Immunotherapy for Ovarian Cancer

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

TIL Absent
40%

CD3+

Stroma

Islet

TIL Present
55%

TIL Absent
40%

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>
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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>
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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>
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</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>
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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>
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<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>
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<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>
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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>
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<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>
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<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>2.05 [1.83, 2.28]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 66.57, df = 9 (P < 0.000001); I² = 86%
Test for overall effect: Z = 12.72 (P < 0.000001)

Hwang et al, Gynecol Oncol 2011
Classification of ovarian tumors

Understand the biology and Think of the Therapeutic interventions which induce immunity
CELL-BASED IMMUNOTHERAPY

DRUG-BASED IMMUNOTHERAPY
Cellular Immunotherapy Approaches

Tumor

Extract, activate and expand

Administer

Success of Adoptive Therapy Using TILs in Melanoma

From July 2002 to July 2007, 787 tumors from 402 patients were processed for TIL. Active, specific TILs were identified in 269 patients (67%), leading to the eventual treatment of 107 patients (27%).

Goff SL et al. J Immunother 2010

Prolonged Disease-free Period in Patients with Advanced Epithelial Ovarian Cancer after Adoptive Transfer of Tumor-infiltrating Lymphocytes

Fig. 2 Overall survival rate of patients with ovarian cancer stage II, III, and IV who were diagnosed as having no evidence of disease after completion of chemotherapy.
Patients are hospitalized during treatment (approximately 3 weeks)

Patients are admitted to hospital day -8 and receive lymphodepleting chemotherapy (cyclophosphamide and fludarabine= on day -7 to day -1.

TILs are infused on day 0

Interleukin-2 is administered in an i.v. continous decrescendo regimen starting approximately 6 hours after TIL infusion with a duration of approximately 5 days.
Different Types of Vaccines and Antigens

Antigen Type:
- Tumor Lysate
- Virus
- mRNA
- DNA
- Peptide Antigen
- Protein

DC Type:
- Plasmacytoid
- Myeloid Derived
- Langerhans

Routes of Administration:
- Intravenous
- Intranalodal
- Subcutaneous
- Intradermal

Combinations:
- Adjuvants
- Chemotherapy
- Checkpoint inhibitors
- Antiangiogenic
- Cytokines

**Vaccines in ovarian cancer: overview**

Published results from Clinical Trials between 2000 and 2015

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Pilot</th>
<th>Trials published</th>
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<tr>
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<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>DC</td>
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<td>Lm strain</td>
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<td>Peptide</td>
<td>15</td>
<td>8</td>
<td>5</td>
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<tr>
<td>Protein</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>8</td>
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<td>Virus</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
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<td>WTC</td>
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</table>

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Pilot</th>
<th>Total</th>
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<tr>
<td>DC auto WTL</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
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<td>DC protein</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DC synth.pept.</td>
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<td>2</td>
<td></td>
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<td>2014</td>
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<tr>
<td>2015</td>
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*NOTE: CarboHydrate (CH) vaccine shown here in Phase II failed to demonstrate any improvement in patient survival in a big Phase III trial reported in 2011 for more than 1000 breast cancer patients.*
Advantages of Whole Tumor Vaccines

1) Target multiple antigens at the same time

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

1) TCGA DATA: Average of 60 private, non-synonymous mutations per tumor (Integrated genomic analyses of ovarian carcinoma, Nature 2011)

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

2) 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
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
Clinical Results of UPCC-11807

RESPONSE:

- 2 PR
- 2 SD
- 2 PD

Graphs showing changes in tumor volume, T-cell numbers, and IFN-g production over time for patients S-01 to S-06.
Dendritic cell vaccinations administered to patient

Apheresis

3 months later

T Cell expansion

T Cell isolation

Graph showing cell growth over days of culture
Patients' Tumor Reactive T Cells Correlate with Clinical Outcome

PR post vaccination
CR post T-cells

PR post vaccination
PD post T-cells

SD post vaccination
SD post T-cells

Kandalaft et al, OncoImmun. 2013
Day-4 Myeloid Dendritic Cells Pulsed with Whole Tumor Lysate Are Highly Immunogenic and Elicit Potent Anti-Tumor Responses

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

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
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

Janos Tanyi

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

Adapted Kandalaft et al, JTM 2013
71% OF PATIENTS HAD A PROLONGED PROGRESSION FREE SURVIVAL ON IMMUNOTHERAPY
Increased PFS in Tumor-Responding Patients (All Cohorts Pooled)
Overall survival – Vaccine Study – D730

Kaplan Meier estimates of overall survival

- Cyclophosphamide + Bevacizumab
- Cyclophosphamide + Bevacizumab + Vx
- Control group
- Cohort 1
- Cohort 2
- Cohort 3
- Cohort 4

Analysis time (days)

Survival probability

Rosie Mick
## 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>

*Kandalaft et al, In Prep*
Cellular Immunotherapy Approaches

3

A T-cell attacking a tumor

Genetically Engineer T cells

Viral vector

Administer

collect
Cell therapy shows remarkable ability to eradicate cancer in clinical study

Date: February 19, 2014

Source: Memorial Sloan-Kettering Cancer Center

Investigators from Memorial Sloan Kettering Cancer Center have reported more encouraging news about one of the most exciting methods of cancer treatment today. The largest clinical study ever conducted to date of patients with advanced leukemia found that 88 percent achieved complete remissions after being treated with genetically modified versions of their own immune cells. The results were published today in Science Translational Medicine.
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
Current Adoptive T cell studies

1) White blood cells genetically engineered to recognize NY-ESO-1, given along with dendritic cells pulsed with NY-ESO-1 antigen as a vaccine, in a phase II trial for patients with stage IV, advanced, or refractory malignancies (NCT01697527).

2) A phase I/II trial to test T cells genetically engineered to target VEGFR (a protein necessary for blood vessel formation) in patients with metastatic cancer, including ovarian cancer (NCT01218867).

3) A phase I/II trial to test T cells genetically engineered to target the MAGE-A3 or NY-ESO-1 antigens in patients with ovarian cancer (NCT01567891).

4) A phase I trial to test chimeric antigen receptor (CAR) T cell therapy targeting mesothelin, which is overexpressed in ovarian cancer, pancreatic cancer, and mesothelioma, at the University of Pennsylvania (NCT02159716).
Drug-based Immunotherapy for Ovarian Cancer

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

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

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

**Combinations**

Immunotherapy for ovarian cancer: recent advances and perspectives. Zsiros, E; Tanyi, J; Balint, K, Kandalaft, L
Checkpoint Blockade
Ipilimumab and Tremelimumumab
CTLA-4 Antibodies.
CTLA-4 antibody blockade accomplishes the durable regression of advanced ovarian carcinoma in the absence of significant toxicity.
Clinical Studies of CTLA-4 Antibody as Monotherapy or in combination

Phase II study of ipilimumab monotherapy in patients with platinum-sensitive ovarian cancer is ongoing  (NCT01611558).

PARP-inhibition and CTLA-4 Blockade in BRCA-deficient Ovarian Cancer (NCT02571725)

Study of Tremelimumab Alone or Combined With Olaparib for Patients With Persistent EOC (Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma) (NCT02485990)

Nivolumab With or Without Ipilimumab in Treating Patients With Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer (NCT02498600)

A Phase 1 Study to Evaluate MEDI4736 in Combination With Tremelimumab NCT01975831
PD-1/PDL-1 Antibodies
Best overall responses in all patients in two cohorts with anti–programmed death 1 (PD-1) antibody.
Activity of anti–programmed death 1 (PD-1) antibody in two patients with a complete response to recurrent ovarian cancer.

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>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Relapsed platinumR 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>
</tr>
<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>PlatinumR or chemotherapyR 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>
</tr>
<tr>
<td>BMS-936559</td>
<td>PD-L1</td>
<td>Advanced ovarian cancer</td>
<td>17</td>
<td>any</td>
<td>23.5%</td>
<td></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; platinumR, platinum-resistant; chemotherapyR, chemotherapy resistant; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease.
Clinical Studies of PD-1/PDL-1 Antibody as Monotherapy or in combination

A phase I trial testing urelumab (BMS-663513), an anti-4-1BB/CD137 antibody made by Bristol-Myers Squibb, in patients with advanced cancers (NCT01471210).

Another phase I/II trial of urelumab given along with nivolumab (anti-PD-1) in patients with solid tumors (NCT02253992).

A phase I trial to test PF-05082566, an anti-4-1BB/CD137 antibody developed by Pfizer, in patients with solid tumors (NCT01307267).

A phase I study of lirilumab, an anti-KIR antibody being developed by Bristol-Myers Squibb, in combination with nivolumab (anti-PD-1) in patients with advanced solid tumors (NCT01714739).

A phase I trial to test BMS-986016, a LAG-3 antibody, with or without nivolumab (anti-PD-1) in patients with solid tumors (NCT01968109).
Combination cancer immunotherapy and new immunomodulatory targets

Kathleen M. Mahoney, Paul D. Rennert, and Gordon J. Freeman
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
COMBINATIONS
Standard Chemotherapy and Immunomodulation

Immunogenic Cell Death and DC activation

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

VTX-2337

activates myeloid dendritic cells
activates monocytes and NK cells

(G. Coukos and A. Facciabene)
**GOG-9925:** VTX-2337, a TLR8 agonist, plus chemotherapy (DOXIL) in recurrent ovarian cancer: A phase I study

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<tr>
<th>VTX-2337 Dose</th>
<th>No. of Cycles</th>
<th>Best Response</th>
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<tbody>
<tr>
<td>2.5 mg/m²</td>
<td>2</td>
<td>Stable Disease</td>
</tr>
<tr>
<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>
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<td>3.0 mg/m²</td>
<td>6</td>
<td>Complete Response*</td>
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<td>3.5 mg/m²</td>
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* presented by Monk et al. at ASCO 2013
GOG-3003 Trial Design

A Randomized, Double-Blind, Placebo-Controlled Phase II Study of VTX-2337 in Combination with Pegylated Liposomal Doxorubicin (PLD) in Patients with Recurrent or Persistent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
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.

PI: George Coukos
Blockade of PGE2 + VEGF-A and PD-1 results in positive interactions.

Anita Wolfer
George Coukos
Lana Kandalaft
Roche / Genentech
Bevacizumab plus atezolizumab in RCC

RCC = renal cell carcinoma
Sznol, et al. ASCO GU 2015
Phase II trial of bevacizumab + aspirin + atezolizumab in platinum-resistant ovarian cancer: trial design

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

1:1:1:1

- Bevacizumab 15mg/kg q3w
- Atezolizumab 1,200mg q3w
- Atezolizumab 1,200mg q3w + aspirin 325mg/day
- Bevacizumab 15mg/kg q3w + atezolizumab 1,200mg q3w
- Bevacizumab 15mg/kg q3w + atezolizumab 1,200mg q3w + aspirin 325mg/day

**Mandatory biopsy**

**Optional biopsy**

Upon progression:
- Continue treatment until PD
- Continue tumour assessment q9w until PFS2

Pre-cycle 3

**PFS** = progression-free survival
Phase II trial of Avastin + aspirin + MPDL3280A

Primary objectives

- Biological activity (and functional correlates) of Avastin + aspirin + MPDL3280A on peripheral blood T cell subsets and on the tumour microenvironment, including intratumoural T cells
- Safety of Avastin + aspirin + MPDL3280A

Secondary objectives

- 6-month PFS
- mTTP
- ORR using immune-related response criteria (irRC)
- Effect of pre-existing intratumoural T cells on the clinical results

Countries

9 countries planned: Switzerland, UK, Belgium, Netherlands, Italy, Spain, Germany, France and Austria