Immunotherapy for Ovarian Cancer

Prof. Lana E. Kandalaft

Director | Centre of Experimental Therapeutics, Department of Oncology, UNIL CHUV

Assistant Professor, Ludwig Cancer Research Branch
Adjunct Assistant Professor, University of Pennsylvania
Is there a role for immunotherapy in Ovarian Cancer?

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.

After CR with chemotherapy, only patients with TILs survive or are in remission long-term.

At 96–132 months:
- >60% alive

At 96 months:
- 50% in remission

Meta-analysis of intraepithelial TIL impact in ovarian cancer: 10 studies; 1,815 patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang (2003)</td>
<td>1.65</td>
<td>0.18</td>
<td>9.8%</td>
<td>5.21 [3.66, 7.41]</td>
<td>2003</td>
</tr>
<tr>
<td>Sato (2005)</td>
<td>0.67</td>
<td>0.26</td>
<td>4.7%</td>
<td>1.95 [1.17, 3.25]</td>
<td>2005</td>
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<tr>
<td>Hamanishi (2007)</td>
<td>2.03</td>
<td>0.5</td>
<td>1.3%</td>
<td>7.61 [2.86, 20.29]</td>
<td>2007</td>
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<tr>
<td>Han (2008)</td>
<td>0.56</td>
<td>0.23</td>
<td>6.0%</td>
<td>1.75 [1.12, 2.75]</td>
<td>2008</td>
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<td>Tomsova (2008)</td>
<td>1.32</td>
<td>0.25</td>
<td>5.1%</td>
<td>3.74 [2.29, 6.11]</td>
<td>2008</td>
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<tr>
<td>Adams (2009)</td>
<td>0.69</td>
<td>0.21</td>
<td>7.2%</td>
<td>1.99 [1.32, 3.01]</td>
<td>2009</td>
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<td>Clarke (2009)</td>
<td>0.28</td>
<td>0.09</td>
<td>39.1%</td>
<td>1.32 [1.11, 1.58]</td>
<td>2009</td>
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<td>Stumpf (2009)</td>
<td>0.89</td>
<td>0.15</td>
<td>14.1%</td>
<td>2.44 [1.81, 3.27]</td>
<td>2009</td>
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<tr>
<td>Leffers (2009)</td>
<td>1.02</td>
<td>0.25</td>
<td>5.1%</td>
<td>2.77 [1.70, 4.53]</td>
<td>2009</td>
</tr>
<tr>
<td>Milne (2009)</td>
<td>0.78</td>
<td>0.2</td>
<td>7.9%</td>
<td>2.18 [1.47, 3.23]</td>
<td>2009</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 2.05 [1.83, 2.28]

Heterogeneity: Chi² = 66.57, df = 9 (P < 0.00001); I² = 86%
Test for overall effect: Z = 12.72 (P < 0.00001)
Two (or three) immunophenotypes of ovarian cancer

- Immunogenic
- Non-Immunogenic

- Immune exclusion
- Immune ignorance
What do we know about the “immunogenic subtype”?

Pharmacological Intervention
- Checkpoint Inhibitors
- Cyclophosphamide
- IDO inhibitor
- Aspirin
Natural “completely personal” TILs
The generation of anti-tumour T cells used for adoptive cell therapy
TILS are powerful: Compelling Results in Late Stage Disease
TILs: Regressions in Late-Stage Disease
TILs: Durable Responses in Advanced Melanoma

19 of 20 complete responders are ongoing to >10 years
TILs in Ovarian Cancer

- TILs recognize Tumors
- TILs are antigen specific
- TILs are activated
- TILs are polyfunctional

- TIL Therapy for Metastatic Ovarian Cancer, NCT02482090
  Inge Marie Svane, Herlev Hospital

- TIL And Low-Dose Interleukin-2 Therapy in Patients With Platinum Resistant High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, NCT01883297
  University Health Network, Toronto
Challenges of TIL Therapy

• Patients have to undergo surgery - Tissue needs to be stored PROPERLY

• T cells are functionally ‘exhausted’

• TILs are of unknown antigen specificity

• Need for IL-2 and lymphodepletion (toxic)
Patient had previously been treated with 30 billion conventional nontransduced TILs, plus 7 doses of IL2 (720,000 IU/kg) and tumors progressed.

Using TILs expanded from the same original culture, the patient was retreated with a culture of $3 \times 100$ million NFAT.IL12 gene-modified TILs and has an ongoing complete regression at 38 months of disease metastatic to lung and lymph nodes.
Overcoming the Challenges

A “blueprint” for the treatment of patients with T cells recognizing tumor-specific mutations.
Patient with metastatic cholangiocarcinoma

Identified a T cell contained (CD4+ T helper 1 (TH1) cells) recognizing a mutation in erbb2 interacting protein (ERBB2IP) expressed by the cancer.

ACT of TIL containing about 25% of the mutation-specific T-cells

the patient achieved a decrease in target lesions with prolonged stabilization of disease.

The patient was retreated with a >95% pure population of mutation-reactive T cells
Naturally-occurring neo-epitope specific CD8+ T cells ARE detected in Ovarian Cancer Patients

19 Patients
1300 non-synonymous somatic mutations
Average of 69 somatic substitutions/patient
776 (9mer or 10mer) peptide neoepitopes were predicted to bind with high affinity to HLA-1

one-third (6/19)

Sara Bobisse
Alex Harari
George Coukos
Ovarian TILs recognize tumor neo-epitopes

<table>
<thead>
<tr>
<th>patient</th>
<th>somatic mutations</th>
<th>HLA-I</th>
<th>targeted mutations</th>
<th>peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>1758</td>
<td>26</td>
<td>HLA-A23:01</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLA-A29:01</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLA-B39:06</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLA-B44:03</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLA-C04:01</td>
<td>1</td>
<td>1</td>
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<td></td>
<td></td>
<td>HLA-C07:02</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>10</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What about Drugs?

- TGF-B
- IL-10
- Myeloid cells
- T-regulatory cells
- Myelosuppressive Chemotherapy
- Antibody –IL-10
- Antibody TGF-beta (Genzyme)
- Aspirin/Celebrex
- IDO Inhibitor (Incyte/Genentech/MS)

IDO-Positive Tumors are more likely to respond.
Lessons From Non Small Cell Lung Cancer

June 16, 2016

Merck’s Pembrolizumab demonstrates superior PFS and OS to Chemotherapy in Front line NSCLC patients whose tumors expressed high levels of PD-L1

Market Reaction to Merck

August 5, 2016

BMS’s Nivolumab failed to demonstrate superior PFS to Chemotherapy in Front line NSCLC patients whose tumors expressed high levels of PD-L1

Market Reaction to BMS

PD-L1 expression on at least 50% of tumor cells

PD-L1 expression on at least 5% or greater

Adapted - Courtesy of Priti Hedge
Summary of the PD-1/PDL-1 Clinical Trials to date

**Table 4. Clinical Trials Targeting the PD-1 Pathway in Ovarian Cancer.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Population</th>
<th>No. of Cases</th>
<th>PD-L1 Status</th>
<th>ORR</th>
<th>DCR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Relapsed platinum² ovarian cancer</td>
<td>18</td>
<td>Any</td>
<td>17%</td>
<td>44%</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>(Hamanishi et al., 2014)</td>
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<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Advanced ovarian cancer</td>
<td>26</td>
<td>PD-L1+</td>
<td>11.5%</td>
<td>34.6%</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>(Varga et al., 2015)</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Platinum² or chemotherapy² ovarian cancer</td>
<td>75</td>
<td>Any</td>
<td>10.7%</td>
<td>54.7%</td>
<td>0</td>
<td>8</td>
<td>33</td>
<td>(Disis et al., 2015)</td>
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<tr>
<td>BMS-936559</td>
<td>PD-L1</td>
<td>Advanced ovarian cancer</td>
<td>17</td>
<td>any</td>
<td></td>
<td>23.5%</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>(Brahmer et al., 2012)</td>
</tr>
</tbody>
</table>

**Abbreviations:** PD-1, programmed death-1; PD-L1, programmed death ligand 1; platinum², platinum-resistant; chemotherapy², chemotherapy resistant; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease.
PD-1/CTLA-4 dual blockade are beneficial in vivo

ID8 model
Immunocompetent B6 mice

A dual blockage of PD-1 and CTLA-4 resulted in the reversal of CD8+ T-cell dysfunction and led to tumor rejection in two thirds of the mice.
Immune check-point inhibitors trials in OC

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial number</th>
<th>Trial</th>
<th>Disease status</th>
<th>Immuno therapy agent(s)</th>
<th>Concurrent therapy</th>
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<tbody>
<tr>
<td>3</td>
<td>NCT02580058</td>
<td>A Study Of Avelumab Alone Or In Combination With Pemetrexed</td>
<td>recurrent platinum resistant</td>
<td>Avelumab</td>
<td>Liposomal Doxorubicin</td>
</tr>
<tr>
<td>3</td>
<td>NCT02718437</td>
<td>Avelumab In Previously Untreated Patients With Epithelial Ovarian Cancer (JAVELIN Ovarian 203)</td>
<td>primary</td>
<td>Avelumab</td>
<td>Carboplatin Paclitaxel</td>
</tr>
<tr>
<td>3</td>
<td>ENGOT-ev20- GCIG</td>
<td>A randomized, double-blinded, phase II study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab</td>
<td>recurrent platinum sensitive</td>
<td>Atezolizumab</td>
<td>Carboplatin Paclitaxel</td>
</tr>
<tr>
<td>2</td>
<td>NCT02440425</td>
<td>Nivolumab With or Without Ipilimumab In Treating Patients With Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer</td>
<td>recurrent platinum resistant</td>
<td>Nivolumab</td>
<td>Carboplatin Paclitaxel</td>
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<tr>
<td>2</td>
<td>NCT2520154</td>
<td>Pembrolizumab In Combination With Carboplatin Paclitaxel</td>
<td>recurrent platinum resistant</td>
<td>Pembrolizumab</td>
<td>Carboplatin Paclitaxel</td>
</tr>
<tr>
<td>2</td>
<td>NCT2693938</td>
<td>Anti-programmed Cell Death-1 Ligand Antibody Atezolizumab, Bevacizumab, and/or Paclitaxel In Ovarian Cancer</td>
<td>recurrent platinum resistant</td>
<td>Atezolizumab</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>2</td>
<td>NCT2674061</td>
<td>Efficacy and safety of pembrolizumab (MK-3475) in platinum resistant ovarian cancer patients</td>
<td>recurrent platinum sensitive/resistant</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>NCT02484404</td>
<td>Nivolumab With or Without Carboplatin/Taxotere in Ovarian Cancer</td>
<td>recurrent platinum resistant</td>
<td>Nivolumab</td>
<td>Carboplatin Paclitaxel</td>
</tr>
<tr>
<td>1/2</td>
<td>NCT02485990</td>
<td>Study of Pembrolizumab Alone or Combined With Olaparib for Advanced Solid Tumors and Recurrent Ovarian Cancer</td>
<td>recurrent or persistent</td>
<td>Pembrolizumab</td>
<td>Olaparib</td>
</tr>
<tr>
<td>1/2</td>
<td>NCT02571725</td>
<td>PARP-inhibition and CTLA-4 blockade in BRCA-deficient Ovarian Cancer</td>
<td>recurrent platinum resistant</td>
<td>Pembrolizumab</td>
<td>Olaparib</td>
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<tr>
<td>1/2</td>
<td>NCT02658889</td>
<td>Study of Niraparib In Combination With Pembrolizumab (MK-3475) in Patients With Triple-negative Breast Cancer or Ovarian Cancer (KEYNOTE-162)</td>
<td>recurrent platinum resistant</td>
<td>Pembrolizumab</td>
<td>Niraparib</td>
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<td>1/2</td>
<td>NCT02726997</td>
<td>Matched Paired Pharmacodynamics and Feasibility Of Duvelumab In Combination With Chemotherapy In Frontline Ovarian Cancer</td>
<td>primary</td>
<td>Duvelumab</td>
<td>Carboplatin Paclitaxel</td>
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<td>1</td>
<td>NCT02737877</td>
<td>A Study of WT1 Vaccine and Nivolumab For Recurrent Ovarian Cancer</td>
<td>2nd remission</td>
<td>Nivolumab</td>
<td>WT1 vaccine</td>
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<tr>
<td>0</td>
<td>NCT02738830</td>
<td>A Study of Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>primary</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
</tbody>
</table>

Stéphanie L. GaillardEmail author, Angeles A. Secord and Bradley Monk, Gynecologic Oncology Research and Practice 2016
What do we know about the Immunology of “non-immunogenic” Tumors?

Immune exclusion

Immune ignorance
The Immune Excluded Tumor

“A Homing Defect”

Angiogenesis
Extracellular Matrix
Chemokines
Protease processing
B cells
Abnormalities in tumor endothelial cells (TEC)

High VEGF-A secreted by the tumor → morphological changes of TEC

Low adhesion molecules → lymphocytes cannot penetrate

Why is there a negative correlation?
The Endothelial Tumor Barrier Hypothesis
Many More Players

Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy

R. Buckanovich
A. Facciabene
G. Motz
G. Coukos
VEGF and PGE2 blockade reduce endothelial FasL & allow TIL accumulation

George Coukos

Greg Motz
# Anti-VEGF therapy and immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>NCT Reference</th>
<th>Condition</th>
<th>Treatment</th>
<th>Early results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01472081</td>
<td>RCC</td>
<td>Nivolumab + Sunitinib</td>
<td>Encouraging anti-tumor activity, frequent AEs [Amin, J Clinical Oncology, 32:5s, 2014]</td>
</tr>
<tr>
<td>NCT01984242</td>
<td>RCC</td>
<td>Atezolizumab + Bevacizumab or Sunitinib</td>
<td>Bevacizumab arm: good anti-tumor response in PDL1+ patients</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sunitinib arm: recruiting [Dermott, J Clin Oncol 35, 2017]</td>
</tr>
<tr>
<td>NCT01633970</td>
<td>Advanced Solid Cancer</td>
<td>Atezolizumab + Bevacizumab +/- Chemotherapy</td>
<td>Increased intratumoral CD8+ T cells in the Bevacizumab + atezolizumab arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[Sznol, J Clin Oncol 33, 2015]</td>
</tr>
<tr>
<td>NCT00790010</td>
<td>Melanoma Patients</td>
<td>Ipilimumab +/- Bevacizumab</td>
<td>Increased T cell infiltration in presence of Bevacizumab</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>[Hodi, Cancer Immun Research, 2014]</td>
</tr>
<tr>
<td>NCT02348008</td>
<td>RCC</td>
<td>Pembrolizumab + Bevacizumab</td>
<td>Acceptable safety profile [Dudek, J Clin Oncol 34, 2016]</td>
</tr>
<tr>
<td>NCT02366143</td>
<td>NSCLC</td>
<td>Atezolizumab + Bevacizumab + SOC</td>
<td>Not yet reported, outcome include TIL evaluation [Papadimitrakopoulou, J Clinic Oncol 34, 2016]</td>
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Clinical studies with anti-VEGF therapy and immune checkpoint inhibitors

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Blockade of VEGF-A and PD-1 and PGEDE2

Anti-programmed Cell Death-1 Ligand 1 (aPDL-1) Antibody Atezolizumab, Bevacizumab and Acetylsalicylic Acid in Recurrent Platinum Resistant Ovarian Cancer

This study is currently recruiting participants. (see Contacts and Locations)
Verified December 2016 by European Organisation for Research and Treatment of Cancer - EORTC
Sponsor:
European Organisation for Research and Treatment of Cancer - EORTC
ClinicalTrials.gov Identifier:
NCT02659384
First received: January 14, 2016
Last updated: December 23, 2016
Last verified: December 2016

Upon progression:
Continue treatment until PD
Pre-cycle 3

1:1:1:1

Bevacizumab 15mg/kg q3w

Atezolizumab 1,200mg q3w

Atezolizumab 1,200mg q3w + aspirin 325mg/day

Bevacizumab 15mg/kg q3w + aezolizumab 1,200mg q3w

Bevacizumab 15mg/kg q3w + aezolizumab 1,200mg q3w + aspirin 325mg/day

Investigator’s choice

Mandatory biopsy
Optional biopsy

Recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer

Anita Wolfer
Lana Kandalaft
George Coukos

Anita Wolfer
Lana Kandalaft
George Coukos

Anita Wolfer
Lana Kandalaft
George Coukos

Anita Wolfer
Lana Kandalaft
George Coukos

Anita Wolfer
Lana Kandalaft
George Coukos
The Immune Ignored Phenotype

“A T Cell Priming Defect”

Induce Immunogenicity

- Radiation
- Vaccines
- Chemotherapy
- CAR-T cells
- Oncolytic Viruses
- T cell-directed bispecific antibodies
Complete Remission Rates are increased when PDL-1 is combined with PLD (doxil)

JAVELIN 200 phase III study: Avelumab in Platinum Resistant/Refractory Ovarian Cancer

PI: E Pujade-Lauraine

Enrollment Criteria
- Progression ≤ 6 mo or no response to most recent platinum-based therapy
- No more than 3 prior therapies for platinum-sensitive disease, and no prior therapies for platinum-resistant disease
- Measurable disease
- ECOG PS 0 or 1
- Available tissue at baseline

Randomization
1:1:1

Avelumab

PLD + Avelumab

PLD
pegylated liposomal doxorubicin

n = ~550 (282 events)

Stratification: Platinum refractory vs resistant, #prior therapies, bulky disease.

Co-Primary Endpoints:
OS, PFS

Secondary Endpoints:
ORR, Duration of response, PROs, Safety
Whole Tumor Antigen Dendritic Cell Vaccine Study

1. Debulking
2. Tumor cells
3. HOCL Lysate
4. Apheresis
5. Monos
6. GM-CSF + IL-4
7. Pulsing with Whole Tumor Antigen
8. LPS + IFN-g
9. DC Vaccinations
10. Immature DC

Cheryl Chiang
What About the Mutational Load of Ovarian Cancer?

The prevalence of somatic mutations across human cancer types

Indications with higher mutational load have a higher frequency of neoantigens

High neoantigen load is associated with better outcome

Neoantigen based vaccines are feasible in tumors with high mutational load

Alexandrov et al., Nature (2013)
Naturally-occurring neo-epitope specific CD8+ T cells ARE detected in Ovarian Cancer Patients

19 Patients
1300 non-synonymous somatic mutations
Average of 69 somatic substitutions/patient
776 peptide neoepitopes were predicted to bind with high affinity to HLA-1

Patients with spontaneous neo-epitope-specific CD8 T-cell responses (n=19)

Sara Bobisse
Alex Harari
George Coukos

CONFIDENTIAL

Kandalaft et al, submitted
A Personalized NeoAntigen Specific Vaccine Could be Feasible in Ovarian Cancer
CAR/TCR T CELL THERAPY
Adoptive T cell Therapy with Genetically Engineered Peripheral Blood Lymphocytes.
The CD19 CAR T Cell Success Story for relapsed ALL and CLL

- Complete remission and long-term responses in up to 90% of acute lymphoblastic leukemia (ALL) patients (both adult and pediatric)
- And in > 50% of chronic lymphocytic leukemia (CLL) patients.
- On target side effects include B cell aplasia and cytokine release syndrome.

Emily Whitehead

Maud et al, NEJM 2015 & Blood 2015
Anti-mesothelin chimeric antigen receptor T cells in patients with Ovarian Cancer

Janos L. Tanyi (Univ. of Pennsylvania)

- **6 recurrent serous ovarian cancer** patients were treated with autologous lentiviral vector transduced T cells expressing a second generation chimeric antigen receptor (CAR) construct targeting mesothelin.

- **100% of the manufacturing** and administration were successful
- **No** Acute AEs and no CRS
- Anti-tumor efficacy is suggested by all **SD** from 6 treated patients on Day 28
- CART-meso cells **trafficked** to several tumor sites
A phase I clinical trial of adoptive transfer of folate receptor-alpha redirected autologous T cells for recurrent ovarian cancer

Lana E Kandalaft, Daniel J Powell Jr and George Coukos
Three Phenotypes of Ovarian Cancer represent
Three different limiting steps in the
Cancer Immunity Cycle

- Immune Ignored
- Immune excluded
- Disrupt the barrier
- Immunogenic

COMBINATIONS
- Induce Immunogenicity

DEVELOPMENT OF A BETTER IMMUNOSCORE
- CRYOPRESERVE TUMOR

Activate T cells ✖ Immunosupressive mechanisms

Adapted from Chen & Mellman, Immunity, 2013
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Our Patients

THANK YOU