sertoli-Leydig cell, DICER1
- MMR deficiency

**Pathway alterations:**
- PI3K/RAS/NOTCH/FOXM1

**CCN New Strategies**

### Estimates of New Cancer Cases and Deaths in the US 2016

<table>
<thead>
<tr>
<th>Females</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>246,660</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>106,470</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>63,670</td>
<td>8%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>60,050</td>
<td>7%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>49,350</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>32,410</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>29,510</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>26,050</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>25,400</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>23,050</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>843,820</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>72,160</td>
<td>26%</td>
</tr>
<tr>
<td>Breast</td>
<td>40,450</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>23,170</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,330</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>14,240</td>
<td>5%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>10,470</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10,270</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>8,990</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>8,630</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>6,610</td>
<td>2%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>281,400</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Five Years Survival in Gynecologic Cancers
2005 - 2011

Ovarian Carcinoma: Clinical Course

1. Diagnosis
   - Symptoms
   - Staging
     - Primary cytoreduction

2. Chemotherapy #1
   - Interval Cytoreduction
   - Second-Look

3. Consolidation/Maintenance
   - Progression
   - Secondary Cytoreduction
   - Death

4. Chemo #2
   - Chemo #3+
   - Supportive Care
   - Cure
How Do We Treat Newly Diagnosed Ovarian Cancer?

- Current Approach -- Surgery and Chemotherapy
  - Primary Tumor Reductive Surgery
    - Surgery → Chemotherapy
  - Neoadjuvant Chemotherapy (NACT)
    - Chemotherapy → Surgery → Chemotherapy
- Goal of Surgery → remove all visible disease
- Goal of Chemotherapy → kill all cancer cells
Recurrent Ovarian Cancer is a Chronic Disease Process

• For most women who are diagnosed with ovarian cancer, the cancer will recur and the cancer becomes a chronic disease.
  – Over 70% of all women diagnosed with ovarian cancer will have recurrent disease.
• Good news is that women are living longer with better quality of life with recurrent ovarian cancer.
  – Better control of the cancer with newer treatment options
Recurrent Ovarian Cancer?

- How long after completion of the initial treatment does the recurrence happen?
  - > 6-12 months: platinum sensitive disease
  - < 6-12 months: platinum resistant disease

- What is the extent and nature of disease recurrence?
  - Is a second surgery an option?

- What kind of therapy does the patient tolerate?
  - Side effects from previous chemotherapy, complication of surgery

- What are the goals for the patient and the physician?
  - Cure!!!
  - Prolongation of survival, symptoms management, improved quality of life?

- At what point should a clinical trial be considered?
# Chemotherapy for Recurrent Ovarian Cancer

## Frequently used:
- Carboplatin
- Cisplatin
- Topotecan
- Paclitaxel
- Docetaxel
- Liposomal doxorubicin
- Oral etoposide
- Gemcitabine
- Tamoxifen
- Cyclophosphamide
- Hexamethylmelamine

## Other Drugs:
- Oxaliplatin
- Vinorelbine
- 5-FU/leucovorin
- Irinotecan
- Ifosfamide
- Capecitabine
- Abraxane
- Letrozole
- Anastrazole
- Pemetrexed
## Effect of Platinum-Free Interval on Response Rate

<table>
<thead>
<tr>
<th>Platinum-Free Interval (mos)</th>
<th>% Response to Second-line Platinum Therapy</th>
<th>Non-Platinum Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Markman</td>
<td>Gore</td>
</tr>
<tr>
<td>0-6</td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>7-12</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>13-18</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td>19-24</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td>&gt;24</td>
<td>59%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Recurrent Ovarian Cancer
New Directions

- Anti-angiogenic therapy
- PARP inhibition
- Immunotherapy
Platinum Sensitive Ovarian Cancer

• Combination platinum based chemotherapy

New Directions
• Chemotherapy + anti-angiogenic therapy
• PARP inhibitors: high grade serous ovarian cancer
ICON 4 Schema

International Collaborative Ovarian Neoplasm Group

- Relapsed ovarian or primary
- Peritoneal requiring chemotherapy
- Previous platinum-based chemotherapy

Prior chemotherapy
- Carboplatin (31%)
- Paclitaxel/platinum (40%)
- Other (30%)

TFI > 12 months for 75% (TFI = treatment-free interval)

<table>
<thead>
<tr>
<th></th>
<th>Plat (n = 128)</th>
<th>Pac-Plat (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR or PR</td>
<td>54%</td>
<td>66%</td>
</tr>
</tbody>
</table>

PFS
- HR = 0.76. (p < 0.001)
- Absolute diff at 1 year = 10%
  (40% to 50%)

OS
- HR = 0.82
  (p = 0.0023)
- Absolute diff at 2 years = 7%
  (50% to 57%)

Gemcitabine/Carboplatin vs. Carboplatin:

- Recurrent ovarian cancer
- 6+ months after platinum
- Strata
  - PFI (6-12, >12 months)
  - 1st-line therapy (platinum ± paclitaxel)
  - Measurable vs evaluable
- Primary endpoint = PFS

Gem 1,000 mg/m², days 1 + 8
Carboplatin AUC 4 day 1 every 21 days x 6 cycles

Carboplatin AUC 5 day 1, every 21 days x cycles

<table>
<thead>
<tr>
<th></th>
<th>Gem/Carbo</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS: HR =0.71; p= 0.0038</td>
<td>8.6 mo</td>
<td>5.8 mo</td>
</tr>
<tr>
<td>OS: HR= 0.92; p=0.73</td>
<td>18 mo</td>
<td>17.3 mo</td>
</tr>
</tbody>
</table>

GCIG CALYPSO Trial:

Pegylated liposomal doxorubicin/Carboplatin vs. Carboplatin

**Ovarian Cancer**
Platinum Sens.
Stratify:
< 0.5 cm
> 0.5-2 cm

**Randomize**

**PLD**
30 mg/m2
Carboplatin AUC = 5
q 28 days x 6

**Paclitaxel**
175 mg/m2
Carboplatin AUC = 5
q 21 days x 6

<table>
<thead>
<tr>
<th></th>
<th>Doxil/Carbo</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td>HR = 0.82</td>
<td>11.3 mo</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>HR= 0.99</td>
<td>30.7</td>
</tr>
</tbody>
</table>

Treating Ovarian Cancer with Bevacizumab (Avastin™)

- Humanized Antibody, 93% human, 7% murine
- Binds to VEGF with high affinity
- Prevents VEGF from binding to its receptors, inhibits VEGF induced angiogenesis
Oceans: Chemotherapy with or without Bevacizumab in Patients with Platinum-Sensitive Recurrent Ovarian Cancer

Patients randomized to Gemcitabine + Carboplatin (GC) +/- Bevacizumab

- **GC + PL**: 242
- **GC + BV**: 242

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>GC + PL (n=242)</th>
<th>GC + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>187 (77)</td>
<td>151 (62)</td>
</tr>
<tr>
<td>Stratified analysis HR (95% CI)</td>
<td>0.484</td>
<td>0.484</td>
</tr>
<tr>
<td>Log-rank P</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

**Progression-Free Survival (proportion)**

Aghajanian et al, Journal of Clinical Oncology, June 2012
Poly (ADP-ribose) Polymerase (PARP): Mechanism of Action

- PARPs: family of enzymes that repair single-strand DNA breaks (SSB)
- Unrepaired SSB may result in double strand breaks (DSB) in replicating DNA
- BRCA genes encode for proteins that are important for the repair of double-strand DNA breaks by the HRR pathway
- PARP inhibition leads to DSB persistent DNA lesions normally repaired by HRR, causing apoptosis of the BRCA deficient cells.
Olaparib and cediranib
Synergy between hypoxia and inhibition of DNA repair

![Graph showing survival probability over months for Olaparib and Cediranib/Olaparib treatments with median PFS of 9.0 months for Olaparib and 17.7 months for Cediranib/Olaparib, with p-value of 0.005 and HR of 0.42 (95% CI: 0.23-0.76).

Circulating endothelial cells d3/d0

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Ced/Olap</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Median PFS</td>
<td>9.0 mo</td>
<td>17.7 mo</td>
</tr>
</tbody>
</table>

**NRG GY004**: O/OC/SoC Phase III, Liu PI  
**NRG GY005**: O/C/OC/SoC Phase II/III, Lee PI

Liu et al, poster updating tablet olaparib results

Liu et al, Lancet Oncol, 2015; Lee et al, Front Womens Cancers, in press

Presented By Elise Kohn at 2015 ASCO Annual Meeting
Overall survival in patients with platinum-sensitive relapsed serous ovarian cancer receiving olaparib maintenance monotherapy: An interim analysis

Jonathan A Ledermann,1 Philipp Harter,2 Charlie Gourley,3 Michael Friedlander,4 Ignace Vergote,5 Gordon Rustin,6 Clare Scott,7 Werner Meier,8 Ronnie Shapira-Frommer,9 Tamar Safra,10 Daniela Matei,11 Anitra Fielding,12 Stuart Spencer,12 Philip Rowe,12 Elizabeth Lowe13 and Ursula Matulonis14

1UCL Cancer Institute, University College London and UCL Hospitals, London, UK; 2Kliniken Essen Mitte, Essen, Germany; 3University of Edinburgh Cancer Research UK Centre, Medical Research Council Institute of Genetics and Molecular Medicine, Edinburgh, UK; 4University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia; 5University of Leuven, Leuven, Belgium; 6Mount Vernon Hospital, Northwood, UK; 7Royal Melbourne Hospital, Parkville, Australia; 8Evangelisches Krankenhaus, Dusseldorf, Germany; 9Chaim Sheba Medical Center, Tel Hashomer, Israel; 10Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; 11Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 12AstraZeneca, Macclesfield, UK; 13AstraZeneca, Gaithersburg, MD, USA; 14Dana-Farber Cancer Institute, Boston, MA, USA

ClinicalTrials.gov identifier: NCT02755545. This study was sponsored by AstraZeneca

ASCO ANNUAL MEETING ’16

Presented By Jonathan Ledermann at 2016 ASCO Annual Meeting
Study 19: Phase II trial design, endpoints and BRCA testing

N=265
- ‘Platinum-sensitive’ recurrent high-grade serous ovarian cancer
- ≥2 prior regimens of platinum-based chemotherapy
- Complete or partial response to most recent platinum-based regimen

Double-blind randomization 1:1
n=136
- Olaparib maintenance monotherapy (400 mg bid, capsules)
- Treatment until progression
n=129
- Placebo (bid, capsules)

Primary endpoint: Progression-free survival (PFS) by RECIST 1.0
Secondary endpoints included:
  - Overall survival (OS), safety and tolerability
  - Exploratory endpoints:
    - Time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST)

BRCA testing:
- Previous local germline BRCA testing (case report forms)
- Retrospective germline BRCA testing or tumour BRCA testing

BRCAm: n=136
BRCAwt: * n=118

*BRCAwt patients did not have a detected BRCAm or had a BRCAm of unknown significance
bid, twice daily; BRCAwt, BRCA1/2 wild type; RECIST, Response Evaluation Criteria in Solid Tumors

ASCO ANNUAL MEETING ‘16
Presented By Jonathan Ledermann at 2016 ASCO Annual Meeting
Study 19: Olaparib maintenance monotherapy leads to a meaningful clinical benefit in ovarian cancer patients

- PFS: Statistically significant improvement in progression-free survival with olaparib\(^1\)\(^2\)
  - **Overall population:**
    - Median PFS (olaparib vs placebo): 8.4 months vs 4.8 months
    - HR=0.35, \(P<0.0001\)
  - **BRCAm subgroup:**
    - Median PFS (olaparib vs placebo): 11.2 months vs 4.3 months
    - HR=0.18, \(P<0.0001\)

- TFST: Time to first subsequent therapy or death significantly improved with olaparib\(^2\)
  - Represents the time women are free from next line of chemotherapy

- TSST: Time to second subsequent therapy or death significantly improved with olaparib\(^2\)
  - Can demonstrate benefit beyond the next line of chemotherapy; helps address the confounding impact of crossover

- **Patients with a BRCAm** received the greatest benefit from maintenance olaparib\(^2\)

- TFST and TSST are clinically meaningful exploratory endpoints

HR, hazard ratio

Presented By Jonathan Ledermann at 2016 ASCO Annual Meeting
ARIEL2 designed to assess rucaparib efficacy in three prospectively defined molecular subgroups

Key Eligibility (N=180)
- High-grade serous or endometrioid OC
  - Known gBRCA enrollment capped at N=15
- ≥1 prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Tumor tissue (screening biopsy and archival)

Analysis of HRD Subgroups
Primary endpoint
- PFS
Secondary endpoints
- ORR
  - RECIST
  - RECIST + CA-125
- Safety
- PK

NGS of tumor tissue allows patients to be classified

600 mg BID rucaparib until disease progression

BRCA\textsuperscript{mut}

BRCA-like

Biomarker Negative

gBRCA = germline BRCA.
Primary efficacy analysis: PFS in BRCAmut and BRCA-like versus Biomarker Negative patients

Progression-free survival by HRD molecular subgroup

<table>
<thead>
<tr>
<th>HRD Subgroup</th>
<th>Median PFS, mo (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA\text{mut}</td>
<td>9.4 (7.3, Not Reached)</td>
</tr>
<tr>
<td>BRCA-like</td>
<td>7.1 (3.7, 10.8)</td>
</tr>
<tr>
<td>Biomarker Negative</td>
<td>3.7 (3.5, 5.5)</td>
</tr>
</tbody>
</table>

### Subgroup Comparison

<table>
<thead>
<tr>
<th>Subgroup Comparison</th>
<th>Hazard Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA\text{mut} vs Biomarker Negative</td>
<td>0.47 (0.35, 0.64)</td>
</tr>
<tr>
<td>BRCA-like vs Biomarker Negative</td>
<td>0.61 (0.41, 0.92)</td>
</tr>
</tbody>
</table>

CI=confidence interval.
Platinum Resistant Ovarian Cancer

- Single agent chemotherapy
- Bevacizumab in combination with chemotherapy, FDA approved 2014
- Olaparib (+BRCA; ≥ 3 prior lines of chemotherapy), FDA approved 2014

**New Directions:**
- Chemotherapy + new anti-angiogenic agents
- Other PARP inhibitors
- Immunotherapy
Bevacizumab in Platinum Resistant Ovarian Cancer AURELIA Trial

<table>
<thead>
<tr>
<th></th>
<th>CT (N=182)</th>
<th>BEV + CT (N=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>166 (91)</td>
<td>135 (75)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.4 (2.2–3.7)</td>
<td>6.7 (5.7–7.9)</td>
</tr>
<tr>
<td>HR (not stratified) (95% CI)</td>
<td>0.48 (0.38–0.60)</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value(^a)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)2-sided, not stratified

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)
A Phase II Study to Evaluate Safety and Efficacy of Niraparib in Advanced Ovarian Cancer (Active at the City of Hope)

Primary Objective:
• Evaluate anti-tumor activity of Niraparib (RR)

Secondary Objective:
• Evaluate the durability of anti-tumor activity of Niraparib.
• Evaluate anti-tumor activity of Niraparib in HRD-positive patients and in patients with gBRCAmut
• To evaluate the following additional clinical benefit measures of Niraparib
  • Disease control rate (DCR)
  • PFS
• To evaluate safety and tolerability
# PARP Inhibitors in Development

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>Company</th>
<th>Clinical development</th>
<th>Target disease site</th>
<th>Route of admin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-7338 (AG014699)</td>
<td>Pfizer</td>
<td>Phase II</td>
<td>Melanoma, Breast, NSCLC</td>
<td>IV</td>
</tr>
<tr>
<td>Veliparib (ABT 888)</td>
<td>Abbott</td>
<td>Phase II</td>
<td>Melanoma, NSCLC</td>
<td>PO</td>
</tr>
<tr>
<td>Olaparib (AZ 228)</td>
<td>Astra Zeneca</td>
<td>Phase II</td>
<td>Breast, Ovarian, Melanoma</td>
<td>PO</td>
</tr>
<tr>
<td>BSI 201</td>
<td>BiPar Sciences</td>
<td>Phase III</td>
<td>Breast, NSCLC</td>
<td>IV</td>
</tr>
<tr>
<td>BSI 401</td>
<td>BiPar Sciences</td>
<td>Preclinical</td>
<td></td>
<td>PO</td>
</tr>
<tr>
<td>MK4827</td>
<td>Merck</td>
<td>Phase I</td>
<td>BRCA breast</td>
<td>PO</td>
</tr>
<tr>
<td>CEP 9722</td>
<td>Cephalon</td>
<td>Phase I</td>
<td>With TMZ</td>
<td>PO</td>
</tr>
<tr>
<td>INO1001</td>
<td>Inotek</td>
<td>Phase I</td>
<td>TMZ in melanoma</td>
<td>IV</td>
</tr>
<tr>
<td>GPI 21016</td>
<td>MGI Pharma</td>
<td>Phase I</td>
<td>TMZ in melanoma</td>
<td>PO</td>
</tr>
<tr>
<td>BMN-673</td>
<td>LEAD Parma</td>
<td>Preclinical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Combination Clinical Trials with PARP inhibitors

- PARP inhib + DNA damaging agents (chemotherapy or radiotherapy)
- PARP inhib + Cell cycle checkpoints inhibit Chk1/2 (these agents impair HR repair)
- PARP inhib + PI3K inhibition (Impairs BRCA1/2 expression and sensitizes BRCA-proficient cancer cells to PARP inhibition)
- PARP inhib + anti-angiogenic agents
- PARP inhib + immunotherapy
General Approaches for Cancer Immunotherapy

- Peptide vaccine
- DC vaccine
- Genetic vaccine
- IL-2
- IFN
- IL-15
- IL-21
- Active immunotherapy
- CD40
- CD137
- OX40
- CTLA-4
- PD-1
- Adoptive cell transfer immunotherapy
- T cell cloning
- TCR or CAR genetic engineering
Cancer Vaccines in Ovarian Cancer

- **Peptide Vaccines**: Various ovarian CA antigens are potential targets: CEA, NY-ESO, HER-2/neu. Studies have shown long lasting T cell responses, usually not accompanied by durable clinical responses.

- **Dendritic Cell Therapy**: *In vitro* generation of autologous DC vaccines on a per patient basis is laborious and costly. Despite anti-tumor T cell responses, these vaccines demonstrated only modest clinical benefit.

- **Viral Vaccines**: Vaccinia and Fowlpox vectors (used to express NY-ESO-1 antigen) or Adp53 (which delivers the wild type p53 gene).
Cancer Vaccines: Issues

- Induce immune reaction against vaccine, but not the tumor
- Immune system mainly recognizes “neo-antigens” from “passenger” mutations rather than shared antigens
  - Antigens different for each tumor
  - Vaccine must involve autologous tumor cells
- Most immune-responsive tumors “autovaccinate”, but immune regulation prevents an effective response
- Even if vaccine enhances antitumor immunity, cells likely to be suppressed in the tumor microenvironment
- Conclusion: Vaccines are unlikely to have a major effect in the absence of immune checkpoint control
COH Clinical Trial Design

- Gemcitabine 1000mg/m2 IV days 1,8 every 3 weeks
- p53MVA: sc, upper arm 5 x10^8 pfu day 15

- p53MVA taken up by APCs in the skin which traffic to LN, prime a T cell response against overexpressed p53 protein in tumor cells

- Immune monitoring
  Biochemical (SMA18)
  Hematological (CBC)

- Primary endpoints Safety
  Immune response  RR, PFS
Study Design:

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>MVAp53 Dose</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.6 x 10^8 pfu MVAp53 every 3 weeks starting on Day 15</td>
<td>1000mg/m2 IV, days 1, 8 every 3 weeks.</td>
</tr>
<tr>
<td>-1</td>
<td>1.0 x 10^8 pfu MVAp53 every 3 weeks starting on Day 15</td>
<td>1000mg/m2 IV, days 1, 8 every 3 weeks.</td>
</tr>
</tbody>
</table>

**Treatment Plan:**
Patients will receive 3 cycles of subcutaneous injections of 5.6 x 10^8 pfu MVAp53, 3 weeks apart. Subcutaneous vaccine injections will be administered in the upper arm over the deltoid muscle.

Gemcitabine will be administered at 1000mg/m2 IV, days 1,8 every 3 weeks.

In case of hematologic or non-hematologic toxicity secondary to chemotherapy, the dose of gemcitabine will be decreased based on pre-specified dose modifications criteria. In case of suspected toxicity to MVAp53, the vaccine will be de-escalated to 10^8 pfu subcutaneously every 3 weeks, since this dose had been tested in a previous phase I study.
Immune Checkpoint Inhibition in Ovarian Cancer
PD-L1 Is Poor Prognostic Factor in Ovarian Cancer

PD-1/PD-L1 blockade may be a good target in ovarian cancer

PD-L1 Expression and Relationship With Response

- Among first 411 patients enrolled, 67% evaluable for PD-L1 status
- Correlation between PD-L1 expression and ORR ($P < 0.0001$)

ORR, RECIST v1.1

APS, Allred proportion score.
Analysis cut-off date: October 18, 2014

Presented By Adil Daud at 2015 ASCO Annual Meeting
Efficacy and Safety of anti-PD-1 Antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant Ovarian Cancer

Demographics:
- All patients platinum resistant (DFI < 6 months)
- 11 patients had > 4 prior chemotherapeutic regimen
- 2 ovarian clear cell carcinomas included

Overall Best Response to Nivolumab in Patients with Platinum Resistant Ovarian Cancer

KEYNOTE-028 (NCT02054806): Phase Ib Multicohort Study of Pembrolizumab for PD-L-1 + Advanced Solid Tumors

- **Patients**
  - Advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma
  - Failure of or inability to receive standard therapy
  - ECOG PS 0 or 1
  - ≥1 measurable lesion
  - PD-L1 positivity

Pembrolizumab 10 mg/kg IV Q2W

- **Response Assessment**
  - Complete or partial response or stable disease
  - Confirmed progressive disease or unacceptable toxicity
  - Treat for 24 months or until progression or intolerable toxicity
  - Discontinue pembrolizumab

*Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter
*Primary end points: ORR per RECIST v1.1 and safety
*Secondary end points: PFS, OS, duration of response

*If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy is received.

Antitumor Activity

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>3</td>
<td>11.5</td>
<td>2.4–30.2</td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td>3.8</td>
<td>0.1–19.6</td>
</tr>
<tr>
<td>Partial response</td>
<td>2</td>
<td>7.7</td>
<td>0.9–25.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6</td>
<td>23.1</td>
<td>9.0–43.6</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>17</td>
<td>65.4</td>
<td>44.3–82.8</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>9</td>
<td>34.6</td>
<td>17.2–55.7</td>
</tr>
</tbody>
</table>

Grade 3 toxicities 3.8%.
No treatment related deaths

RECIST v1.1, Investigator Review
Both confirmed and unconfirmed responses are included
Data cutoff date: March 13, 2015

Avelumab (MSB0010718C; anti-PD-L1) in Patients with Recurrent Ovarian Cancer JAVELIN Solid Tumor phase Ib trial

**Patients**
- Patients with refractory or recurrent ovarian cancer (n=75)
  - ECOG PS 0 or 1
  - No PD-L1 preselection

**Dosing**
- Avelumab 10 mg/kg IV Q2W until progression

**Objectives**
- **Primary:** safety and tolerability
- **Secondary:** ORR, PFS, OS, PD-L1 status

- RECIST 1.1 and irRC

Presented By Mary Disis at 2016 ASCO Annual Meeting
Avelumab in Recurrent Ovarian Cancer Update ASCO 2016

- 124 pts were treated with avelumab (the largest study of anti-PD(L)1 agents in pts with OC to date)
- Median number of prior therapies was 4 (range 1-13)
- Grade 3/4 TRAEs were reported in 8 pts (6.5%); of these, only increased lipase occurred in > 1 pt (n = 2). There were no treatment-related deaths
- ORR = 9.7% (95% CI: 5.1-16.3)
- SD= 44.4% and disease control rate (DCR)= 54.0%
- PD-L1 expression was evaluable in 74 pts (59.7%). Using a ≥1% cutoff for tumor cell staining, ORR was 12.3% in PD-L1+ vs. 5.9% in PD-L1− pts
- PFS = 11.3 wks and OS = 10.8 mos

Conclusions:
- Single-agent avelumab has modest activity in heavily pretreated pts with OC and an acceptable safety profile
- Ongoing Phase II study of Avelumab ± pegylated liposomal doxorubicin vs. pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory ovarian cancer
Adoptive T Cell Therapy: Directing the Immune System to Recognize and Attack Ovarian Cancer Cell
A Phase I/IIa, Open Label, Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer

Autologous Blood Collection

Patient screening (HLA and antigen)

Infusion of T Cells

Patient conditioning (lymphodepleting chemotherapy)

~21-28 days: apheresis to infusion

Monocyte and CD25 depletion

Antibody-Coated Beads and NY-ESO TCR Vector

Cells

Activation Expansion

Bead Removal and Formulation

T cell Product
Anti-angiogenic therapy, PARP inhibitors, and Immunotherapy in ovarian cancer: Conclusions

- **Anti-angiogenic therapy**
  - Bevacizumab was FDA approved in platinum resistant-recurrent epithelial ovarian cancer in combination with chemotherapy in 2014

- **PARP INHIBITORS**
  - Olaparib was FDA approved in 2014
  - Ongoing clinical trials with PARP inhibitors with various agents
  - Unanswered questions: predictive biomarkers, optimal timing, schedule, combination regimens, balancing risks and benefits

- **Immunotherapy**
  - Vaccines are unlikely to have a major effect as single agents; may have activity in combination with chemotherapy or immunotherapy agents
  - Check point inhibitors have modest activity in unselected patients but induce durable responses in a small number of patients
  - **T**cell strategies are investigational
Clinical Trials for Ovarian Cancer
City of Hope

- PHII-139, NCI#9825: A Phase 2 Study of Olaparib and Cediranib for the Treatment of Recurrent Ovarian Cancer
- A Phase 2, Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Niraparib in Women with Advanced, Relapsed, High-Grade Serous Epithelial Ovarian Cancer Who Have Received at Least Three Previous Chemotherapy Regimens
- PHII-131, NCI#9568: A Randomized Placebo-Controlled Phase II Trial Comparing Gemcitabine Monotherapy to Gemcitabine in Combination with AZD 1775 (MK 1775) in Women with Platinum Resistant Ovarian Cancer
- A Phase I/IIa, Open Label, Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1/LAGE-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer
- Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Optional Postoperative IP Chemotherapy in Patients with Recurrent Carcinoma of Ovarian, Fallopian Tube, Uterine, or Peritoneal Origin
Acknowledgements

• Patients and Families
• COH Medical and Gyn oncology teams
• Drs. R. Morgan, L. Leong, D. Diamond, S. Forman
• Funding Support
  - City of Hope
  - Grateful Patient Programs
  - Princess Margaret and Chicago N01 Consortia.
  - Industry (Adaptimmune, Tesaro)