Chimeric antigen receptor T-cell therapy for lymphoma

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Hematology/Oncology Fellow
Objective

• Review the basic knowledge of CAR T-cell therapy
• Review the recent two publications on Dec 2017 in NEJM, regarding therapy in refractory large B-cell lymphoma
• Major limitation of current CAR T-cell therapy
• Strategies for overcoming the side effects and future direction
Cancer immune evasion/tolerance

- Down regulate MHC molecule
- Reduce antigen presentation
- Down regulation of co-stimulatory signal
- Increase Treg
CAR T-cell therapy

• Engineered receptors to overcome immune tolerance
• Independent of MHC complex
• High specificity by targeting surface neo-antigen.
• Safer and more effective than allo-HSCT
• Had single-chain variable fragment (scFV), co-stimulatory region and T-cell activation domain.

Nat Rev Clin Oncol. 2018, 15: 31
Generation of CAR T-cell

- ScFv+CD3 zeta
- Lack of self persistence, require high dose IL-2
- Add on co-stimulatory domain
  - CD28: MSKCC, MDACC, NCI
  - 4-1BB: Upenn
- Better persistence
- More specific, stronger activation

Nat Rev Clin Oncol. 2018, 15: 31
General approach

1) T Cell Collection
2) T Cell Transfection
   1. Binding
   2. Fusion
3) T Cell Adoptive Transfer
   3. Integration
   4. Transcription and protein expression
   5. CAR cell membrane insertion
4) Patient Monitoring
   a) Disease response
      - CT scans
      - Bone marrow biopsies
      - Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      - Immunohistochemistry of bone marrow biopsy
      - RT-PCR and flow cytometry of blood and bone marrow aspirate
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

Background and Methods

• SCHOLAR-1 trial reported ORR: 26%, CR: 7%, OS: 6.3 months in B-cell NHL that resistant to chemotherapy or relapsed in 12 months after auto-SCT.

• Phase I study since 2012 showed ORR: 60-90% in NHL

• Axicabtagene ciloleucel (axi-cel) (Kite Pharma®) was developed by NCI using CD28 domain.

• ZUMA-1 trial (phase 2) ran from Nov 2015 to Sep 2016 at 22 centers.
  • B cell lymphoma (cohort 1) or PMBL + transformed FL (cohort 2)
  • Refractory disease: progress after recent chemo, or relapsed within 12 months after auto-SCT
  • Conditioning regimen: Flu 30mg/m2 and Cy 500mg/m2 on D-5, D-4, and D-3.
  • Axi-cel: 2 million cells/kg on D0
  • Primary end point: ORR; Secondary end point: PFS, duration of response, OS, AE
Median time from leukapheresis to divery of axi-cel was 17 days.

### Table 1. Treatment Disposition and Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with DLBCL</th>
<th>Patients with PMBCL or TFL</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients enrolled</td>
<td>81</td>
<td>30</td>
<td>111</td>
</tr>
<tr>
<td>Treatment disposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>77 (95)</td>
<td>24 (80)</td>
<td>101 (91)</td>
</tr>
<tr>
<td>No</td>
<td>4 (5)</td>
<td>6 (20)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Death before treatment†</td>
<td>1 (1)</td>
<td>2 (7)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Adverse event‡</td>
<td>3 (4)</td>
<td>2 (7)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Other§</td>
<td>0</td>
<td>2 (7)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

* Median time from leukapheresis to divery of axi-cel was 17 days.
**Result**

<table>
<thead>
<tr>
<th>Age</th>
<th>Median (range) — yr</th>
<th>58 (25–76)</th>
<th>57 (23–76)</th>
<th>58 (23–76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 yr — no. (%)</td>
<td>17 (22)</td>
<td>7 (29)</td>
<td>24 (24)</td>
<td></td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>50 (65)</td>
<td>18 (75)</td>
<td>68 (67)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance-status score of 1 — no. (%)</td>
<td>49 (64)</td>
<td>10 (42)</td>
<td>59 (58)</td>
<td></td>
</tr>
<tr>
<td>Disease stage — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>10 (13)</td>
<td>5 (21)</td>
<td>15 (15)</td>
<td></td>
</tr>
<tr>
<td>III or IV</td>
<td>67 (87)</td>
<td>19 (79)</td>
<td>86 (85)</td>
<td></td>
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<tr>
<td>International Prognostic Index score — no. (%)</td>
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<tr>
<td>0–2</td>
<td>40 (52)</td>
<td>13 (54)</td>
<td>53 (52)</td>
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</tr>
<tr>
<td>3 or 4</td>
<td>37 (48)</td>
<td>11 (46)</td>
<td>48 (48)</td>
<td></td>
</tr>
<tr>
<td>CD-19 status — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>7/63 (11)</td>
<td>1/19 (5)</td>
<td>8/82 (10)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>56/63 (89)</td>
<td>18/19 (95)</td>
<td>74/82 (90)</td>
<td></td>
</tr>
</tbody>
</table>
## Result

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with DLBCL</th>
<th>Patients with PMBCL or TFL</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Refractory subgroup at study entry — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>2 (3)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Refractory to second-line or subsequent therapy</td>
<td>59 (77)</td>
<td>19 (79)</td>
<td>78 (77)</td>
</tr>
<tr>
<td>Relapse after autologous stem-cell transplantation</td>
<td>16 (21)</td>
<td>5 (21)</td>
<td>21 (21)</td>
</tr>
<tr>
<td><strong>Prior therapies — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥Three prior lines of therapy</td>
<td>49 (64)</td>
<td>21 (88)</td>
<td>70 (69)</td>
</tr>
<tr>
<td>History of primary refractory disease**</td>
<td>23 (30)</td>
<td>3 (12)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>History of resistance to two consecutive lines</td>
<td>39 (51)</td>
<td>15 (62)</td>
<td>54 (53)</td>
</tr>
</tbody>
</table>
## Result

Median time to response was 1 (95% CI: 0.8-6.0) month
Median duration of response was 8.1 (95% CI: 3.3-NR) months
ORR is 76% in patients with history of auto-SCT.

<table>
<thead>
<tr>
<th>Response — no. (%)</th>
<th>DLBCL (n = 72)</th>
<th>PMBCL/TFL (n = 20)</th>
<th>All Patients (N = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>58 (81)</td>
<td>17 (85)</td>
<td>75 (82)</td>
</tr>
<tr>
<td>Complete response</td>
<td>34 (47)</td>
<td>14 (70)</td>
<td>48 (52)</td>
</tr>
<tr>
<td>Partial response</td>
<td>24 (33)</td>
<td>3 (15)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (13)</td>
<td>2 (10)</td>
<td>11 (12)</td>
</tr>
</tbody>
</table>
Result

- Response is irrelevant of biologic covariates, e.g. CD19 expression or CD4/CD8 ratio.
- Of the patients who did not have CR in 1st month, 23 pts (33%) had CR without additional treatment as late as 15 months.
- Three pts (progression) had CD19 phenotype transformation.

<table>
<thead>
<tr>
<th>Response — no. (%)</th>
<th>ABC (n = 17)</th>
<th>GCB (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>13 (76)</td>
<td>43 (88)</td>
</tr>
<tr>
<td>Complete response</td>
<td>10 (59)</td>
<td>28 (57)</td>
</tr>
<tr>
<td>Ongoing response</td>
<td>6 (35)</td>
<td>23 (47)</td>
</tr>
</tbody>
</table>
Result

A Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>DLBCL (N=77)</th>
<th>PMBCL or TFL (N=24)</th>
<th>All Patients (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
<td>ORR</td>
<td>82 (38%)</td>
<td>71 (17%)</td>
<td>82 (55%)</td>
</tr>
<tr>
<td>SD</td>
<td>49 (32%)</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>PD</td>
<td>12 (9%)</td>
<td>8 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>NE</td>
<td>12 (3%)</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>ORR</td>
<td>28 (28%)</td>
<td>54 (55%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>11 (11%)</td>
<td>11 (11%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5 (5%)</td>
<td>5 (5%)</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

Legend:
- Complete response
- Partial response
- Stable disease
- Disease progression
- Could not be evaluated
### Subgroup Analysis at 6 Months Follow-up

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients Who Could Be Evaluated</th>
<th>No. of Patients with Event</th>
<th>Objective Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>101</td>
<td>83</td>
<td>0.82 (0.73–0.89)</td>
</tr>
<tr>
<td>Refractory subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to a second-line therapy</td>
<td>78</td>
<td>65</td>
<td>0.83 (0.73–0.91)</td>
</tr>
<tr>
<td>Relapse after ASCT</td>
<td>21</td>
<td>16</td>
<td>0.76 (0.53–0.92)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>77</td>
<td>61</td>
<td>0.79 (0.68–0.88)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>24</td>
<td>22</td>
<td>0.92 (0.73–0.99)</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>15</td>
<td>13</td>
<td>0.87 (0.60–0.98)</td>
</tr>
<tr>
<td>III or IV</td>
<td>86</td>
<td>70</td>
<td>0.81 (0.72–0.89)</td>
</tr>
<tr>
<td>IPI risk score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>53</td>
<td>46</td>
<td>0.87 (0.75–0.95)</td>
</tr>
<tr>
<td>3 or 4</td>
<td>48</td>
<td>37</td>
<td>0.77 (0.63–0.88)</td>
</tr>
<tr>
<td>Extramedullary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>56</td>
<td>0.80 (0.69–0.89)</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>27</td>
<td>0.87 (0.70–0.96)</td>
</tr>
<tr>
<td>Bulky disease (≥10 cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>12</td>
<td>0.71 (0.44–0.90)</td>
</tr>
<tr>
<td>No</td>
<td>84</td>
<td>71</td>
<td>0.85 (0.75–0.91)</td>
</tr>
<tr>
<td>Treatment history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary refractory disease</td>
<td>26</td>
<td>23</td>
<td>0.88 (0.70–0.98)</td>
</tr>
<tr>
<td>Refractory to two consecutive lines</td>
<td>54</td>
<td>42</td>
<td>0.78 (0.64–0.88)</td>
</tr>
<tr>
<td>CD19 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>74</td>
<td>63</td>
<td>0.85 (0.75–0.92)</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>6</td>
<td>0.75 (0.35–0.97)</td>
</tr>
<tr>
<td>CD19 histologic score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤150</td>
<td>26</td>
<td>22</td>
<td>0.85 (0.65–0.96)</td>
</tr>
<tr>
<td>&gt;150</td>
<td>56</td>
<td>47</td>
<td>0.84 (0.72–0.92)</td>
</tr>
<tr>
<td>Cell of origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germinal center B-cell-like subtype</td>
<td>49</td>
<td>43</td>
<td>0.88 (0.75–0.95)</td>
</tr>
<tr>
<td>Activated B-cell-like subtype</td>
<td>17</td>
<td>13</td>
<td>0.76 (0.59–0.83)</td>
</tr>
<tr>
<td>CD4:CD8 ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>47</td>
<td>41</td>
<td>0.87 (0.74–0.95)</td>
</tr>
<tr>
<td>≤1</td>
<td>52</td>
<td>40</td>
<td>0.77 (0.63–0.87)</td>
</tr>
<tr>
<td>Tocilizumab use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>36</td>
<td>0.84 (0.69–0.93)</td>
</tr>
<tr>
<td>No</td>
<td>38</td>
<td>47</td>
<td>0.81 (0.69–0.90)</td>
</tr>
<tr>
<td>Glucocorticoid use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>21</td>
<td>0.78 (0.58–0.91)</td>
</tr>
<tr>
<td>No</td>
<td>74</td>
<td>62</td>
<td>0.84 (0.73–0.91)</td>
</tr>
<tr>
<td>Subgroup Analysis at 12 Months Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Refractory Subgroup:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory to ≥ 2nd line therapy (N=80)</td>
<td>31</td>
<td>0.39</td>
<td>0.28</td>
<td>0.50</td>
</tr>
<tr>
<td>Relapse post ASCT (N=25)</td>
<td>14</td>
<td>0.56</td>
<td>0.35</td>
<td>0.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 Years (N=81)</td>
<td>32</td>
<td>0.40</td>
<td>0.29</td>
<td>0.51</td>
</tr>
<tr>
<td>≥ 65 Years (N=27)</td>
<td>13</td>
<td>0.48</td>
<td>0.29</td>
<td>0.68</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Stage:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II (N=18)</td>
<td>11</td>
<td>0.61</td>
<td>0.36</td>
<td>0.83</td>
</tr>
<tr>
<td>III-IV (N=90)</td>
<td>34</td>
<td>0.38</td>
<td>0.28</td>
<td>0.49</td>
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<table>
<thead>
<tr>
<th>IPI Risk Score:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 (N=60)</td>
<td>30</td>
<td>0.50</td>
<td>0.37</td>
<td>0.63</td>
</tr>
<tr>
<td>3-4 (N=48)</td>
<td>15</td>
<td>0.31</td>
<td>0.19</td>
<td>0.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment History:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Refractory Disease (N=27)</td>
<td>11</td>
<td>0.41</td>
<td>0.22</td>
<td>0.61</td>
</tr>
<tr>
<td>Refractory to 2 Consecutive Lines (N=55)</td>
<td>19</td>
<td>0.35</td>
<td>0.22</td>
<td>0.49</td>
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<table>
<thead>
<tr>
<th>CD19 Status:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
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</thead>
<tbody>
<tr>
<td>Positive (N=77)</td>
<td>33</td>
<td>0.43</td>
<td>0.32</td>
<td>0.55</td>
</tr>
<tr>
<td>Negative (N=10)</td>
<td>5</td>
<td>0.50</td>
<td>0.19</td>
<td>0.81</td>
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<table>
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<tr>
<th>CD19 H-Score:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤150 (N=28)</td>
<td>14</td>
<td>0.50</td>
<td>0.31</td>
<td>0.69</td>
</tr>
<tr>
<td>&gt;150 (N=59)</td>
<td>24</td>
<td>0.41</td>
<td>0.28</td>
<td>0.54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell of Origin:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal Center B Cell-like (GCB) (N=52)</td>
<td>23</td>
<td>0.44</td>
<td>0.30</td>
<td>0.59</td>
</tr>
<tr>
<td>Activated B-Cell like (ABC) (N=18)</td>
<td>6</td>
<td>0.33</td>
<td>0.13</td>
<td>0.59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4/CD8 Ratio:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 (N=51)</td>
<td>21</td>
<td>0.41</td>
<td>0.28</td>
<td>0.56</td>
</tr>
<tr>
<td>≤1 (N=57)</td>
<td>24</td>
<td>0.42</td>
<td>0.29</td>
<td>0.56</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tocilizumab Use:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (N=49)</td>
<td>17</td>
<td>0.35</td>
<td>0.22</td>
<td>0.50</td>
</tr>
<tr>
<td>No (N=59)</td>
<td>28</td>
<td>0.47</td>
<td>0.34</td>
<td>0.61</td>
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<table>
<thead>
<tr>
<th>Corticosteroid Use:</th>
<th>45</th>
<th>0.42</th>
<th>0.32</th>
<th>0.52</th>
</tr>
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<tbody>
<tr>
<td>Yes (N=30)</td>
<td>10</td>
<td>0.33</td>
<td>0.17</td>
<td>0.53</td>
</tr>
<tr>
<td>No (N=78)</td>
<td>35</td>
<td>0.45</td>
<td>0.34</td>
<td>0.57</td>
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</tbody>
</table>
Duration of response
Overall survival

Median (95% CI)

mo

NR (12.0–NE)
Example
Safety

- Grade 3 toxicity: 95%
- Most common grade 3: neutropenia (78%), anemia (43%) and thrombocytopenia (38%)
- Cytokine release syndrome (CRS): occurred in 93%, with 13% of grade 3 or higher, with median onset time 2 days and resolution time of 8 days.
- Grade 5 CRS: 1 case of HLH and 1 case of cardiac arrest
- Neurology: encephalopathy (21%), early symptom include dysphasia, attention or calculation defects, handwriting problem. Median onset time on day 5, resolution on day 17.
- Tocilizumab was used in 43%, and 27% received steroid. It didn’t affect outcome.
Biomarkers
Biomarkers

• CAR T-cells were detected up to 24 months post-treatment.
• Expansion was significantly associated with response.
• Peak expansion and AUC were associated with neurologic event but not CRS.
• IL-6, -10, -15, and 2Ra and granzyme B were significantly associated with neurologic event and CRS.
## Comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No. of pts</th>
<th>Follow-up</th>
<th>CAR T-cell</th>
<th>Condition</th>
<th>Dose</th>
<th>Time to infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-1</td>
<td>DLBCL, PMBL, FL</td>
<td>111</td>
<td>15.4m</td>
<td>CD28 (axi-cel)</td>
<td>Flu/Cy</td>
<td>2 x 10^6/kg</td>
<td>17 days</td>
</tr>
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<td></td>
<td>22 centers</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Upenn</td>
<td>DLBCL, FL</td>
<td>28</td>
<td>28.6m</td>
<td>4-1BB (CTL019)</td>
<td>Multiple: Cy, Bu, XRT, Ben, EPOCH</td>
<td>6 x 10^6/kg</td>
<td>39 days</td>
</tr>
<tr>
<td></td>
<td>Single center</td>
<td></td>
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<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>Time to response</th>
<th>PFS</th>
<th>Duration</th>
<th>Neuro Gr 3</th>
<th>CRS Gr 3</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-1</td>
<td>82</td>
<td>52</td>
<td>1m</td>
<td>5.8m</td>
<td>41%</td>
<td>28%</td>
<td>13%</td>
<td>3.0%</td>
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</tr>
<tr>
<td>Upenn</td>
<td>64</td>
<td>57</td>
<td>3m (?)</td>
<td>DLBCL: 3.2m, FL: NR, 70%</td>
<td>~90%</td>
<td>11%</td>
<td>18%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

- **ZUMA-1**
  - DLBCL, PMBL, FL
  - No. of pts: 111 (22 centers)
  - Follow-up: 15.4 months
  - CAR T-cell: CD28 (axi-cel)
  - Condition: Flu/Cy
  - Dose: 2 x 10^6/kg
  - Time to infusion: 17 days

- **Upenn**
  - DLBCL, FL
  - No. of pts: 28 (Single center)
  - Follow-up: 28.6 months
  - CAR T-cell: 4-1BB (CTL019)
  - Condition: Multiple: Cy, Bu, XRT, Ben, EPOCH
  - Dose: 6 x 10^6/kg
  - Time to infusion: 39 days
Discussion

• 8 pts with CD19-negative disease had response
  • Limitation in CD19 detection

• Ratio of CD4/CD8 and T-cell phenotype did not affect outcome

• Lack of molecular/cytogenetic characteristics in ZUMA-1
  • Upenn: two pts had double-hit, both had CR

• The production was manufactured in 99% of patients, and administered in 91%
  • Quick and efficient with only 17 days turnaround time

• CRS and neurologic event are manageable
  • Reversible without sequelae
  • Early administer of tocilizumab or steroid, but not affect outcome
  • 3% death rate is better than allo-SCT
Future direction

• What is the best conditioning regimen?
  • Without Flu, the CAR T-cell proliferation is poor
  • Conditioning regimen is not expected to have substantial anti-tumor effect in refractory DLBCL

• What is the better CAR T-cell?
  • Focus on co-stimulatory domain

• CAR T-cell vs. Allo-SCT/DLI?
  • CAR T-cell didn’t induce GVHD, better than DLI
  • Whether CAR T-cell can be used along with SCT as sequential treatment is under evaluation

• Target antigens other than CD19?
  • Why CD19? Frequent and high expression in B cell malignancy. It is associated with B cell aplasia, which is portend long-term remission (“on-target off-tumor effect”). Easy to be managed by IVIG.
  • Required for normal B cell maturation; not expressed outside B cell lineage.
  • Third generation of anti-CD20 CAR (ORR: 82%, CR: 55%), anti-k light chain, anti-CD22, BCMA (myeloma) and anti-CD30 (HL) are under evaluation.
Future direction

• Toxicity
  • ICU admission rate is ~13%. CRS has been associated with tumor burden and CAR T-cell dose
  • CNS can occur asynchronously with CRS indicating different pathophysiology.
  • CRS: managed by tocilizumab (IL-6 Ab); CNS: prefer steroid alone
  • “suicide gene”: e.g. inducible capase-9 suicide switch, may affect therapeutic response (?)

• Limitation
  • Self persistence: whether need long-term persistence
  • Immunological rejection: design less immunogenic CAR
  • Antigen escape

• Improving CAR-T-cell therapy
  • Design: Less immogenic, e.g. hinge and transmembrane regions; “full humanized” (Hu)scFv
  • Co-stimulatory signal: dual- or triple-specific CAR
  • Gene editing: CRISPR/Cas9; TALENs
  • Focus on T cell subsets: CD4/CD8 ratio, less differentiated T cell (e.g. memory T cell)
Future direction

- Conditioning regimen: Flu>CTX or CTX/Eto
- Combination: exhausted phenotype has increased PD-1, e.g. add PD-1 blockage showed response to PMBL; add BTK inhibitor; add IL-15; auto-SCT and then “adjuvant” CAR-T-cell therapy (?)

• Solid tumor challenge
  - Trafficking: e.g. local injection (GBM)
  - Tumor antigen that can provide sufficient discrimination without significant off-target effect. “on-target off-tissue” effect (e.g anti-HER2) and “off-target” effect.
  - Proliferation and persistence
  - Overcoming immuosuppressive microenvironment
  - Control side effects
  - Different T cell subsets
Conclusion

• CAR-T-cell therapy showed significant response rate and long term control of refractory large B-cell lymphoma.
• Carefully manage the side effect is feasible.
• Future direction includes better design of CAR T-cell, peri-procedure management, and extension to solid tumor treatment.