Immunotherapy for Ovarian Cancer

Lana E. Kandalaft, Pharm.D, Ph.D, MTR

Adjunct Assistant Professor, University of Pennsylvania
Director, Center of Experimental Therapeutics, LICR, CHUV
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.

TIL Absent 40%

TIL Present 55%

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

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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<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)

Hwang et al, Gynecol Oncol 2011
Classification of ovarian tumors

Pre-existing immunity
Can be activated

No pre-existing immunity
Tumor barriers must be attenuated
Immunity must be induced

CD3^+ Stroma Islet
Cellular Immunotherapy Approaches

1. Tumor

Extract, activate and expand

Dendritic Cell Vaccines

Administer Immunotherapy for ovarian cancer: recent advances and perspectives. Zsiros, E; Tanyi, J; Balint, K, Kandalaf, L
Trial 3
Extract and Expand TILs

Debulking surgery performed

Lymphocytes isolated

Tumor infiltrating lymphocytes administered into the patient

Lymphocytes expanded
Cellular Immunotherapy Approaches

1. Tumor

2. Dendritic Cell Vaccines

Administer

Immunotherapy for ovarian cancer: recent advances and perspectives. Zsiros,E; Tanyi,J; Balint, K, Kandalaft, L
Whole Tumor Vaccines

ADVANTAGES

1) Target multiple antigens at the same time

1) Bypass the limitations of molecularly defined Ag (eg NYESO-1 30%).

2) Patients are vaccinated against their own tumor-associated antigens

4) Meta-analysis (Neller et al 2008) (3444 patients in 173 trials were examined) Patients with Objective Response:
   (8.1%): Whole tumor or tumor extracts as antigens
   (3.6%): Molecularly defined antigens were used

5) TCGA DATA: Average of 60 private, non-synonymous mutations per tumor (Integrated genomic analyses of ovarian carcinoma, Nature 2011)
Phase I Clinical Trial Of Autologous Dendritic Cell Vaccine Loaded With Autologous Tumor Cell Lysate For Recurrent Ovarian or Primary Peritoneal Cancer

Adoptive Transfer of Vaccine-Primed CD3/CD28-Costimulated Autologous T-cells Combined with Vaccine Boost

Lymphodepletion: intravenous cyclophosphamide (Cy, 300 mg/m²/day) and fludarabine (Flu, 30 mg/m²/day) for 3 days

Kandalaft et al, OncoImmun. 2013
UPCC-11807: Study Schema

Mo/Mφ → GM-CSF + IL-4 → imDC

Mo/Mφ → OVCA LYSATE → DCVax-L

DCVax-L: Pulsing with Whole Tumor Antigen

Kandalaft et al., OncoImmun. 2013
Clinical Results of UPCC-11807

RESPONSE:

- 2 PR
- 2 SD
- 2 PD

IFN-γ spots/10^6 Lymphocytes

Kandalaft et al, OncoImmun. 2013
1. Leukapheresis

2. Elutriation

3. Wave Perfusion / Expansion

4. Bead Removal

5. Resuspension

6. Infusion
Patients’ Tumor Reactive T Cells Correlate with Clinical Outcome

Kandalaft et al, OncoImmun. 2013
OPTIMIZING THE DENDRITIC CELL PLATFORM

Day-4 Myeloid Dendritic Cells Pulsed with Whole Tumor Lysate Are Highly Immunogenic and Elicit Potent Anti-Tumor Responses

http://www.translational-medicine.com/content/9/1/198

RESEARCH

Optimizing parameters for clinical-scale production of high IL-12 secreting dendritic cells pulsed with oxidized whole tumor cell lysate

COMMENTARY

A Phase I vaccine trial using dendritic cells pulsed with autologous oxidized lysate for recurrent ovarian cancer

Lana E Kandalaft1*, Cheryl L Chiang1, Janos Tanyi1, Greg Motz1, Klara Balint1, Rosemarie Mick2 and George Coukos1
Whole Tumor Antigen Dendritic Cell Vaccine Study

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

Kandalaft et al, JTM 2013
A PILOT CLINICAL TRIAL OF DENDRITIC CELL VACCINE LOADED WITH AUTOLOGOUS TUMOR FOR RECURRENT OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER

Cohort 1: OC-DC vaccine alone q 2 weeks

Cohort 2: OC-DC vaccine + Bevacizumab (10 mg/kg) q 2 weeks

Cohort 3: OC-DC vaccine + Bevacizumab (15 mg/kg) + Cyclophosphamide (200 mg/m²) q 3 weeks

Cohort 4: OC-DC vaccine + Bevacizumab (15 mg/kg) + Cyclophosphamide (200 mg/m²) q 3 weeks + Daily 325 mg Enteric Coated Aspirin (currently enrolling)

Kandalaft et al, JTM 2013
Rationale of combining antiangiogenesis therapy and metronomic chemotherapy on the tumor microenvironment

Kandalaft et al, JTM 2013
19809-105 A Patient who has been cured after receiving vaccine

Surgery 1
Oct 2007
(14 months)

Surgery 2
Dec 2008
(7 months)

Surgery 3
Jul 2009
(64 months)

Jan 2008
CHEMO
Mar 2008
RT
Jan 2009
CHEMO
Nov 2009
PERSONALIZED WHOLE TUMOR VACCINES
Nov 2014
May 2011
No Treatment
19809-203
Experienced Remission-Inversion

PFS$_1$ (26 months)  
PFS$_2$ (46 months)  
Hernia Repair

CHEMOTHERAPY
IMMUNOTHERAPY (VACCINE AND T CELLS)

CA125 U/mL

Number of IFN-gamma spots

Pre-Vac  Post-Vac  3 months  6 months
71% of patients have a prolonged progression free survival on immunotherapy.

Surgery 1

Surgery 2

PFSB

PFSA

Recurrence

Recurrence

Only 3 of those patients who have a shorter PFS, have a PFS interval of 0.5 or below.

Kandalaft et al, In Prep
Clinical Results: Comparison with a Control Group

Kaplan Meier estimates of overall survival - UPCC 19809

P=0.03
## Clinical Results

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Chemotherapy + Vaccine</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Free Survival at 6 months</td>
<td>75%</td>
<td>45%</td>
</tr>
<tr>
<td>Time to progression</td>
<td>15 months</td>
<td>6 months</td>
</tr>
<tr>
<td>1-year survival</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>2-year survival</td>
<td>75%</td>
<td>47%</td>
</tr>
</tbody>
</table>
Cellular Immunotherapy Approaches

- Collect
- Genetically Engineer T cells
- Viral vector
- Administer

A T-cell attacking a tumor
CAR Based Immunotherapy

Treatment of large, established human ovarian cancer using Folate Receptor alpha CAR gene therapy

Dan Powell, PhD, Cancer Res 2011
Drug-based Immunotherapy for Ovarian cancer

**Dendritic Cell Activation**
- Toll-like Receptor Agonists
- CD40L

**T cell Activation**
- Checkpoint Blockade
- IDO-1 Blockade
- Cytokine Therapy

**Combinations**

**Immunogenic Cell Death**
- Immunogenic chemotherapy
- Radiation

**Ovarian cancer cells**

**Dendritic cell**
- CD80/86
- MHC
- CD40

**T cell**
- CD3
- CD40L
- PD-L1
- CTLA-4
- CD28
- LAG-3
- TCR

**Regulatory T cell**
- CD25
- CTLA-4
- PD-1
- Anti-CD25

**Anti-CTLA4**

**Anti-CD40L**

**Anti-LAG3**

**Anti-PD-L1**

Chemotherapy Resistant Ovarian Cancer Cured by IL-2

Controls:
50% dead within 1 year
0% survival at 2 years

59 patients receiving IL-2
17% cleared the tumor
8% cured, no relapse for 7 years

Edwards R JCO 1997; CII 2009
DC Activation and Immunogenic Cell Death

VTX-2337 (A TLR8 agonist) in combination with Doxil Abrogate Tumors in mice

(G. Coukos and A. Facciabene)
### GOG-9925: VTX-2337 + PLD

**Preliminary Data**

<table>
<thead>
<tr>
<th>VTX-2337 Dose</th>
<th>No. of Cycles</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg/m²</td>
<td>2</td>
<td>Stable Disease</td>
</tr>
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<td>2.5 mg/m²</td>
<td>2</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>2.5 mg/m²</td>
<td>6</td>
<td>Complete Response*</td>
</tr>
<tr>
<td>3.0 mg/m²</td>
<td>4</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>3.0 mg/m²</td>
<td>6</td>
<td>Complete Response*</td>
</tr>
<tr>
<td>3.0 mg/m²</td>
<td>2</td>
<td>Progressive Disease</td>
</tr>
<tr>
<td>3.5 mg/m²</td>
<td>1</td>
<td>Progressive Disease</td>
</tr>
<tr>
<td>3.5 mg/m²</td>
<td>3</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>3.5 mg/m²</td>
<td>5</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>3.5 mg/m²</td>
<td>4</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>3.5 mg/m²</td>
<td>8</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>3.5 mg/m²</td>
<td>2</td>
<td>TBD</td>
</tr>
</tbody>
</table>

* presented by Monk et al. at ASCO 2013
## Phase 2 Ovarian Study: VTX-2337 + PLD (GOG-3003)

<table>
<thead>
<tr>
<th>Population</th>
<th>Study Design</th>
<th>Objectives</th>
</tr>
</thead>
</table>
| Patients with platinum resistant ovarian cancer n=300 | 28-day dose cycle:  PLD (40 mg/m²): Day 1  
VTX-2337 (3.0 mg/m²): Day 3, 10*, and 17*  
*Starting with Cycle 5, dosing with VTX-2337 is on Day 3 only  
Repeat cycles until confirmed disease progression  
Tumor assessment starting at week 12 and Q8 weeks thereafter | Primary: Overall Survival  
Secondary: PFS (irRECIST), tolerability  
Other: Response rate, DCR, biomarkers (including TruCulture, Immune Score), TLR8 SNPs |

G. Coukos and R Hershberg
A Phase 1/2 Study of Chemo-immunotherapy with Toll-like Receptor 8 Agonist Motolimod (VTX-2337) and anti-PD-L1 Antibody MEDI4736 in Subjects with Ovarian Cancer After Failure of Platinum-Based Chemotherapy.

Sponsor: Ludwig Institute for Cancer Research, New York, NY

PI: George Coukos

Multisite clinical trial run in The US and in Lausanne