CD19 CAR T Cells in Acute Lymphoblastic Leukemia

Jae Park, MD
Assistant Attending Physician
Leukemia Service, Department of Medicine
Cellular Therapeutics Center
Memorial Sloan Kettering Cancer Center
Outline

• Overview of CAR designs, mechanism of action, and application as cancer therapy
• CD19 CAR T cell efficacy in R/R ALL in adults and children
• CD19 CAR T associated toxicity
• Future directions of CAR T cells in ALL & other hematologic malignancies
Design of a Tumor Targeted Chimeric Antigen Receptor (CAR)

- Specificity of antibody target recognition
- Effector mechanisms of T cell
**Generation of CAR T Cells**

1. **Construct a CAR**
2. **Subclone CAR gene into a vector**
3. **Transduce and expand patient T cells *ex vivo***

Retroviral vector encoding CAR cDNA

---

**Diagram Details**

- **ScFv**
- **CD28**
- **CD3ζ**
- **5' LTR**
- **3' LTR**
- **ψ**
- **SD**
- **SA**
- **V<sub>H</sub>**
- **V<sub>L</sub>**
- **CD28**
- **ζ chain**

---

**Genetically modified Tumor antigen-targeted T cell**

**Tumor cell**

**Tumor Antigen**

---

*Memorial Sloan Kettering Cancer Center.*
Advantages of CAR T cell therapy

- HLA-independent antigen recognition, therefore universal application
- Target antigens include proteins, carbohydrates and glycolipids
- Rapid generation of tumor specific T cells
- Minimal risk of GvHD
- A living drug: potential for lasting immunity
- Selective modification of specific T cell subtypes
- Additional modification capability of CAR construct
CD19 as a Target of B Cell Malignancies

Stem Cell → pro B → pre B → immature B → mature B → plasma cell

CD19

CD22

CD20
Evolution in CAR design

First-generation CAR

mAB scFv
TM domain
Hinge

CD3ζ or FCRγ
One co-stimulatory domain (CD28, 4-1BB, OX-40)

Second-generation CAR

Two co-stimulatory domains (CD28, 4-1BB, OX-40)

Third-generation CAR


CAR T Cells as Cancer Therapy

T cells are isolated from patient

T cells are engineered to express CARs that recognize cancer cells

Modified T cells are grown and expanded in culture

Modified T cells are infused into patient

Source: mskcc.org
Brief report

Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19

James N. Kochenderfer,1 Wyndham H. Wilson,2 John E. Janik,2 Mark E. Dudley,1 Maryalice Stettler-Stevenson,3 Steven A. Feldman,1 Irina Maric,4 Mark Raffeld,3 Debbie-Ann N. Nathan,1 Brock J. Lanier,1 Richard A. Morgan,1 and Steven A. Rosenberg1

Blood 2010 Nov 18; 116(20):4099-4102

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

NEJM 2011 Aug 25;365(8):725-33

Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias

*Renier J. Brentjens,1-3 *Isabelle Riviere,1-4 Jae H. Park,1,2 Marco L. Davila,1,2 Xiuyan Wang,2-4 Jolanta Stefanski,2-4 Clare Taylor,2-4 Raymond Yeh,1,2 Shirley Bartido,2,3 Oriana Borquez-Ojeda,2-4 Malgorzata Olszewska,2-4 Yvette Bernal,1 Hollie Pegram,1,2 Mark Przybylowski,2-4 Daniel Hollyman,2-4 Yelena Usachenko,1,2 Domenick Pirraglia,2-4 James Hosey,2-4 Elmer Santos,3,5 Elizabeth Halton,1 Peter Maslak,1 David Scheinberg,1-3 Joseph Jurcic,1 Mark Heaney,1 Glenn Heller,6 Mark Frattini,1 and Michel Sadelain1-3

Blood 2011 Nov 3; 118(18):4817-28
CD19-CAR T Cells in Clinical Trials

• Similarities: Target, study design

• Key differences:
  – CAR construct component: scFv, co-stimulatory domain (CD28, 4-1BB)
  – Mode of transduction: retrovirus, lentivirus, electroporation
  – Cell source (patient vs. donor-derived) & Cell dose
  – Patient population: adults vs. peds, pre-HSCT vs. post-HSCT
  – Choice of lymphodepletion: various chemotherapy regimen
Timeline of Clinical Development of CD19 CAR T Cells in Hematologic Malignancies

- First CLL patient treated with CD19 CAR T cells (MSK)
- More reports of response in CLL patients t/w CD19 CAR T cells
- Phase II trials of CD19 CAR T cells in ALL/NHL
- First report of ALL eradication in mice with CD19 CAR T cells
- First report of response in FL patient t/w CD19 CAR T cells
- Reports of CR in ALL patients t/w CD19 CAR T cells
Prognosis of adult patients with R/R ALL remains poor

**Blinatumomab**
- Hazard ratio, 0.55 (95% CI, 0.43–0.71)
- P < 0.001

**Inotuzumab**
- Hazard ratio, 0.77 (97.5% CI, 0.58–1.03)
- P = 0.04

**PFS**
- Median Overall Survival (mo)
  - Blinatumomab: 7.7 (95% CI, 5.6–9.6)
  - Chemotherapy: 4.0 (95% CI, 2.9–5.3)

**OS**
- Hazard ratio, 0.71 (95% CI, 0.55–0.93)
- P = 0.01

A phase I trial of 19-28z CAR T cells in adults with R/R ALL at MSKCC

Stage 1 (n=20)

All patients → Cy Conditioning → 3x10^6 CAR T cells/kg

Stage 2 (n=23)

Morphologic disease patients → Cy Conditioning → 1x10^6 CAR T cells/kg
MRD patients → Cy Conditioning → 3x10^6 CAR T cells/kg

Stage 3 (n=10)

Morphologic disease patients → Flu/Cy Conditioning → 1x10^6 CAR T cells/kg
MRD patients → Flu/Cy Conditioning → 3x10^6 CAR T cells/kg

MRD: minimal residual disease; Cy: cyclophosphamide; Flu: fludarabine

## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, Median (range) – yr</strong></td>
<td>44 (23-74)</td>
</tr>
<tr>
<td><strong>Salvage-treatment phase – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (2)</td>
</tr>
<tr>
<td>2</td>
<td>16 (30)</td>
</tr>
<tr>
<td>3</td>
<td>17 (32)</td>
</tr>
<tr>
<td>4</td>
<td>9 (17)</td>
</tr>
<tr>
<td>≥5</td>
<td>10 (19)</td>
</tr>
<tr>
<td><strong>Primary refractory disease – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (23)</td>
</tr>
<tr>
<td>No</td>
<td>41 (77)</td>
</tr>
<tr>
<td><strong>Prior allogeneic HSCT – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (36)</td>
</tr>
<tr>
<td>No</td>
<td>34 (64)</td>
</tr>
<tr>
<td><strong>Bone marrow blasts, Distribution – no. %</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>21 (40)</td>
</tr>
<tr>
<td>≥5%</td>
<td>27 (51)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>63 (5-97)</td>
</tr>
<tr>
<td>&lt;5% with extramedullary disease</td>
<td>5 (9)</td>
</tr>
<tr>
<td><strong>Philadelphia chromosome (Ph)-positive – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (30)</td>
</tr>
<tr>
<td>No</td>
<td>37 (70)</td>
</tr>
</tbody>
</table>
Study Outcome:
Complete Remission (CR) Rates

- Overall CR rate: 84.6% (44 of 52 pts)
- MRD-CR rate: 66.6% (32 of 48 evaluable pts)

### Subgroup Analysis of Complete Remission

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Complete Remission (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>53</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Disease burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>21</td>
<td>95 (3 to 38)</td>
<td>0.07</td>
</tr>
<tr>
<td>High</td>
<td>32</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Pre-CAR HSCT</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>82 (-23 to 19)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>No. of previous therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>90 (-17 to 29)</td>
<td>0.37</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>85 (-17 to 39)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>19</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Ph status</td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Ph−</td>
<td>37</td>
<td>79 (-32 to 4)</td>
<td></td>
</tr>
<tr>
<td>Ph+</td>
<td>16</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Conditioning chemotherapy</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Cyclophosphamide+fludarabine</td>
<td>10</td>
<td>80 (-31 to 23)</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>43</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>18–30 yr</td>
<td>14</td>
<td>93 (-7 to 32)</td>
<td></td>
</tr>
<tr>
<td>31–60 yr</td>
<td>31</td>
<td>81 (-27 to 39)</td>
<td></td>
</tr>
<tr>
<td>&gt;60 yr</td>
<td>8</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>
Long-Term Outcome:
All Patients

Median follow up: 29 months (range, 1 – 65)

Event-Free Survival
Median EFS: 6.1 mos

Overall Survival
Median OS: 12.9 mos

Long-Term Outcome: Responders vs. Non-responders

Event-free survival

Median EFS = 12.5 mos (95% CI, 6.3 – 20.1)  

Overall survival

Median OS = 20.7 mos (95% CI, 15.3 – NR)

Median follow up = 29 months (range, 1 – 65)

Long-Term Outcome: By Post-CAR AlloHSCT Status

Event-Free Survival

Overall Survival

No. at Risk

No HSCT 16 7 3 2 1 0 0
HSCT 16 9 4 3 3 2 1

P = 0.64

P = 0.89

Long-Term Outcome: By Pretreatment Disease Burden

Median EFS: 10.6 vs. 5.3 mos

Median OS: 20.1 vs. 12.4 mos

Long-Term Outcome & Effector:Target Ratio

Tisagenlecleucel in Children and Young Adults with R/R B-ALL

• Phase 2, global, 25-center study
  – Primary endpoint: Overall response in 3 months
• 92 pts enrolled → 75 pts (82%) treated
  – Median age: 11 (range, 3 to 23)
  – Median prior # of tx: 3 (range, 1 to 8)
  – Prior alloHSCT: 61%
• Conditioning regimen: Cy and Flu
• T cell dose (median): 3.1x10^6 CAR T cells/kg

EFS at 12 months: 50%
OS at 12 months: 76%

Tisagenlecleucel in R/R B-ALL: Remission duration & Survival

- Overall Response Rate: 81% (60% CR + 21% CRi)

Tisagenlecleucel for B-Cell ALL

- FDA approved **August 2017** for treatment of patients **up to age 25** years with B-cell precursor ALL that is refractory or in second or later relapse
  - First chimeric antigen receptor T-cell immunotherapy approved by FDA

- FDA approved with a Risk Evaluation and Mitigation Strategy
## Clinical Efficacy of CD19 CAR T Cells in R/R ALL

<table>
<thead>
<tr>
<th>T Cell Product</th>
<th>Age, med (range)</th>
<th>No. of Pts.</th>
<th>Prior HSCT</th>
<th>T Cell Dose</th>
<th>CR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-28z (MSKCC)</td>
<td>44 (23-74)</td>
<td>53</td>
<td>36%</td>
<td>1-3x10^6 CAR T cells/kg</td>
<td>85%</td>
<td>Med OS: 13 mos Med EFS: 6.1 mos Post-CAR HSCT: 39%</td>
</tr>
<tr>
<td>19-41BBz (Upenn)</td>
<td>N/A</td>
<td>12</td>
<td>N/A</td>
<td>4x10^7 - 1x10^9 CAR T cells</td>
<td>89%</td>
<td>N/A</td>
</tr>
<tr>
<td>19-41BBz (FHRC)</td>
<td>40 (20-73)</td>
<td>30</td>
<td>37%</td>
<td>2x10^5-10^7 CAR T cells/kg</td>
<td>100%</td>
<td>31% relapse (17% died in CR) Post-CAR HSCT: 48%</td>
</tr>
<tr>
<td>19-41BBz (CTL019)**</td>
<td>12 (3-23)</td>
<td>68</td>
<td>61%</td>
<td>0.2 -5x10^6 CAR T cells/kg</td>
<td>83%</td>
<td>Med OS: 19 mos 6m EFS: 73% Post-CAR HSCT: 12%</td>
</tr>
<tr>
<td>19-28z (NCI)</td>
<td>14 (5-27)</td>
<td>20</td>
<td>38%</td>
<td>1-3x10^6 CAR T cells/kg</td>
<td>70%</td>
<td>6m OS: ~65% Post-CAR HSCT: 71%</td>
</tr>
<tr>
<td>19-41BBz (SCRI)</td>
<td>12 (1-25)</td>
<td>45</td>
<td>62%</td>
<td>0.5-10x10^6 CAR T cells/kg</td>
<td>89%</td>
<td>12m EFS: 51% (45% relapse) 12m OS: 70%</td>
</tr>
</tbody>
</table>

# Common Toxicities of CD19 CAR T cells

<table>
<thead>
<tr>
<th>Cytokine Release Syndrome (CRS) Clinical Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Capillary leak</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
</tr>
<tr>
<td>Hyperferritinemia/MAS</td>
</tr>
<tr>
<td>Coagulopathy/DIC</td>
</tr>
<tr>
<td>Multi-organ failure</td>
</tr>
</tbody>
</table>

Symptoms rapidly resolve with IL-6R blockade

<table>
<thead>
<tr>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
</tr>
<tr>
<td>Global encephalopathy</td>
</tr>
<tr>
<td>Aphasia</td>
</tr>
<tr>
<td>Seizure, seizure-like activity</td>
</tr>
<tr>
<td>Tremor/myoclonus</td>
</tr>
<tr>
<td>Hallucinations</td>
</tr>
</tbody>
</table>

“CAR T cell related encephalopathy syndrome (CRES)”

Rapid onset cerebral edema

Severe symptoms do not resolve with IL-6R blockade and treatment with steroid preferred
## CD19 CAR Associated CRS & NTX Incidences

<table>
<thead>
<tr>
<th>T Cell Product</th>
<th>Disease</th>
<th>No. of Patients</th>
<th>CRS, All grades (%)</th>
<th>≥Gr3 CRS (%)</th>
<th>≥Gr3 NTX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-28z (MSK)</td>
<td>ALL</td>
<td>53</td>
<td>85</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>KTE-C19 (ZUMA-3)</td>
<td>ALL</td>
<td>29</td>
<td>93</td>
<td>28</td>
<td>52</td>
</tr>
<tr>
<td>KTE-C19 (ZUMA-1)</td>
<td>DLBCL</td>
<td>101</td>
<td>93</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>CTL019 (JULIET)</td>
<td>DLBCL</td>
<td>99</td>
<td>58</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>JCAR017 (TRANSCEND)</td>
<td>DLBCL</td>
<td>55</td>
<td>35</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td><strong>Peds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTL019 (ELIANA)</td>
<td>ALL</td>
<td>75</td>
<td>77</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>JCAR017 (PLAT-02)</td>
<td>ALL</td>
<td>43</td>
<td>93</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>19-28z (NCI)</td>
<td>ALL</td>
<td>21</td>
<td>76</td>
<td>29</td>
<td>5</td>
</tr>
</tbody>
</table>

CRS Is Associated with Elevated Proinflammatory Cytokines

CRP as a Surrogate Biomarker for IL-6/CRS

CRS is abrogated by IL-6R blockade

High Tumor Burden & Greater *In vivo* T cell Expansion Correlate with CAR-associated Toxicity

Muller K et al. *Blood* 2017;130(21):2317-2325
Severity of CRS correlates with CAR T cell dose in ALL

CTL019 in Adult Patients with R/R B-ALL

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>Schedule</th>
<th>N</th>
<th>CRS ≥ Gr 3, %</th>
<th>Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High dose (5 x 10^8)</td>
<td>Split</td>
<td>15</td>
<td>66</td>
<td>86 (0 TRM)</td>
</tr>
<tr>
<td>2</td>
<td>High dose (5 x 10^8)</td>
<td>Single</td>
<td>6</td>
<td>100</td>
<td>100 (3 TRM)</td>
</tr>
<tr>
<td>3</td>
<td>Low dose (5 x 10^7)</td>
<td>Split</td>
<td>6</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Low dose (5 x 10^7)</td>
<td>Single</td>
<td>3</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>Overall</td>
<td>---</td>
<td>---</td>
<td>30</td>
<td>75</td>
<td>72 (3 TRM)</td>
</tr>
</tbody>
</table>

Frey N et al. ASCO 2016 Annual Meeting. Abstract 7002
Choice of Conditioning Chemotherapy May Impact CAR T Cell Expansion

19-41BBz CAR T Cells in NHL

CD22 CAR in R/R B-ALL

- Patient Population (N=21):
  - Age: 7-30, median 19
  - Prior HSCT: 100%
  - Prior CD19 CAR: 15/21 (75%)
  - CD19⁺/CD19dim: 10/21 (45%)

Overall CR rate: 57%
CR rate in Dose level 2/3: 73%

Relapse rate: 8/12 (67%)
- Median time: 6 mos (1.5-12)
- A/w diminished CD22 expression

CD19 and CD22-Bispecific CAR T cells

Clinical trials of these bi-specific CARs just began enrolling patients.

Universal or “off-the-shelf” CAR T cells

Disruption of CD52 gene & TRAC (loss of TCRαβ)

Qasim et al. Sci Transl Med 2017

Study Updates

PALL study of pediatric ALL:
• 5 children treated
• CRS: 1 Gr1, 3 Gr2 and 1 Gr3
• 4/5 pts w/ viral complications
• Response: 5/5 CRi → alloHSCT → 2 relapse, 1 death in CR and 2 alive in CR

CALM study of adult ALL:
• 6 adults treated (4 MRD+ pts)
• CRS: 1 Gr1, 4 Gr2, 1 Gr4 → 1 death on D15
• Response: 4/6 Cri → alloHSCT → 1 relapse, 1 death in CR and 2 alive in CR

Qasim W et al. ASH 2017, Abstract 1271; Graham C et al. ASH 2017, Abstract 887
Moving Forward: Armored CARs

CAR T cells are not just “tumor killers” and can be harnessed to reprogram the TME.
Timeline of Clinical Development of CD19 CAR T Cells in Hematologic Malignancies

2007
- First CLL patient treated with CD19 CAR T cells (MSK)

2010
- First report of response in ALL with CD19 CAR T cells

2011
- More reports of response in CLL patients t/w CD19 CAR T cells

2013
- Phase II trials of CD19 CAR T cells in ALL/NHL

2014
- Approval of CD19 CAR T cells in ALL & DLBCL

2017
- Trials of:
  1) “Armored” CAR T cells,
  2) Bi-specific or novel target CAR T cells
  3) Combination with immunomodulators

2018-9

Memorial Sloan Kettering Cancer Center
Summary

• High CR rates and durable responses can be achieved in both adults and children with R/R B-ALL, regardless of different disease risk factors

• CRS and NTX are the most common AE a/w CD19 CAR T cells in ALL
  • CRP can serve as a surrogate marker of IL-6
  • CRS can be managed effectively with tocilizumab and/or steroid.
  • Mechanism of NTX unclear but correlate with early systemic inflammation and T cell expansion. Steroid more effective and preferred over tocilizumab

• Future studies in ALL will focus on:
  • Incorporation of CAR T cells in earlier lines of treatment in low disease burden setting
  • Addressing CD19 negative relapses (CD22, Bi-specific CD19/22 CAR)
  • Improve duration of remission and reduce toxicity with more potent “armored CAR” T cells and with various combination approach
Acknowledgements

Center for Cell Engineering
Michel Sadelain
Renier Brentjens
Isabelle Riviere
Prasad Adusumilli

Cellular Therapeutics Center
Renier Brentjens
Prasad Adusumilli
Craig Sauter
Kevin Curran
Elizabeth Halton, NP
Claudia Diamonte, RN
Yvette Bernal
Elena Mead
Bianca Santomasso

Leukemia Service
Martin Tallman
Omar Abdel-Wahab
Ellin Berman
Stephen Chung
Jacob Glass
Virginia Klimek
Ross Levine
Michael Mauro
Raajit Rampal
Alan Shih
Eytan Stein
Aaron Viny
M12 NP/PA & Nurses

CTCEF
Isabelle Riviere
Xiuyan Wang
Yongzeng Wang
Jolanta Stefanski
Oriana Borquez-Ojeda
Teresa Wasielewska
Jinrong Qu
Mitsu Fink, Qing He
Annieisha Hack, Fang Du
Mark Satter
James Hosey
Willard Joseph
Maria Scaringi

Funding Source
NCCN Young Investigator Award
Leukemia and Lymphoma Society
ASH CDA
ASCO CDA

Our Patients!!!
Thank You for your attention!

Please email with any questions:
parkj6@mskcc.org