Strategies for personalized cell therapy

*Lessons from CAR T Cells*

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Disclosure Information

David L Porter

- Speaker and members of study team have financial interest due to potential upstream IP and patents and licensure to Novartis

- COI managed in accordance with University of Pennsylvania policy and oversight

- Funding support for trials: ACGT, LLS, NCI, Novartis

- Member, ABIM Hematology Board exam writing committee.

- Please note that some of the studies reported in this presentation were published as an abstract and/or presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.
Adoptive Cell Therapy: 3 Approaches in Advanced Development

- Harvest PBMCs by apheresis
- T cell activation
- Transduction
- Excise tumor mass
- TIL cell isolation
- TIL cell expansion
- Infusion
- CAR T cells
- TCR T cells

Host condition chemotherapy
Lymphodepleted cancer patient
Rationale for Targeted Cellular Therapy with CAR T Cells

• Ultimately, targeted cellular immunotherapy could overcome many limitations of conventional chemotherapy and other forms of adoptive immunotherapy

• Genetically modified, immune (T) cells with redirected specificity to tumor antigens may combine advantages of:
  – Antibody therapy (specificity)
  – Cellular therapy (amplified response)
  – Vaccine therapy (memory activity)
CD19: An Ideal Tumor Target in B-Cell Malignancies

• CD19 expression is generally restricted to B cells and B cell precursors\(^1\)
  – CD19 is not expressed on hematopoietic stem cells\(^1\)

• CD19 is expressed by most B-cell malignancies\(^1\)
  – CLL, B-ALL, DLBCL, FL, MCL\(^1\)

• Antibodies against CD19 inhibit tumor cell growth

Targeting with **Chimeric Antigen Receptors**

- Antibody to target a specific protein on cancer cell.
- Sequences bring and keep protein on the surface of T cell.
- Signals for T cell activation (killing), growth, and survival.
Targeting CD19+ CLL with CAR-Modified T cells

- CARs combine an antigen recognition domain of antibody with intracellular signaling domains into a single chimeric protein
- Gene transfer (lentiviral vector) to stably express CAR on T cells confers novel antigen specificity

CAR, chimeric antigen receptor; TCR, T-cell receptor.
Overview of CTL019 Therapy

1. Leukapheresis
2. T-cell activation/transduction
3. Modified T-cell expansion
4. Chemotherapy
5. Modified T-cell infusion

14 days

*Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.*
2 Studies for CAR T cells in CLL: Design and Considerations

- Single center **pilot** trial of CTL019 (formally CART19) cells
- Primary objective:
  - Safety, feasibility and immunogenicity of CTL019
  - Detailed inclusion/exclusion at clinicaltrials.gov (NCT01029366)
  - CD19+ B cell malignancies with no available curative options (such as autologous or allogeneic SCT)
  - CLL: failed >2 prior therapies, progression within 2 years of last treatment.
  - Limited prognosis (<2 year) with available therapies.

CTL019 Dose Optimization Trial

• What is the optimal dose of CTL019 cells for future study?

Randomized phase 2 trial (NCT01747486)

**Primary Endpoint:** CR at 3 months
### CLL: Overall Response to CTL019

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>11/43</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(no progression)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>10/43</td>
<td>23%</td>
</tr>
<tr>
<td>Overall Response</td>
<td>21/43</td>
<td>49%</td>
</tr>
</tbody>
</table>
UPN02 Marrow Response by Day 31

Pre-infusions marrow: >50% involved by CLL (40x)

Day 31
No evidence CLL and negative by flow cytometry, cytogenetics, FISH or deep sequencing

Porter et al. NEJM, 2011
## Clinical Responses:
Bulky Tumor Eradicated Following CART19 Infusion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total Baseline Tumor Burden</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># cells</td>
<td>tumor mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(pounds)</td>
</tr>
<tr>
<td>UPN 01</td>
<td>2.51E+12</td>
<td>5.52</td>
</tr>
<tr>
<td>UPN 02</td>
<td>3.48E+12</td>
<td>7.67</td>
</tr>
<tr>
<td>UPN 03</td>
<td>1.32E+12</td>
<td>2.90</td>
</tr>
</tbody>
</table>

*Porter et al. NEJM, 2011
Kalos et al. Sci Trans Med 2011*
Rapid expansion of CART cells, rapid eradication of CLL in responders

UPCC04409-09

<table>
<thead>
<tr>
<th>D+1</th>
<th>D+6</th>
<th>D+8</th>
<th>D+10</th>
<th>D+28</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR19</td>
<td>42.7%</td>
<td>4.9%</td>
<td>1.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>CD8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CART-19 Persistence and B cell Aplasia (04409-02)
### Clinical Response: 04409

<table>
<thead>
<tr>
<th>UPN</th>
<th>Resp</th>
<th>Age</th>
<th>P53-</th>
<th># prior Rx</th>
<th>Dose CART10^8</th>
<th>CRS</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>CR</td>
<td>65</td>
<td>N</td>
<td>7</td>
<td>1.100</td>
<td>Y</td>
<td>Median age 66</td>
</tr>
<tr>
<td>02</td>
<td>CR</td>
<td>64</td>
<td>Y</td>
<td>4</td>
<td>0.140</td>
<td>Y</td>
<td>Median prior therapies 4</td>
</tr>
<tr>
<td>03</td>
<td>PR</td>
<td>78</td>
<td>Y</td>
<td>3</td>
<td>5.900</td>
<td>Y</td>
<td>P53 del, 3/8</td>
</tr>
<tr>
<td>05</td>
<td>PR</td>
<td>66</td>
<td>N</td>
<td>2</td>
<td>3.9</td>
<td>N?</td>
<td>Med CAR dose 1.45</td>
</tr>
<tr>
<td>09</td>
<td>CR</td>
<td>59</td>
<td>N</td>
<td>10</td>
<td>1.700</td>
<td>Y</td>
<td>Expansion &gt;3 logs</td>
</tr>
<tr>
<td>10</td>
<td>CR</td>
<td>78</td>
<td>N</td>
<td>5</td>
<td>3.700</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>PR+</td>
<td>66</td>
<td>N</td>
<td>5</td>
<td>1.2</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>PR+</td>
<td>60</td>
<td>Y</td>
<td>3</td>
<td>0.86</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>NR</td>
<td>63</td>
<td>N</td>
<td>4</td>
<td>0.650</td>
<td>N</td>
<td>Median age 67</td>
</tr>
<tr>
<td>07</td>
<td>NR</td>
<td>51</td>
<td>Y</td>
<td>5</td>
<td>0.170</td>
<td>N</td>
<td>Median prior therapies 4</td>
</tr>
<tr>
<td>14</td>
<td>NR</td>
<td>70</td>
<td>N</td>
<td>4</td>
<td>1.6</td>
<td>N</td>
<td>P53 del, 3/6</td>
</tr>
<tr>
<td>17</td>
<td>NR</td>
<td>78</td>
<td>N</td>
<td>8</td>
<td>1.15</td>
<td>N</td>
<td>Med CAR dose 1.3</td>
</tr>
<tr>
<td>18</td>
<td>NR</td>
<td>64</td>
<td>Y</td>
<td>3</td>
<td>2.8</td>
<td>N</td>
<td>Expansion &lt; 3 logs</td>
</tr>
<tr>
<td>25</td>
<td>NR</td>
<td>75</td>
<td>Y</td>
<td>7</td>
<td>2.7</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>
**No Dose:Response Relationship Observed?**

<table>
<thead>
<tr>
<th>Response*</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR/PR</strong></td>
<td>6 (54%)</td>
<td>4 (31%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td><strong>No response</strong></td>
<td>5 (46%)</td>
<td>9 (69%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11</td>
<td>13</td>
<td>24 (p=0.41)</td>
</tr>
</tbody>
</table>

unpublished
No Dose: Toxicity Relationship Observed
(n=28)

<table>
<thead>
<tr>
<th>CTL019 Dose</th>
<th>CRS*</th>
<th>No CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Dose (5 x 10^8)</td>
<td>5 (36%)</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Low Dose (5 x 10^7)</td>
<td>6 (43%)</td>
<td>8 (57%)</td>
</tr>
</tbody>
</table>

*CRS severity (0-1 vs 2-4) did not correlate with dose
CART19 (CTL019) Cells For Relapsed, Refractory ALL

- Structure of a Lenti-virus
- Lenti-viruses used for T-cell transduction
- Transduced T-cell attacks a tumor cell
ALL: Rationale for Novel Therapies

- Prognosis for relapsed or refractory ALL poor
- Median survival < 1yr
- 3 yr survival <25%
- Allogeneic SCT for refractory ALL largely ineffective
- There is a desperate need for newer, more effective therapies for advanced and high risk ALL.
CTL019 for Relapsed Refractory ALL

- N=30 (evaluable)
- 25 pediatric and 5 adult patients
- 40% female, 60% male
- Median age 14 (5-61)
- Disease status
  - Primary refractory 10%
  - 1\textsuperscript{st} relapse 17%
  - \geq 2\textsuperscript{nd} relapse 73%

### ALL: Overall Response to CTL019

<table>
<thead>
<tr>
<th>Response</th>
<th>N=30</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>27/30</td>
<td>90%</td>
</tr>
<tr>
<td>No response</td>
<td>3/30</td>
<td>10%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Toxicity: CTL019

• No significant acute infusional toxicity

• Tumor lysis syndrome
  - Delayed, Reversible and manageable

• B cell aplasia and hypogammaglobulinemia in responding patients (toxicity or efficacy?)
  - Supported with intravenous immunoglobulin (IVIG)
  - No excessive or frequent infections

• Cytokine Release Syndrome (CRS)
Toxicity: Cytokine release syndrome and IL-6

- Almost all responding patients developed CRS
  - High fevers, myalgias, nausea, hypotension, hypoxia, etc.
  - Very high levels of IL6
  - IFN-g, modest TNF-a
  - Mild increases in IL-2
IL-6 mediates CTL019 Associated CRS

• Tocilizumab
  – IL-6 receptor antagonist
  – Blocks IL-6 mediated effects

• CRS rapidly reversed with tocilizumab (3) when needed
  – Tocilizumab administered on day 2 to 18
  – Will early treatment for CRS abrogate response?

• CRS associated with HLH/MAS
  – Hemophagocytosis, ferritin >500,000, hemolysis, DIC, altered mental status
Temperature Response to Tocilizumab 21413-32
# Trials of CAR Therapy for ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Construct</th>
<th>N</th>
<th>CR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univ of Penn</td>
<td>CD3z 4-1BB</td>
<td>30</td>
<td>90%</td>
<td>3 went to allo</td>
</tr>
<tr>
<td>NCI (Lee, Lancet 2014)</td>
<td>CD3z CD28</td>
<td>21</td>
<td>67%</td>
<td>10 went to allo OS 52% at median 10 mo</td>
</tr>
<tr>
<td>MSK (Devila, STM 2014)</td>
<td>CD3z CD28</td>
<td>16</td>
<td>88%</td>
<td>7 pts treated in CR 7 went to allo</td>
</tr>
</tbody>
</table>
Key challenges for conducting clinical trials with immunotherapies

“Immunotherapy is Different”
CAR T Cell Therapy: Summary

- Response rates are high, durable in many cases
  - Fill a LARGE unmet need
- Toxicity is unique
- Cells expand: dose administered is different than final dose
- Cells persist: The drug may continue to be active for years
- Every “dose” is unique
Key challenges for conducting clinical trials with immunotherapies

- **CAR T cell therapy evaluated by**
  - Response, relapse free survival, survival
  - Most applied for patients without other options so there is no comparator. May need to be assessed without comparison trials

- **Regulatory approaches to accelerated approval:**
  “Breakthrough designations” helpful and important

- **Oversight and regulatory boards will need education on patient population studied and therapies used.**
  - Unique patients
  - Unique toxicities
  - Unique trial designs
Key challenges for conducting clinical trials with immunotherapies

• Expensive
  – Funding initially available to treat 3 patients in 2010
  – It took > 1yr to obtain additional funding
  – Academia-pharma alliance, collaboration necessary for scale
  – Funding for clinical trials has to be on different scale than what we are used to

• Insurance approval – standard vs clinical research

• Out of state medicaid not covered
  – Each case individually handles by contracting office

• International patients
  – Penn Global Medicine

• Pharmacy and formulary limitations

• Regulatory and staff education
Key challenges for conducting clinical trials with immunotherapies

• Dosing scheduling:
  – Cells expand making dose and schedule issues very different than standard drug therapies.
  – Old rules don’t apply.

• Potency: Ever dose is different?

• Identify most appropriate patients
  – Disease and patient specific factors
  – Cell specific factors: How do we test the health of the immune system and how can we modify it?

• Combination studies of cellular therapy and immune modulators may be ideal.
  – New regulatory hurdles
Key challenges for conducting clinical trials with immunotherapies

• **Stopping rules and Endpoints**
  – Progression and response definitions may be different
  – Progression and even response may be difficult to assess with some immunotherapies
  – May not be good comparator group
  – Time without needing alternative therapy?
  – Physical improvement?
  – Patient-reported outcomes such as relief of symptoms, QOL assessments,

• **Safety and toxicity grades were not designed for immunotherapies and need to be redefined** (i.e. for CRS)
Health Care Challenges

Chris Mason et al, Regen Med. 2011
Levine and June, Nature. 2013

Issues
- Patient specific “n of 1”
- Blood bank model?
- Central manufacturing?
CARs Meet Leukemia

206 CTL019 Recipients

• CLL:
  – 50 adults

• ALL:
  – 114 (89 kids, 25 adult)

• NHL:
  – 31 adults

• MM
  – 11 adults
Tech transfer from academia (Penn) to industry (Novartis) accomplished

Novartis now manufacturing for the pediatric r/r ALL global clinical trial and the DLBCL global clinical trial in the US

– expanded into other countries in the second half of 2015.
## Pharma and Biotech in the ACT Space: examples

<table>
<thead>
<tr>
<th>Company</th>
<th>Technology/cell type</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer</strong></td>
<td><strong>Technology</strong></td>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>Lion Biotechnologies</td>
<td>TIL (autologous)</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>Autolus</td>
<td>CAR (autologous)</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Novartis</td>
<td>CAR (autologous)</td>
<td>Pediatric and adult ALL, diffuse large B cell lymphoma, non-Hodgkin’s lymphoma (NHL)</td>
</tr>
<tr>
<td>Juno Therapeutics</td>
<td>CAR (autologous)</td>
<td>Adult and pediatric ALL, NHL, adult acute myeloid leukemia (AML), non–small cell lung cancer (NSCLC)</td>
</tr>
<tr>
<td>Cardio3 Biosciences</td>
<td>CARs targeting NK cell p30-related protein (NKp30); NK group 2, member D (NKG2D); B7 homolog 6 (B7H6)</td>
<td>Range of hematological malignancies and solid tumors</td>
</tr>
<tr>
<td>Cellular Biomedicine Group (China)</td>
<td>CARs targeting CD19, CD20, CD30, and EGFR</td>
<td>Range of hematological malignancies and solid tumors</td>
</tr>
<tr>
<td>CARsgen</td>
<td>CARs targeting glypican-3 (GPC-3)</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Celgene/Bluebird</td>
<td>CAR (autologous)</td>
<td>Range of hematological malignancies and solid tumors</td>
</tr>
<tr>
<td>Kite Pharma/Amgen</td>
<td>CAR (autologous)</td>
<td>Relapsed or refractory ALL</td>
</tr>
<tr>
<td>Cellectis/Servier/Pfizer</td>
<td>CAR (allogeneic, UCART 19)</td>
<td>CLL, ALL, and AML in preclinical stage, phase 1 for B cell leukemia to be initiated in 2015</td>
</tr>
<tr>
<td>GSK/Adaptimmune</td>
<td>TCR (autologous)</td>
<td>Trials in multiple myeloma (MM), melanoma, sarcoma, and ovarian cancer</td>
</tr>
<tr>
<td>Janssen/Transposagen</td>
<td>CAR (allogeneic)</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Unum Therapeutics/Sanofi-Genzyme</td>
<td>Antibody-coupled TCR (autologous)</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Ziopharm Oncology/Intrexon</td>
<td>CAR</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Opus Bio</td>
<td>CAR (autologous)</td>
<td>Pediatric and adult ALL and NHL, CD22 licensed to Juno</td>
</tr>
<tr>
<td>Takara Bio (Japan)</td>
<td>CAR (autologous)</td>
<td>NHL, esophageal cancer</td>
</tr>
<tr>
<td>Bellicum Pharmaceuticals</td>
<td>CAR (autologous)</td>
<td>Potential hematological malignancies and solid tumors</td>
</tr>
<tr>
<td>Cellular Therapeutics Ltd (UK)</td>
<td>CAR (autologous)</td>
<td>Metastatic melanoma, esophago-gastric cancer</td>
</tr>
<tr>
<td>Cell Medica (UK)</td>
<td>Virus-specific T cells (allogeneic) targeting Epstein-Barr virus antigen</td>
<td>Advanced NK/T cell lymphoma</td>
</tr>
</tbody>
</table>
The First CAR Assembly Lines
Robotic CAR Assembly Lines
Smarter CAR Assembly Lines
Massive CTL019 expansion (1000 – 10,000 fold *in vivo*)
- E:T ratio 1:1000-93,000

Eradication of bulky tumor

Overall response rate 18/38 CLL (47%)
- 9 CR, 9 PR (Several PR cleared blood and marrow with ongoing node responses)

Overall CR rate 27/30 ALL (90%)
- 5/5 CR in adults
- 22/25 in pediatric pt with 4 relapses
- 22/30 currently in CR (73%)

CTL019 cells persist for >48 months after a single treatment
- Persisting cells remain functional

Summary: CTL019 for B cell malignancies

Summary: CTL019 for B Cell Malignancies

• Most responding patients develop CRS
  – Treated effectively with supportive care and anti-IL6 receptor antagonist therapy when needed
  – Will early treatment abrogate response?

• No obvious dose:response or dose:toxicity effects as yet

• Responding patients develop B cell aplasia
  – Hypogammaglobulinemia has been managed with IVIG

• CAR therapy holds great promise for patients with advanced, relapsed and/or refractory CLL, ALL, NHL, MM

• CAR therapy trials to be expanded to include AML and several solid tumors

• CAR T cells are both “personalized” and “precise”
President Barack Obama calls for a new initiative to fund precision medicine.

• “Tonight, I'm launching a new Precision Medicine initiative to bring us closer to curing diseases like cancer …Such an approach “gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen”.
  – President Barack Obama, State of the Union Address, Jan 20, 2015

• He went on to describe the $215 million initiate.
DREAM BUILDERS

“Whatever we accomplish belongs to our entire group, a tribute to our combined effort.”

-Walt Disney

Near entrance to Fantasy Land, Magic Kingdom, Disney World 2013