Current and Potential Role of CAR T-Cell Therapy for Patients with Non-Hodgkin Lymphoma

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Massachusetts General Hospital Cancer Center
Harvard Medical School
## Four Major anti-CD19 CAR T-cell Products for B-cell NHL

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene Ciloleucel</th>
<th>Tisagenlecleucel</th>
<th>Lisocabtagene Maraleucel</th>
<th>Brexucabtagene Autoleucel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Construct</strong></td>
<td>antiCD19-<strong>CD28</strong>-CD3z</td>
<td>antiCD19-<strong>41BB</strong>-CD3z</td>
<td>antiCD19-<strong>41BB</strong>-CD3z</td>
<td>antiCD19-<strong>CD28</strong>-CD3z</td>
</tr>
<tr>
<td><strong>Vector</strong></td>
<td>Retrovirus</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
<td>Retrovirus</td>
</tr>
<tr>
<td><strong>T-cell</strong></td>
<td>Bulk</td>
<td>Bulk</td>
<td>Defined doses CD4, CD8</td>
<td>Bulk</td>
</tr>
<tr>
<td><strong>manufacturing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>$2 \times 10^6$/kg (max $2 \times 10^8$)</td>
<td>$0.6$ to $6.0 \times 10^8$</td>
<td>$1.0 \times 10^8$</td>
<td>$2 \times 10^6$/kg (max $2 \times 10^8$)</td>
</tr>
<tr>
<td><strong>Lymphodepletion</strong></td>
<td>Flu/Cy 500/30 x 3d</td>
<td>Flu/Cy 250/25 x 3d, or Benda 90 x 2d</td>
<td>Flu/Cy 300/30 x 3d</td>
<td>Flu/Cy 500/30 x 3d</td>
</tr>
<tr>
<td><strong>Approval status</strong></td>
<td>FDA/EMA approved for DLBCL, high grade B-cell lymphoma, transformed FL, PMBCL</td>
<td>FDA/EMA approved for pediatric B-ALL, DLBCL, high grade B-cell lymphoma, transformed iNHL, PMBCL, grade 3B FL</td>
<td>FDA approved for DLBCL, high grade B-cell lymphoma, transformed iNHL, PMBCL, grade 3B FL</td>
<td>FDA/EMA approved for mantle cell lymphoma and B-ALL</td>
</tr>
</tbody>
</table>
ZUMA-1: PFS and OS of patients with R/R DLBCL receiving axicabtagene ciloleucel

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Phase 1 and 2 (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>58 (23–76)</td>
</tr>
<tr>
<td>Age ≥ 65 years, n (%)</td>
<td>27 (25)</td>
</tr>
<tr>
<td>≥ 3 prior therapies, n (%)</td>
<td>76 (70)</td>
</tr>
<tr>
<td>Refractory (no response to prior tx or relapse &lt;1y from ASCT)</td>
<td>108 (100%)</td>
</tr>
<tr>
<td>Refractory to 2nd- or later-line therapy, n (%)</td>
<td>80 (74)</td>
</tr>
<tr>
<td>Best response as PD to last therapy, n (%)</td>
<td>70 (65)</td>
</tr>
<tr>
<td>Relapse post ASCT, n (%)</td>
<td>25 (23)</td>
</tr>
</tbody>
</table>

**ORR:** 83% [74% by IRC]  
**CR:** 58% [54% by IRC]
JULIET: PFS and OS of patients with R/R DLBCL receiving tisagenlecleucel

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>56 (22–76)</td>
</tr>
<tr>
<td>Double-/triple-hit lymphoma, %</td>
<td>27</td>
</tr>
<tr>
<td>Number of prior lines of therapy, %</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>4–6</td>
<td>21</td>
</tr>
<tr>
<td>Refractory to last therapy, %</td>
<td>55</td>
</tr>
<tr>
<td>Prior ASCT, %</td>
<td>49</td>
</tr>
</tbody>
</table>

**ORR: 52%**  
**CRR: 40%**  

TRANSCEND-NHL-001 trial: liso-cel in multiply R/R aggressive B-NHL

**Characteristic***

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (N = 269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>63 (18–86)</td>
</tr>
<tr>
<td>Double- / triple-hit lymphoma, n (%)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>CNS involvement, n (%)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Median prior lines, n (range)</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Chemo-refractory, n (range)</td>
<td>181 (67)</td>
</tr>
<tr>
<td>Prior HSCT, n (%)</td>
<td>94 (35)</td>
</tr>
</tbody>
</table>

*Only CAR T-cell pivotal trial to include: secondary CNS DLBCL; prior allo SCT; transformed non-follicular iNHL; grade 3B FL; no minimal ALC, ANC, Hgb or platelets; moderate renal or cardiac dysfunction

**ORR:** 73%

**CRR:** 53%

**ASH 2021:** 2 year DOR 49.5%, PFS 40.6%, OS 50.5%

Abrahamson, et al. Abstract 2840
Toxicity of 3 Major CAR T-cell Products for relapsed/refractory DLBCL

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene Ciloleucel</th>
<th>Tisagenlecleucel</th>
<th>Lisocabtagene Maraleucel</th>
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<tbody>
<tr>
<td>Construct</td>
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<td>antiCD19-41BB-CD3z</td>
<td>antiCD19-41BB-CD3z</td>
</tr>
<tr>
<td>n</td>
<td>101</td>
<td>111</td>
<td>269</td>
</tr>
<tr>
<td>Any CRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to onset</td>
<td>93% 2 days</td>
<td>58% 3 days</td>
<td>42% 5 days</td>
</tr>
<tr>
<td>≥ Gr 3 CRS†</td>
<td>11%</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>Any neurotoxicity</td>
<td>64%</td>
<td>21%</td>
<td>30%</td>
</tr>
<tr>
<td>≥ Gr 3 neurotoxicity</td>
<td>32%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>43%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Steroid use</td>
<td>27%</td>
<td>11%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Lancet Onc 2018</td>
<td>NEJM 2018</td>
<td>The Lancet 2020</td>
</tr>
</tbody>
</table>

* Caveats in cross trial comparisons: Different eligibility criteria, phase of study, dose levels
†CRS toxicity grading scales differ across studies. Axi-Cel and Liso-cel used Lee criteria. Tisa-cel used Penn criteria
Algorithm for managing relapsed DLBCL

Relapsed/refractory DLBCL

Fit for high dose therapy

2\textsuperscript{nd} line therapy
(R-ICE, R-DHAP, R-GDP)

- Chemosensitive
- Not chemosensitive

Auto SCT

CAR T-cells

Unfit for high dose therapy

2\textsuperscript{nd} line therapy
(personalized to the patient)

- CR
  - Continue tx

- Less than CR & fit for CAR
  - Relapse & unfit for CAR
- Less than CR & unfit for CAR

3\textsuperscript{rd}+ line treatment

- Relapse
- Relapse & fit for CAR

Relapse

Less than CR & fit for CAR

Relapse & unfit for CAR
High dose chemotherapy with autologous stem cell transplant

Pre-rituximab era

**Induction response**

<table>
<thead>
<tr>
<th></th>
<th>R-DHAP n=223</th>
<th>O-DHAP n=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>42%</td>
<td>38%</td>
</tr>
<tr>
<td>CRR</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>Transplanted</td>
<td>37%</td>
<td>33%</td>
</tr>
</tbody>
</table>

van Imhoff, et al. JCO 2017
Randomized trials of CAR T-cells vs. SOC in 2\textsuperscript{nd} line transplant-eligible DLBCL with primary refractory disease or relapse within 1 year of 1\textsuperscript{st} line therapy

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-7</th>
<th>TRANSFORM</th>
<th>BELINDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR T-cell</td>
<td>Axicabtagene Ciloleucel</td>
<td>Lisocabtagene Maraleucel</td>
<td>Tisagenlecleucel</td>
</tr>
<tr>
<td>n</td>
<td>359</td>
<td>184</td>
<td>322</td>
</tr>
<tr>
<td>% infused in CAR arm</td>
<td>94%</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>Median EFS</td>
<td>8.3 mo vs. 2 mo</td>
<td>10.1 mo vs. 2.3 mo</td>
<td>3 mo vs. 3 mo</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.398 (P&lt;0.0001)</td>
<td>0.349; (P&lt;0.0001)</td>
<td>1.07 (P=0.69)</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>25 months</td>
<td>6 months</td>
<td>10 months</td>
</tr>
<tr>
<td>CR rate</td>
<td>65% vs 32%</td>
<td>66% vs 39%</td>
<td>28% vs 28%</td>
</tr>
<tr>
<td>Grade (\geq 3) CRS/NT</td>
<td>6% / 21%</td>
<td>1% / 4%</td>
<td>5% / 3%</td>
</tr>
</tbody>
</table>

Locke, et al. Abstract 2
Kamdar, et al. Abstract 91
Bishop, et al. Abstract LBA-6
ZUMA-12 study for early axi-cel in high-risk DLBCL

Phase 2

High-Risk LBCL
- High-grade B cell lymphoma, with MYC and BCL2 and/or BCL6 translocations, or
- LBCL with IPI score ≥ 3 any time before enrollment

Systemic Therapy
- 2 Cycles of an anti-CD20 mAb + anthracycline-containing regimen

Dynamic Risk Assessment
- Positive interim PET (DS 4 or 5)

Additional Key Inclusion Criteria
- Age ≥ 18 years
- ECOG 0 – 1

Enrollment / Leukapheresis

Optional Nonchemotherapy Bridging Therapy

Conditioning Chemotherapy + Axi-Cel Infusion
- Conditioning:
  Fludarabine 30 mg/m² IV and cyclophosphamide 500 mg/m² IV on
  Days −5, −4, and −3
- Axi-Cel: Single IV infusion of 2 × 10⁶ CAR T cells/kg on Day 0

Primary Endpoint
- CR (investigator-assessed per Lugano classification)¹

Key Secondary Endpoints
- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum
ZUMA-12 study for early axi-cel in high-risk DLBCL (n=40)

12-month estimates:
- DOR 81%
- PFS 75%
- OS 91%

Grade ≥3 CRS in 3 pts (8%), Grade ≥3 NE 9 pts (23%)
ZUMA-5 Study of Axi-cel in relapsed/refractory FL and MZL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FL n=124</th>
<th>MZL N=22</th>
<th>All Patients N=146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>60 (34-79)</td>
<td>66 (48-77)</td>
<td>61 (34-79)</td>
</tr>
<tr>
<td>FLIPI 3-5</td>
<td>54 (44%)</td>
<td>14 (64%)</td>
<td>68 (47%)</td>
</tr>
<tr>
<td>High tumor burden (GELF)</td>
<td>64 (52%)</td>
<td>8 (36%)</td>
<td>72 (49%)</td>
</tr>
<tr>
<td>Median prior tx (range)</td>
<td>3 (1-10)</td>
<td>3 (2-8)</td>
<td>3 (1-10)</td>
</tr>
<tr>
<td>Refractory</td>
<td>84 (68%)</td>
<td>16 (73%)</td>
<td>100 (68%)</td>
</tr>
<tr>
<td>POD24</td>
<td>68 (55%)</td>
<td>11 (52%)</td>
<td>79 (55%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=104)</th>
<th>FL (n=84)</th>
<th>MZL (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>92%</td>
<td>94%</td>
<td>85%</td>
</tr>
<tr>
<td>CRR</td>
<td>76%</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>PRR</td>
<td>16%</td>
<td>14%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Progression-free survival

AEs of Special Interest (n=140)

<table>
<thead>
<tr>
<th></th>
<th>Any grade</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine Release Syndrome</td>
<td>82%</td>
<td>7%</td>
</tr>
<tr>
<td>Neurologic Events</td>
<td>60%</td>
<td>19%</td>
</tr>
</tbody>
</table>

• Follicular lymphoma (n=124)
  - Median follow-up 30.9 months
  - CR rate 79%
  - Estimated median DOR was 38.6 months, PFS 39.6 months, TTNT 39.6 months

• Marginal zone lymphoma (n=25)
  - Median follow-up 23.8 months
  - CR rate 63%
  - Median PFS 17.3 months. Medians for DOR and TTNT not reached
ELARA Study of Tisa-cel in relapsed/refractory FL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FL  n=97</th>
<th>All patients n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>57 (29-73)</td>
<td>ORR 86%</td>
</tr>
<tr>
<td>Median prior tx (range)</td>
<td>4 (2-13)</td>
<td>CRR 66%</td>
</tr>
<tr>
<td>Refractory</td>
<td>78%</td>
<td>PRR 20%</td>
</tr>
<tr>
<td>POD24</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

Refractory 78%

POD24 60%

All patients n=94

ORR 86%

CRR 66%

PRR 20%

AEs of Special Interest (n=97)

| Cytokine Release Syndrome | Any grade | Grade ≥ 3 | 48.5% | 0%
|---------------------------|-----------|-----------|-------|---
| Neurologic Events         | Any grade | Grade ≥ 3 | 9.3%  | 1%

Progression-free survival

76% at 6 m

Mantle cell lymphoma: Survival after BTK inhibitor failure is poor

ZUMA-2: Brexucabtagene Autoleucel in Relapsed/Refractory MCL

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>65 (38–79)</td>
</tr>
<tr>
<td>Median no. of prior treatments (range)</td>
<td>3 (1–5)</td>
</tr>
<tr>
<td>Prior BTKi, n (%)</td>
<td>68 (100)</td>
</tr>
<tr>
<td>BTKi refractory, n (%)</td>
<td>42 (62)</td>
</tr>
<tr>
<td>Prior ASCT, n (%)</td>
<td>29 (43)</td>
</tr>
</tbody>
</table>

**Toxicity**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>n = 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade CRS, n (%)</td>
<td>62 (91)</td>
</tr>
<tr>
<td>Grade 3 or 4 CRS, n (%)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Time to onset, median, days (range)</td>
<td>2 (1–13)</td>
</tr>
<tr>
<td>Any-grade neurological toxicity, n (%)</td>
<td>43 (63)</td>
</tr>
<tr>
<td>Grade 3 or 4 neurological toxicity, n (%)</td>
<td>21 (31)</td>
</tr>
<tr>
<td>Time to onset, median, days (range)</td>
<td>7 (1–32)</td>
</tr>
</tbody>
</table>

**Best objective response (%)**

- 94% ORR (n = 16)
- 67% CR (n = 40)
- 27% PR (n = 2)
- 3% SD (n = 2)
- 3% PD (n = 2)

**PFS (%)**

Median PFS (95% CI), months: NR (9.2–NE)

**Graphs and Figures**

- Graph showing PFS with median PFS at NR (9.2–NE)
- Bar chart showing ORR, CR, PR, SD, PD rates
Lisocabtagene Maraleucel in Relapsed/Refractory MCL

### Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>67 (36–80)</td>
</tr>
<tr>
<td>Median no. of prior treatments (range)</td>
<td>3 (1–7)</td>
</tr>
<tr>
<td>Prior BTKi, n (%)</td>
<td>24 (75)</td>
</tr>
<tr>
<td>Refractory, n (%)</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Prior ASCT, n (%)</td>
<td>11 (34)</td>
</tr>
</tbody>
</table>

### Toxicity

<table>
<thead>
<tr>
<th></th>
<th>n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade CRS, n (%)</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Grade 3 or 4 CRS, n (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Time to onset, median, days (range)</td>
<td>6 (2–10)</td>
</tr>
<tr>
<td>Any-grade neurological toxicity, n (%)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Grade 3 or 4 neurological toxicity, n (%)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Time to onset, median, days (range)</td>
<td>8 (2–25)</td>
</tr>
</tbody>
</table>
CAR T-cell Updates in Lymphoma

- Liso-cel, axi-cel and tisa-cel induce durable responses in heavily pretreated DLBCL and are approved after at least 2 lines of prior therapy.
- Initial randomized data show liso-cel and axi-cel superior to standard 2nd line chemotherapy and transplant in primary refractory and early relapsed patients.
- Axi-cel and tisa-cel are effective in heavily pretreated follicular lymphoma and can be considered after at least 2 prior lines of therapy.
- Brexu-cel and liso-cel produce high rates of CR in relapsed MCL patients who have failed a prior BTK inhibitor.
- Additional indications likely to emerge as data evolve.
Thank you for your attention!

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