CARs vs. BiTE in ALL

David L Porter, MD
Jodi Fisher Horowitz Professor
University of Pennsylvania Health System
Abramson Cancer Center
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.
Refractory ALL: Case 1

- 45 yo male diagnosed with Ph- pre-B ALL:
  - R-Hyper CVAD 1A
    - Extensive residual dz
  - R-Hyper CVAD 1B
    - MRD+
  - R-IME (modified)
    - BM with extensive disease (62%)
- R-MTX/ARA C
  - 10% blasts
Refractory ALL: Question 1

- Patient has residual disease despite multiple induction attempts. He has an HLA matched sibling. You would:
  - A. Proceed to allogeneic SCT
  - B. Select alternative induction chemotherapy
  - C. Enroll in CAR T cell trial
  - D. Administer blinatumomab
  - E. Institute supportive and palliative care
Targeting CD19+ ALL 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.
Rationale for Targeted Cellular Therapy

• 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)
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
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%
  - 1st relapse 17%
  - >2nd 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>

CTL019 for Relapsed Refractory ALL: Survival

Overall Survival

6-month OS: 78% (95% CI: 64,95)

Maude, Frey et al. NEJM 2014;371:1507-1517.
CTL019 for Relapsed Refractory ALL: EFS

Event-free Survival

6-month EFS: 66% (95% CI: 49,87)

Maude, Frey et al. NEJM 2014;371:1507-1517.
Rapid expansion of CART cells, rapid eradication of in responding patients

**UPCC04409-09**

<table>
<thead>
<tr>
<th>Time</th>
<th>CD5</th>
<th>CD19</th>
<th>CAR19</th>
<th>CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+1</td>
<td>42.7%</td>
<td>0%</td>
<td>4.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>D+6</td>
<td>4.9%</td>
<td>2.5%</td>
<td>2.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>D+8</td>
<td>4.9%</td>
<td>2.5%</td>
<td>58.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>D+10</td>
<td>0.2%</td>
<td>0.2%</td>
<td>78.5%</td>
<td>25.4%</td>
</tr>
<tr>
<td>D+28</td>
<td>0.2%</td>
<td>0.2%</td>
<td>78.5%</td>
<td>25.4%</td>
</tr>
</tbody>
</table>

**PDCS**
PDL & TCSL

Eurasian Hematology Congress | JJ Melenhorst, PhD | 10/17/2014 | CARs for CLL
## ALL: Adult response

<table>
<thead>
<tr>
<th>Response</th>
<th>N=25</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>16/25</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>4/25</td>
<td>16%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frey, Porter ASH 12/10/15, ASCO 2016
CAR T cells have dramatic activity in relapsed and refractory ALL: ASCO 2016 (n=205)

<table>
<thead>
<tr>
<th>Study</th>
<th>Construct</th>
<th>N</th>
<th>CR</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle (Turtle, ASCO 102, and JCI 5/16)</td>
<td>CD3z 4-1BB</td>
<td>30-34</td>
<td>93%</td>
<td>Adults age 20-73</td>
</tr>
<tr>
<td>Penn (Frey ASCO 7002)</td>
<td>CD3z 4-1BB</td>
<td>27</td>
<td>60-83%</td>
<td>Adults</td>
</tr>
<tr>
<td>MSK (Park, ASCO 7003)</td>
<td>CD3z CD28</td>
<td>46</td>
<td>78%</td>
<td>Adults 24-73 (median 40)</td>
</tr>
<tr>
<td>Seattle Children’s (Gardner, 3048)</td>
<td>CD3z 4-1BB</td>
<td>36</td>
<td>91%</td>
<td>Peds and YA age 1-25</td>
</tr>
<tr>
<td>Penn (Maude 3011)</td>
<td>CD3z 4-1BB</td>
<td>59</td>
<td>93%</td>
<td>Peds 2-24 (med 11)</td>
</tr>
</tbody>
</table>
CAR T cells for ALL: Broader Access

(Grupp et al, ASH 2016, abstract 22)

• ELIANA: first global multi-center CAR T cell trial: Pediatric ALL
  – Industrial cell processing of **CTL019 therapy**
  – US manufactured cell therapy with global supply and chain of custody
  – 25 centers across 11 countries (US, EU, Canada, Australia, Japan), n=57
  – Site training program: logistics and patient management

• Global trial; most pts received CTL019 in timely manner (~94% success)
• Toxicity (CRS) manageable with no deaths due to CRS
• Efficacy Maintained: CR/CRi 82%
CAR T Cells are an effective “Bridge to Transplant”
CAR T Cells Before Transplant

- Transplant for refractory or active ALL largely ineffective and typically not attempted.
- Achieving CR may improve outcome of allogeneic SCT.
- CAR T cells induce CR in ~90% of patients with relapsed/refractory ALL.
- CAR T cells are an effective bridge to get patients to potentially curative transplant.
After: High response rates for relapse after allo-SCT

- 27 patients post-allo SCT
- T cells collected from patient
  - 6 months post-SCT
- Median donor chimerism 100%
- No GVHD to date
- Dramatically superior to DLI
  - DLI response 0-20%

Maude, Grupp et al, unpublished (Dec 2015)
Instead: Overall survival similar with or without allo SCT after CAR T Cells (MRD-CR Patients) (Bridging may not be necessary)
93% CR rate for r/r ALL after CTL019

- 59 r/r pediatric ALL pts:
- 55 in CR at 1 mo (93%)
- Median f/u 12 mo
- 6 mo RFS: 76% (95%ci 65-89%)
- 12 mo RFS: 55% (95%ci 42-73%)
- No relapses past 1 year
- 18 patients in remission beyond 1 year,
  • 13 without further therapy
- 6 went to subsequent transplant, 1 to DLI
Blinatumomab vs Chemotherapy: Outcomes

A. Overall Survival

No. at Risk
Blinatumomab 271 176 124 79 45 27 9 4 0
Chemotherapy 134 71 41 27 17 7 4 1 0

B. Overall Survival Censored at Time of Stem-Cell Transplantation

No. at Risk
Blinatumomab 271 163 80 44 21 13 2 0 0
Chemotherapy 134 56 21 12 5 1 0 0 0

C. Event-free Survival

No. at Risk
Blinatumomab 271 95 55 25 11 7 2 1 0
Chemotherapy 134 17 12 7 3 2 1 0 0

Toxicity: CTL019

- Toxicity manageable and predictable
  - TRM <10%, may be product, dose, schedule related and improving with experience
  - Severe CRS ~25%
  - Neurologic toxicity ~25-50%
- Not all CARs are the same (JCAR15 trial closing due to cerebral edema should not be generalized to all studies)
- Hard to compare or generalize outcomes with different CAR T cells
Summary: CTL019 for B cell malignancies

• CAR T cells are an effective bridge to transplant for most patients with relapsed, refractory ALL.
  – Does CAR T cell (or blina) induced CR have same favorable implication as chemotherapy induced CR?
• CAR T cells for relapsed ALL AFTER transplant is dramatically more effective than DLI
  – Response, OS and RFS not dependent on prior allo SCT.
• For some patients, CAR T cells may be an effective alternative INSTEAD of transplant.
  – No difference in OS, RFS or relapse between patients who have and do not have subsequent transplant though data still limited.
  – Select patients at highest risk for relapse to proceed to allogeneic SCT.
    • no persistence?
• CAR therapy holds great promise for patients with advanced, relapsed and/or refractory B cell malignancies
# CAR T cells vs Blinatumomab

**CAR T Cells**

- One time infusion
  - Almost all patients with recovery by day 28
- CAR T cell expansion 1000-10,000 fold amplifies activity
- CAR T cells persist
- CR/Cri in ~90% of patients across many trials
- Large international experience (5 presentations on 206 recipients at ASCO 2016)
  - Multicenter Eliana trial of 57 pts
- Sustained remissions (DFS 66%)
- Overall survival similar with or without allo SCT after CAR T cells
- High rate of OS, EFS across different trials
- Toxicity manageable and predictable
  - TRM <10%, may be product, dose, schedule related and improving with experience
  - Not all CARs are the same (JCAR15 trial closing should not be generalized to all studies)
- No randomized trials
- Time to treatment 2-4 weeks due to manufacturing
- Difficult to compare to other therapies

**Blinatumomab**

- “Off the shelf” product
- CR ~43%
- Likely to be an effective bridge to transplant
- Large experience in several hundred patients
- Better than standard chemotherapy (randomized trial)
- DFS 20-30% (after SCT)
- Toxicity manageable and predictable
  - includes CRS and neurologic toxicity
- Prolonged, continuous infusion over several months
- Difficult to compare to other therapies
The patient received CAR T cells.

Treatment complicated by grade 3 CRS requiring tocilizumab.

Symptoms rapidly resolved

By Day 27, patient is in CR, MRD negative. You would:
- A. Proceed to allogeneic SCT (has HLA matched sibling)
- B. Begin consolidation chemo
- C. Observation