Novel Immunotherapy Approaches and Cellular-based Therapies for Gynecologic Oncology Patients

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Disclosures

• Research Funding
  – Iovance
  – Pfizer
  – BMS
  – AZ

• Advisory Board
  – Aravive
  – Almac

• DSMB
  – Genentech-Roche
Approaches for Increasing the Efficacy of Checkpoint Inhibitors

- Increasing tumor cell death and/or DNA damage
  - Chemotherapy, radiotherapy, PARPi

- Combining with other immune-modulating drugs
  - Co-stimulatory (OX40, 4-1BB)
  - Co-inhibitory (TIM3, LAG3)
  - Vaccines, STING agonists, ACT

- Modulating the tumor micro-environment
  - Targeting components of the microenvironment (e.g. macrophages, cancer associated fibroblasts)
  - Targeting the tumor and draining lymph nodes directly

- Importance of on-treatment biopsies
Biomarkers for Response to ICB?

Biomarkers: When not What?

Pre-Treatment

CD8  CD4  CD3
Nonresponder
Responder

Early On-Treatment

CD8  CD4  CD3
Nonresponder
Responder

Chen..Wargo, Cancer Discovery, 2016
Checkpoint Inhibitors in Patients Treated with Neoadjuvant Chemotherapy

NACT

Bx  Carbo+Taxol  →  Debulking  →  chemo + Pembrolizumab  →  Pembro

Tissue acquisition

Adjuvant

Maintenance

Bx  chemo + Durvalumab  →  Debulking  →  chemo + Durvalumab  →  Durvalumab

Tissue acquisition

PI: Rob Coleman

PI: Shannon Westin
Combination versus Sequential Checkpoint Inhibitors in Patients with Platinum Resistant Ovarian Cancer

PI: Amir Jazaeri
Can Efficacy be Improved by Route of Administration?

Carlino and Vong Clin Cancer Res 2016
Adoptive Cell Therapies

- Treatments in which T cells are collected from a patient and grown and/or modified in the laboratory
- Goal is to increase the number of T cells that are able to kill cancer cells
- T cells are given back to the patient to help the immune system fight disease.

<table>
<thead>
<tr>
<th>TIL</th>
<th>Circulating tumor-specific T cells</th>
<th>Engineered Receptors (CAR/TCR)</th>
</tr>
</thead>
</table>


CAR vs Transgenic TCR

Kershaw et al., Clin Trans Immunology 2014
# Transferred Receptor: TCR / CAR

## Target Antigen/ Cancer

<table>
<thead>
<tr>
<th>Antigen</th>
<th>CAR or TCR</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>MART-1, gp100</td>
<td>TCR</td>
<td>Melanoma</td>
</tr>
<tr>
<td>HPV E6</td>
<td>TCR</td>
<td>Cervical, Anal, Vaginal</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>TCR</td>
<td>Sarcoma, Myeloma, (Breast, Lung)</td>
</tr>
<tr>
<td>MAGE-A3</td>
<td>TCR</td>
<td>Any cancer MAGE-A3+</td>
</tr>
<tr>
<td>P53</td>
<td>TCR</td>
<td>Any cancer overexpresses p53</td>
</tr>
<tr>
<td>CD19</td>
<td>CAR</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>EGFRvIII</td>
<td>CAR</td>
<td>Glioblastoma, Breast, Lung</td>
</tr>
<tr>
<td>Kappa Light Chain</td>
<td>CAR</td>
<td>CLL, B cell NHL</td>
</tr>
<tr>
<td>Her2Neu</td>
<td>CAR</td>
<td>Osteosarcoma, Breast</td>
</tr>
<tr>
<td>CD30</td>
<td>CAR</td>
<td>Lymphoma (NHL and HD)</td>
</tr>
<tr>
<td>GD2</td>
<td>CAR</td>
<td>EBV-specific CTL targeting GBM</td>
</tr>
</tbody>
</table>
A phase I clinical trial of adoptive T cell therapy using IL-12 secreting MUC-16^{ecto} directed chimeric antigen receptors for recurrent ovarian cancer

Mythili Konuru^{1,2}, Roisin O’Cearbhaill^{1,2}, Swati Pendharkar^{1}, David R Spriggs^{1,2} and Renier J Brentjens^{1,2*}
Adoptive Cell Therapy: TIL

Adapted from Wu, Forget, Chacon et al. Cancer J. 2012
TIL outcomes in melanoma

43% clinical response rate
Including 6 CR

Adapted from Wu, Forget, Chacon et al. Cancer J. 2012
Complete Regression of Metastatic Cervical Cancer After Treatment With Human Papillomavirus–Targeted Tumor-Infiltrating T Cells

Sanja Stevanović, Lindsey M. Draper, Michelle M. Langhan, Tracy E. Campbell, Mei Li Kwong, John R. Wunderlich, Mark E. Dudley, James C. Yang, Richard M. Sherry, Uday S. Kammula, Nicholas P. Restifo, Steven A. Rosenberg, and Christian S. Hinrichs
# TIL outcomes in melanoma

**Table 1. Characteristics of Patients and Administered T Cells**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Histology</th>
<th>HPV Type</th>
<th>Sites of Disease</th>
<th>Prior RT</th>
<th>Prior Systemic Treatment</th>
<th>Cells (x 10^3)</th>
<th>Within CD3+ (%)</th>
<th>No. of IL-2 Doses</th>
<th>Duration or TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>ASC</td>
<td>18</td>
<td>Iliac lymph nodes, lung, lung hilum, mediastinum, pelvis, vaginal cuff</td>
<td>Yes</td>
<td>Cisplatin</td>
<td>101.4</td>
<td>29</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>SCC</td>
<td>18</td>
<td>Bone, liver, lung, lung hilum, mediastinum, pelvis</td>
<td>Yes</td>
<td>Cisplatin, carboplatin, paclitaxel, topotecan, ixabepilone dimethane sulfonate</td>
<td>126.0</td>
<td>10</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>SCC</td>
<td>16</td>
<td>Iliac lymph nodes, lung hilum, mediastinum, retroperitoneum</td>
<td>Yes</td>
<td>Cisplatin, vinorelbine, docetaxel, gemcitabine, paclitaxel, topotecan</td>
<td>152.0</td>
<td>21</td>
<td>83</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>SCC</td>
<td>16</td>
<td>Axilla, breast, liver, omentum, pleura, soft tissue</td>
<td>Yes</td>
<td>Cisplatin, carboplatin, paclitaxel, docetaxel, irinotecan, dovitinib, pemtrexed</td>
<td>80.1</td>
<td>23</td>
<td>76</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>SCC</td>
<td>18</td>
<td>Brain, mediastinum, supraclavicular nodes</td>
<td>Yes</td>
<td>Cisplatin</td>
<td>90.0</td>
<td>66</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>AC</td>
<td>18</td>
<td>Abdominal wall, liver, peripancreatic, pelvis, retroperitoneum</td>
<td>Yes</td>
<td>Cisplatin</td>
<td>74.7</td>
<td>61</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>AC</td>
<td>18</td>
<td>Abdominal wall, lung</td>
<td>Yes</td>
<td>Cisplatin, paclitaxel, carboplatin, bevacizumab</td>
<td>33.4</td>
<td>36</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>ASC</td>
<td>18</td>
<td>Pelvis, perihepatic mass</td>
<td>Yes</td>
<td>Cisplatin, paclitaxel</td>
<td>46.1</td>
<td>64</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>AC</td>
<td>18</td>
<td>Axilla, bone, lung, mediastinum, pelvis, retroperitoneum</td>
<td>Yes</td>
<td>Cisplatin, carboplatin, paclitaxel, ipilimumab</td>
<td>70.2</td>
<td>33</td>
<td>59</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: AC, adenocarcinoma; ASC, adenocarcinoma squamous cell carcinoma; CR, complete response; HPV, human papillomavirus; IL-2, interleukin-2; PD, progressive disease; PR, partial response; RT, radiotherapy; SCC, squamous cell carcinoma; TTP, time to progression.
OvCa has similar CD3$^+$ infiltration to Melanoma

Sakellariou-Thompson et al. SITC 2016
OvCa has similar CD8+ TIL infiltration to Melanoma

Sakellariou-Thompson et al. SITC 2016
T cell infiltration and CD8/CD4 ratio in primary vs metastasis or pre/post chemotherapy.

CD3+ TIL infiltration in fresh samples

CD8:CD4 ratio in fresh samples

Donastas Sakellariou-Thompson
Upcoming Adoptive Cell Therapy Trials at MDACC

- **2017-0505 (NCT03108495)** A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety Using Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Recurrent, Metastatic, or Persistent Cervical Carcinoma

- **2017-0672 (NCT03449108)** Clinical study to assess efficacy and safety of LN-145 (Manufactured by Iovance) Across Multiple Tumor Types
  - PR ovarian cancer, bone sarcomas, and pancreatic cancer

- **2017-0671** Clinical Study to Assess Efficacy and Safety of MDA-TIL (Manufactured at MDACC) Across Multiple Tumor Types
  - PR ovarian cancer, bone sarcomas, poorly differentiated sarcomas, TBD

- **2016-0400 (NCT03318900)** Phase I/Ib Study of Adoptive Cellular Therapy Using Autologous IL-21-Primed CD8+ Tumor Antigen-Specific T Cells in Combination With Utomilumab (PF-05082566) in Patients With Platinum Resistant Ovarian Cancer
Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

Nikolaos Zacharakis¹, Harshini Chinnasamy¹, Mary Black¹, Hui Xu¹, Yong-Chen Lu¹, Zhili Zheng¹, Anna Pasetto¹, Michelle Langhan¹, Thomas Shelton¹, Todd Prickett¹, Jared Gartner¹, Li Jia¹, Katarzyna Trebska-McGowan², Robert P. Somerville¹, Paul F. Robbins¹, Steven A. Rosenberg¹*, Stephanie L. Goff¹ and Steven A. Feldman¹
Future of Immunotherapy for Gynecologic Cancers

• The goal of rational combination immuno-oncology requires understanding cancer-specific immuno-inhibitory mechanisms at work.

• Significant impact will require innovative clinical trial designs and translational science (e.g. looking for dynamic changes using on-treatment biopsies).

• Partner with and industry, scientific societies, and regulatory agencies to focus on the unique win-win opportunities presented by gynecologic cancers to advance the field and improve outcomes for our patients.
Thank you