Adoptive T Cell Therapy
TILs & TCRs & CARs

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Denmark
Therapeutic approaches to overcome immune tolerance in tumors
Tumor infiltrating lymphocytes (TILs)

T cells infiltrate melanomas

TILs have the potential to recognize multiple targets on tumor cells

Erdag G et al., Cancer Res 2012;72(5):1070-80

Tumors continue to grow

Tumor infiltrating lymphocytes

- TIL Quantity
- TIL Activation
- Immune Suppression

Tumor cell

Lymphocyte
Adoptive T-cell therapy using autologous tumor-infiltrating lymphocytes

30-45 days for TIL production
GMP facility for TIL preparation
Adoptive TIL therapy in combination with lymphodepleting chemotherapy and IL-2

3-step treatment:

Lymphodepleting chemotherapy

2 days: cyclophosphamide (60 mg/kg)
5 days: Fludarabin (25 mg/m²)

Intravenous infusion of in vitro expanded TILs

Day 7: reinfusion of 20–140x10⁹ TILs

High dose IL-2

720,000 IU/kg iv every 8 hours until limiting toxicity

Patients are hospitalized for ~ 3 weeks

Rosenberg et al, PNAS 2004
Adoptive T cell Therapy - NCI, USA

- Response rates
  ~ 50-70%

- > 20%
  long term survivors

20 CR: 3-year survival 100% and 5-year survival 93%
Practical problems in early TIL trials

Patient drop out rate was up to 70% due to:

- criteria for in vitro anti-tumor reactivity could not be satisfied
- extended cell preparation time did not match with rapid disease progression

Optimization of TIL preparation and logistics

Uncertain clinical benefit of culture selection leading to long production time (pre-REP)

Initial TIL Expansion (pre-REP)
Standard or Young TILs

Standard (“Selected”) TILs

- >5x10^7 cells from one single fragment
- Further culture selection
- Potential to select the best TILs

Young TILs

- >5x10^7 cells from all fragments
- “All in” REP
- Faster (20 vs 30 days)
- Less labour intensive
- "younger" phenotype
- Higher success rate

Tran KQ et al., J Immunother 2008
Besser et al., J Immunother 2009
Complicated and labour intensive manufacturing (REP)

Rapid Expansion (REP)
From Static to Dynamic culture (REP)
Introduction of a Practical Protocol for semi-automated TIL expansion

- Less manipulations
- Technician dependent actions x6 only during weekdays
- Scalable to Blood Banks

Anti-CD3
Feeder Cells
IL-2

REP

Day 7

Wave® Bioreactor
A simplified protocol for clinical grade TILs manufacturing using the Wave® bioreactor

Marco Donia, Signe M Larsen, Özcan Met, Inge Marie Svane
Cytoterapy 2014. 16(8):1117-20
CD8+ T cell numbers and tumor reactivity are important for tumor regression

Dudley M et al., J Clin Oncol 2013

Radvanyi et al., Clin Cancer Res 2013

CCIT unpublished 2014
TIL factors associated with response

Factors associated with clinical response

- Telomere (kb) vs. Response
- CD27 CD8 cells ($\times 10^{-10}$) vs. Response
- Persistence at 1 mo (%) vs. Response

*CR+PR vs NR: $< 0.001$
Toxicity

- Intensive chemotherapy
  - Bone marrow suppression
  - Electrolyte derangement
  - Nausea, diarrhoea

- T-cells
  - Fever, chills, dyspnoea

- IL-2
  - Fever, capillary leak syndrome, fluid retention, hypotension, electrolyte derangement, nausea

All patients experience temporary grade III-IV events
All patient receive RBC/platelet transfusion and antibiotics

Detailed guidelines for toxicity management!
Bone marrow suppression

Besser et al
Clin Cancer Res
2010
Evidence for other TIL therapy relevant indications: Improved Survival with “high” lymphocyte infiltration

...in Ovarian Cancer

...in Breast Cancer

...in Gastrointestinal Cancer


Mahmoud SM et al., JCO 2011

Galon J et al., Science 2006
<table>
<thead>
<tr>
<th>Reference</th>
<th>Histology</th>
<th>Patients (n)</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al, 1988</td>
<td>Melanoma</td>
<td>20</td>
<td>11 (55%)</td>
<td>1 (5%)</td>
<td>10 (50%)</td>
<td>First in human trial (TILs + IL-2)</td>
</tr>
<tr>
<td>Dudley et al, 2005</td>
<td>Melanoma</td>
<td>43</td>
<td>21 (49%)</td>
<td>5 (12%)</td>
<td>16 (37%)</td>
<td>Pre-conditioning regimen to improve TIL engraftment using “modern-era” lymphodepletion (NMA) and high dose interleukin-2 (IL-2)</td>
</tr>
<tr>
<td>Dudley et al, 2008</td>
<td>Melanoma (2 Gy TBI)</td>
<td>25</td>
<td>13 (52%)</td>
<td>5 (20%)</td>
<td>8 (32%)</td>
<td>In sequential trials, response rate directly proportional to depth of pre-conditioning lymphodepletion, prompting evaluation in a randomized trial.</td>
</tr>
<tr>
<td>Rosenberg et al, 2011</td>
<td>Melanoma (12 Gy TBI)</td>
<td>25</td>
<td>18 (72%)</td>
<td>10 (40%)</td>
<td>8 (32%)</td>
<td></td>
</tr>
<tr>
<td>Dudley et al, 2010</td>
<td>Melanoma (NMA)</td>
<td>33</td>
<td>19 (58%)</td>
<td>3 (9%)</td>
<td>16 (49%)</td>
<td>Minimally cultured CD8-enriched TILs can mediate effective tumor regression.</td>
</tr>
<tr>
<td>Dudley et al, 2010</td>
<td>Melanoma (6 Gy TBI)</td>
<td>23</td>
<td>11 (48%)</td>
<td>2 (9%)</td>
<td>9 (39%)</td>
<td>Minimally cultured bulk TILs can mediate effective tumor regression.</td>
</tr>
<tr>
<td>Itzhaki et al, 2011</td>
<td>Melanoma</td>
<td>31</td>
<td>15 (48%)</td>
<td>4 (13%)</td>
<td>11 (35%)</td>
<td></td>
</tr>
<tr>
<td>Pilon-Thomas et al, 2012</td>
<td>Melanoma</td>
<td>13</td>
<td>5 (38%)</td>
<td>2 (15%)</td>
<td>3 (23%)</td>
<td>Bulk TIL screened for IFN-γ secretion can mediate durable tumor regression.</td>
</tr>
<tr>
<td>Radvanyi et al, 2012</td>
<td>Melanoma</td>
<td>31</td>
<td>13 (42%)</td>
<td>2 (6%)</td>
<td>11 (35%)</td>
<td>TIL, particularly differentiated effector cells (CD8+/BTLA+) can mediate durable tumor regression.</td>
</tr>
<tr>
<td>Ellebaek et al, 2012</td>
<td>Melanoma</td>
<td>6</td>
<td>2 (33%)</td>
<td>2 (33%)</td>
<td>0</td>
<td>Complete and durable responses were induced after TIL treatment using NMA in combination with low-dose IL-2.</td>
</tr>
<tr>
<td>Besser et al, 2013</td>
<td>Melanoma</td>
<td>80</td>
<td>23 (29%)</td>
<td>5 (6%)</td>
<td>18 (23%)</td>
<td>Complete and durable responses with NMA TIL. First intent-to-treat analysis, demonstrating a 29% dropout rate, mainly due to disease progression</td>
</tr>
<tr>
<td>Tran et al, 2014</td>
<td>Cholangiocarcinoma</td>
<td>1</td>
<td>1 (100%)</td>
<td>-</td>
<td>1 (100%)</td>
<td>First successful treatment of a solid epithelial cancer using TILs targeting a mutated antigen.</td>
</tr>
</tbody>
</table>

* As measured by WHO or RECIST criteria

* An additional 6 patients resected, but not treated

* An additional 5 patients resected, but not treated

* 23 (29%) patients enrolled, but not treated

Seminars in Oncology, Vol 42, No 4, August 2015, pp 626-639
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, Udai S. Kammula, Nicholas P. Restifo, Steven A. Rosenberg, and Christian S. Hinrichs

Purpose
Metastatic cervical cancer is a prototypical chemotherapy-refractory epithelial malignancy for which better treatments are needed. Adoptive T-cell therapy (ACT) is emerging as a promising cancer treatment, but its study in epithelial malignancies has been limited. This study was conducted to determine if ACT could mediate regression of metastatic cervical cancer.

Patients and Methods
Patients enrolled onto this protocol were diagnosed with metastatic cervical cancer and had previously received platinum-based chemotherapy or chemoradiotherapy. Patients were treated with a single infusion of tumor-infiltrating T cells selected when possible for human papillomavirus (HPV) E6 and E7 reactivity (HPV-TILs). Cell infusion was preceded by lymphocyte-depleting chemotherapy and was followed by administration of aldesleukin.
## 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 (\times 10^6)</th>
<th>CD8+</th>
<th>CD9+</th>
<th>No. of IL-2 Doses</th>
<th>Response Type</th>
<th>Duration of 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, retroperitoneum, vaginal cuff</td>
<td>Yes</td>
<td>Cisplatin</td>
<td>101.4</td>
<td>29</td>
<td>72</td>
<td>7</td>
<td>PD</td>
<td>1</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, ifosfamide, dimethane sulfonate</td>
<td>126.0</td>
<td>10</td>
<td>94</td>
<td>3</td>
<td>PR</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, vincristine, bleomycin, gemcitabine, paclitaxel, topotecan</td>
<td>162.0</td>
<td>21</td>
<td>83</td>
<td>2</td>
<td>CR</td>
<td>22+</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>SCC</td>
<td>16</td>
<td>Axilla, breast, liver, omentum, pleura, soft tissue</td>
<td>Yes</td>
<td>Cisplatin, carboplatin, paclitaxel, fluorouracil, irinotecan, dovitinib, pemtrexed</td>
<td>80.1</td>
<td>23</td>
<td>76</td>
<td>7</td>
<td>PD</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>SCC</td>
<td>10</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>
<td>PD</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>AC</td>
<td>18</td>
<td>Abdominal wall, liver, paracolic, pelvis, retroperitoneum</td>
<td>Yes</td>
<td>Cisplatin</td>
<td>74.7</td>
<td>61</td>
<td>35</td>
<td>8</td>
<td>CR</td>
<td>15+</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>58</td>
<td>8</td>
<td>PD</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>ASC</td>
<td>18</td>
<td>Pelvis, perihpatic mass</td>
<td>No</td>
<td>Cisplatin, paclitaxel</td>
<td>46.1</td>
<td>64</td>
<td>29</td>
<td>9</td>
<td>PD</td>
<td>2</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>
<td>PD</td>
<td>1</td>
</tr>
</tbody>
</table>

**Abbreviations:** AC, adenocarcinoma; ASC, adenoacanthoma; SCC, squamous cell carcinoma; CR, complete response; HPV, human papillomavirus; IL-2, interleukin-2; PD, progressive disease; PR, partial response; RT, radiotherapy; TTP, time to progression.

### Graphs

**A**
- **Cell Infusion**
- **Change from Baseline (%)**
- **Time Since HPV-TIL Infusion (months)**

**B**
- **Cell Infusion**
- **Change from Baseline (%)**
- **Time Since HPV-TIL Infusion (months)**
Present status for TIL based therapy

- TIL based therapy has mainly been tested in melanoma patients

- Efficacy has only been confirmed in smaller phase I/II studies
  - but response rates of around 50 % has repeatedly been found in MM

- The treatment is complex with transient high grade toxicity
  - but manageable and safe in the presence of qualified clinical staff

- GMP cell lab facilities and staff is need for TIL production
  - but optimized methods have made it feasible for hospital blood supply unit
Therapeutic approaches to overcome immune tolerance in tumors
Gene modified T-cells for adoptive therapy

Fig. 4. Gene-modification of peripheral blood lymphocytes. In an attempt to broaden the reach of ACT to other cancers, techniques are being developed to introduce antitumor receptors into normal T cells that could be used for therapy. The top panel shows the insertion of a conventional TCR into a patient’s T lymphocytes, followed by the expansion and infusion back into the patient. The bottom panel shows the insertion of a CAR into a patient’s T cell, followed by the expansion of these cells and their re-infusion. TCRs and CARs are fundamentally different in their structures and in the structures that they recognize. TCRs are composed of one α chain and one β chain, and they recognize antigens that have been processed and presented by one of the patient’s own MHC molecules. CARs are artificial receptors that can be constructed by linking the variable regions of the antibody heavy and light chains to intracellular signaling chains (such as CD3-zeta, CD28, 41BB) alone or in combination with other signaling moieties. CARs recognize antigens that do not need to be MHC-restricted, but they must be presented on the tumor cell surface.
### Table 2. ACT Clinical Trials Employing T Lymphocytes Engineered to Express Specific T-Cell Receptors for the Treatment of Solid Cancers

<table>
<thead>
<tr>
<th>Reference</th>
<th>Histology</th>
<th>Antigen (epitope)</th>
<th>HLA</th>
<th>Patients (n)</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgan et al, 2006</td>
<td>Melanoma</td>
<td>MART-1 (aa 27-35)</td>
<td>A*02</td>
<td>15</td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (13%)</td>
<td>First demonstration of use of TCR-engineered T cells to mediate tumor regression. No treatment-related toxicities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson et al, 2009</td>
<td>Melanoma</td>
<td>MART-1 (aa 27-35)</td>
<td>A*02</td>
<td>20</td>
<td>6 (30%)</td>
<td>0</td>
<td>6 (30%)</td>
<td>Demonstrated importance of clonal selection. Grade 3 ototoxicity in 8 patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gp100 (aa 154-162)</td>
<td>A*02</td>
<td>16</td>
<td>3 (19%)</td>
<td>1 (6%)</td>
<td>2 (13%)</td>
<td>Demonstrated use of TCR with murine constant regions. Grade 3 ototoxicity in 1 patient.</td>
</tr>
<tr>
<td>Parkhurst et al, 2011</td>
<td>Colon</td>
<td>CEA (aa 691-699)</td>
<td>A*02</td>
<td>3</td>
<td>1 (33%)</td>
<td>0</td>
<td>1 (33%)</td>
<td>Recognition of CEA in normal colonic mucosa resulted in 3 patients with severe colitis.</td>
</tr>
<tr>
<td>Robbins et al, 2011</td>
<td>Synovial sarcoma, melanoma, breast, ovarian prostate, thyroid</td>
<td>NY-ESO-1 (aa 157-165)</td>
<td>A*02</td>
<td>17</td>
<td>9 (53%)</td>
<td>2 (12%)</td>
<td>7 (41%)</td>
<td>First report using of TCR-engineered T cells targeting a cancer germ line antigen to mediate tumor regressions. Modification of CDR2 of TCR alpha chain to increase TCR avidity without altering antigen specificity. No major toxicities observed.</td>
</tr>
<tr>
<td>Morgan et al, 2013</td>
<td>Melanoma</td>
<td>MAGE-A3 (aa 112-120)</td>
<td>A*02</td>
<td>9</td>
<td>5 (56%)</td>
<td>1 (11%)</td>
<td>4 (44%)</td>
<td>Previously undescribed MAGE-A12 expression in brain tissue resulted in 3 patients with severe neurologic toxicity, including 2 TRM⁵.</td>
</tr>
<tr>
<td>Linette et al, 2013</td>
<td>Melanoma, myeloma</td>
<td>MAGE-A3 (aa 168-176)</td>
<td>A*01</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Off-target activity against myocardial protein titin resulted in 2 TRM secondary to cardiogenic shock.</td>
</tr>
</tbody>
</table>

* HLA: Human leukocyte antigen restriction element recognized by the TCR.

⁵ TRM: Treatment-related mortality
A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1–Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response

Table 3. Clinical response to adoptive transfer of T cells transduced with anti-NY-ESO-1 TCR

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Total</th>
<th>PR</th>
<th>CR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial cell sarcoma</td>
<td>18</td>
<td>10 (55)</td>
<td>1 (6)</td>
<td>11 (61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47+, 18, 11, 10, 8, 7, 5, 4, 3, 3</td>
<td>20+</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>20</td>
<td>7 (35)</td>
<td>4 (20)</td>
<td>11 (55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28, 10, 8, 6+, 5, 3, 3</td>
<td>58+, 54+, 40+, 24</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Response data updated as of December 1, 2014, or the last follow-up date.
Abbreviations: PR, partial response; CR, complete response; OR, objective response.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Histology</th>
<th>CAR Generation</th>
<th>Target</th>
<th>Patients (n)</th>
<th>Response OR(%)</th>
<th>CR(%)</th>
<th>PR(%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamers et al, 2006</td>
<td>Clear Cell RCC</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>CAIX</td>
<td>3</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td>First clinical experience targeting CAIX.</td>
</tr>
<tr>
<td>Lamer et al, 2013</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al, 2007</td>
<td>Neuroblastoma</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>L1-CAM</td>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>0</td>
<td>Reported on-target off-tumor reactivity of CAR-T cells, which could be attenuated by pre-treatment with CAIX monoclonal antibody (G250).</td>
</tr>
<tr>
<td>Pule et al, 2008</td>
<td>Neuroblastoma</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>GD2</td>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>1 (12.5%)</td>
<td>Tumor regression and in vivo persistence of EBV specific CAR-T cells for the treatment of neuroblastoma.</td>
</tr>
<tr>
<td>Louis et al, 2011</td>
<td></td>
<td></td>
<td></td>
<td>11&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 (36%)</td>
<td>3 (27%)</td>
<td>1 (9%)</td>
<td></td>
</tr>
<tr>
<td>Morgan et al, 2010</td>
<td>Colon adenocarcinoma</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>ErbB2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>Mortality because of on-target, off-tumor reaction to low expression in normal lung tissue.</td>
</tr>
<tr>
<td>Beatty et al, 2014</td>
<td>Mesothelioma, pancreatic adenocarcinoma</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>mesothelin</td>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (50%)</td>
<td>0</td>
<td>1 (50%)</td>
<td>Mesothelin-specific CAR mRNA-engineered T cells induce anti-tumor activity</td>
</tr>
</tbody>
</table>

<sup>a</sup> OR, overall response; CR, complete response; PR, partial response; RCC, renal cell carcinoma; CAIX, carbonic-anhydrase IX; L1-CAM, L1 cell adhesion molecule; EBV, Epstein Barr virus; CAR, chimeric antigen receptor; NE, not evaluable for response after treatment.

<sup>b</sup> 4 additional patients enrolled (2 ineligible prior to treatment and unable to generate cell product for 2)
<sup>c</sup> 3 additional NED patients treated
<sup>d</sup> 8 additional NED patients treated
<sup>e</sup> 1 additional NE patient
Table 4. ACT Clinical Trials Employing T Lymphocytes Engineered to Chimeric Antigen Receptors for the Treatment of Hematologic Malignancies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Histology</th>
<th>CAR Generation</th>
<th>Target</th>
<th>Patients (n)</th>
<th>OR(%)</th>
<th>CR(%)</th>
<th>PR(%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Till et al, 2008</td>
<td>NHL, MCL</td>
<td>1st</td>
<td>CD20</td>
<td>5</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td>0</td>
<td>First report using electroporated CAR-T cells.</td>
</tr>
<tr>
<td>Till et al, 2012</td>
<td>Follicular B-cell lymphoma</td>
<td>3rd</td>
<td></td>
<td>3</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td></td>
<td>Increased persistence of CAR-T cells with IL-2 administration.</td>
</tr>
<tr>
<td>Kochenderfer et al, 2010</td>
<td>B-cell lymphoma</td>
<td>2nd</td>
<td>CD19</td>
<td>1</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td></td>
<td>First report of tumor regression in lymphoma patient treated with CD19 CAR.</td>
</tr>
<tr>
<td>Kochenderfer et al, 2014</td>
<td>DLBCL, CLL, SMZL, PMBCL, NHL</td>
<td></td>
<td></td>
<td>13</td>
<td>12 (92%)</td>
<td>8 (62%)</td>
<td>4 (30%)</td>
<td>First successful treatment of patients with DLBCL using CD19 CAR.</td>
</tr>
<tr>
<td>Kalos et al, 2011</td>
<td>CLL</td>
<td>2nd</td>
<td>CD19</td>
<td>3</td>
<td>3 (100%)</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
<td>Demonstrated in vivo expansion, persistence and establishment of memory for CAR-transduced T cells.</td>
</tr>
<tr>
<td>Porter et al, 2011</td>
<td>ALL</td>
<td>2nd</td>
<td>CD19</td>
<td>14</td>
<td>12 (75%)</td>
<td>10 (63%)</td>
<td>2 (13%)</td>
<td>First report of clinical response in ALL.</td>
</tr>
<tr>
<td>Brentjens et al, 2013</td>
<td>ALL</td>
<td>2nd</td>
<td>CD19</td>
<td>6</td>
<td>2</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>Successful use of donor-derived CD19-redirected virus-specific T cells for the treatment of B-cell malignancies following allogeneic stem cell transplant.</td>
</tr>
</tbody>
</table>

Abbreviations: OR, overall response; CR, complete response; PR, partial response; NHL, non-Hodgkin’s Lymphoma; MCL, mantle cell lymphoma; NED, no evaluable disease; NE, not evaluable for treatment response; CAR, chimeric antigen receptor; NCI, National Cancer Institute; DLBCL, diffuse large B cell lymphoma; CLL, chronic lymphocytic leukemia; SMZL, splenic marginal zone lymphoma; PMBCL, primary mediastinal B cell lymphoma; MSKCC, Memorial Sloan Kettering Cancer Center; ALL, acute lymphoblastic leukemia; EBV, Epstein-Barr virus.

a 4 additional NE patient treated, 2 NED and 2 NE
b 1 additional NE patients treated
c 2 additional NE patients treated
d 2 additional patients with molecular CR prior to cell infusion, CR defined as MRD-, PR as MRD+ (morphological residual disease)
e 2 additional NED patients treated
f 2 additional NED patients treated
Strengths and limitations of different forms of adoptive T-cell therapy

<table>
<thead>
<tr>
<th></th>
<th>Engineered TCR</th>
<th>CAR</th>
<th>TIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA dependency</strong></td>
<td>HLA restricted, generation of unique TCR for each HLA type</td>
<td>HLA independent</td>
<td>Autologous</td>
</tr>
<tr>
<td></td>
<td>Susceptible to resistance by HLA downregulation</td>
<td>Not susceptible to resistance by HLA downregulation</td>
<td>Susceptible to resistance by HLA downregulation</td>
</tr>
<tr>
<td><strong>Risk of off-tumor on-target toxicity</strong></td>
<td>Highest risk of off-tumor on-target toxicity due to cross recognition of an off-target peptide, especially in affinity enhanced peptides</td>
<td>Intermediate risk of off-tumor on-target toxicity, preclinical testing easiest</td>
<td>Safest</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Highest sensitivity, especially in affinity enhanced TCRs</td>
<td>Lower sensitivity, may require more antigen</td>
<td>High sensitivity</td>
</tr>
<tr>
<td><strong>Targeting intracellular antigens</strong></td>
<td>Routine</td>
<td>Complicated to target intracellular antigens, new advances permit targeting on HLA/peptide complexes in HLA dependent manner</td>
<td>Routine</td>
</tr>
<tr>
<td><strong>Clinical feasibility</strong></td>
<td>Routine</td>
<td>Routine</td>
<td>Challenging</td>
</tr>
<tr>
<td><strong>Diversity of tumor types applicable</strong></td>
<td>Presence of intracellular tumor associated antigen needed</td>
<td>Presence of tumor specific extracellular antigen needed</td>
<td>Limited application to diverse tumor types, tumors must be accessible and surgery routine</td>
</tr>
</tbody>
</table>

*Curr Opin Oncol 2014, 26:600–607*
Bio-break coming up!