CHIMERIC ANTIGEN RECEPTOR THERAPY

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DISCLOSURES FOR NASHEED M. HOSSAIN

I have no actual or potential conflict of interest in relation to this presentation.

I will be discussing Non-FDA Approved techniques:

1) New models of CAR Therapies for various indications
LEARNING OBJECTIVES

1. A review of Chimeric Antigen Receptor (CAR) Basics
2. Current experience with CARs
   1. DLBCL
   2. ALL
   3. MCL
   4. iNHL
   5. MM
3. Experience with the LRF/Loyola CAR T-cell trial
4. Questions
LEARNING OBJECTIVES

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CAR T-CELL BASICS

Employs gene transfer techniques to “reprogram” a patient’s own T-cells

Target is defined by a customized T-cell Receptor construct ("Chimeric Antigen Receptor")

Many methods to introduce the construct into the T-cell (lentivirus, retrovirus, transposons)

Many different constructs have been developed and tested

Variety of antigens targeted in various diseases
TCR VS CAR

MAKING A CAR

Turn Around Time is 12-45 days

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4. Questions
# PIVOTAL CLINICAL TRIALS IN DLBCL

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<tr>
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<tbody>
<tr>
<td></td>
<td>Axicabtagene ciloleucel</td>
<td>Tisagenlecleucel</td>
<td>Lisocabtagene maraleucel</td>
</tr>
<tr>
<td>Study phase</td>
<td>II</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>Patient population</td>
<td>Adults with refractory DLBCL</td>
<td>Adults with R/R DLBCL</td>
<td>Adults with R/R DLBCL</td>
</tr>
<tr>
<td>Patients pheresed/treated, n</td>
<td>111/101</td>
<td>165/111</td>
<td>344/269*</td>
</tr>
<tr>
<td>Bridging therapy</td>
<td>Not allowed</td>
<td>92%</td>
<td>59%</td>
</tr>
<tr>
<td>ORR, %</td>
<td>82%</td>
<td>52%</td>
<td>73%</td>
</tr>
<tr>
<td>CR, %</td>
<td>54%</td>
<td>40%</td>
<td>53%</td>
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</tbody>
</table>

All currently FDA approved!
• Among 101 patients treated with 4+ years of follow-up (median 51.1 months), the OS 25.8 months and estimate of 4-year OS is 44%
ZUMA-1 SAFETY

<table>
<thead>
<tr>
<th></th>
<th>CRS</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All grades</strong></td>
<td>92%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Grade ≥3</strong></td>
<td>11%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Time to onset</strong></td>
<td>2 (1-12) days</td>
<td>5 (1-17) days</td>
</tr>
<tr>
<td><strong>Time to resolution</strong></td>
<td>8 days</td>
<td>17 days</td>
</tr>
</tbody>
</table>

- 4 deaths due to AEs – 1 cardiac arrest, 1 HLH, 1 pulmonary embolism, 1 ICH
  - 2 related to axi-cel
- Lee criteria used for CRS grading
- CTCAE criteria used for neurological event (NE) grading

JULIET: CLINICAL EFFICACY

- ORR - 52%
  - CR Rate: 40%
  - PR Rate: 12%

- Median Duration of Response: NR

- Estimated PFS@12months is 83% for those with CR or PR @ 3 months

- Median OS: 12 months
**JULIET: SAFETY**

<table>
<thead>
<tr>
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<th>CRS</th>
<th>NE</th>
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<tbody>
<tr>
<td>All grades</td>
<td>64%</td>
<td>23%</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>24%</td>
<td>13%</td>
</tr>
<tr>
<td>Time to onset [Median (Range)]</td>
<td>3 days</td>
<td>6 (1-17) days</td>
</tr>
<tr>
<td>Time to resolution (Median)</td>
<td>7 days</td>
<td>14 days</td>
</tr>
</tbody>
</table>

- Three patients died within 30 days after infusion, all from lymphoma progression
- No deaths related to CAR therapy
- CRS graded by Penn scale

Schuster et al, NEJM 2019
TRANSCEND - RESPONSE

• ORR 73%
  • CR 53%
  • PR 19.5%
• At 6 months, 60.4% of responses were ongoing
• At 12 months, 54.7% of responses were ongoing
• Median OS 21.1 months
• Median PFS 6.8 months
## TRANSCEND – SAFETY

### All liso-cel–Treated Patients (N=269)

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td><strong>CRS</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Any grade, n (%)</td>
<td>113 (42)</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Grade 4, n (%)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Time to onset, median (range), days</td>
<td>5 (1–14)</td>
</tr>
<tr>
<td>Time to resolution, median (range), days</td>
<td>5 (1–17)</td>
</tr>
<tr>
<td><strong>NE</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Any grade, n (%)</td>
<td>80 (30)</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Grade 4, n (%)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Time to onset, median (range), days</td>
<td>9 (1–66)</td>
</tr>
<tr>
<td>Time to resolution, median (range), days</td>
<td>11 (1–86)</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td><strong>CRS or NE, n (%)</strong></td>
<td>127 (47)</td>
</tr>
<tr>
<td>ICU admissions,&lt;sup&gt;c&lt;/sup&gt; n (%)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>For CRS and/or NE</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

### Treatment for CRS and NE

- **CRS ± NE**:
  - Toci and Steroids: 8%
  - Toci: 7%
  - Steroids: 2%
- **CRS**:
  - Toci and Steroids: 13%
  - Toci: 10%
  - Steroids: 8%
- **NE**:
  - Toci and Steroids: 13%
  - Steroids: 0.4%
  - NE: 3%

- 3% of patients received vasopressors for CRS or NE
- 2 patients received other anti-inflammatory/anticytokine agents

### CRS and NE were reversible
- 1 patient had an unresolved NE (grade 1 tremor) at data cutoff
- 8 patients had ongoing CRS/NE at time of death from other reasons
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   4. iNHL
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4. Questions
ELIANA – CLINICAL EFFICACY

- Overall response rate was 82%
  - CR 62%
- 66% of patients with CR in remission at 18 months
- Overall survival rate of 70% at 18 months post CAR
- Reported 15/16 patients with relapse where CD19 negative
<table>
<thead>
<tr>
<th></th>
<th>CRS</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>77%</td>
<td>40%</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>48%</td>
<td>13%</td>
</tr>
<tr>
<td>Time to onset [Median (Range)]</td>
<td>3 days (1-22d)</td>
<td>NR</td>
</tr>
<tr>
<td>Time to resolution (Median)</td>
<td>8 days</td>
<td>18 days</td>
</tr>
</tbody>
</table>

- **Overall 25 deaths**
- With first 30 days:
  - 1 death from cerebral hemorrhage
  - 1 death from progression of disease
- Beyond first 30 days:
  - 18 deaths due to progression of disease
  - 1 death due to HHV6 encephalitis
  - 1 death due to systemic mycosis
  - 1 due to veno-occlusive disease
  - 1 due to bacterial lung infection
  - 1 death with unknown etiology
ZUMA-3: CAR IN ADULT ALL

• Multicenter, open-label phase I/II trial of axicabtagene ciloleucel for adult patients with R/R B-precursor ALL

• Phase 1 results recently reported, showing very promising results

At a median follow-up of 22.1 months, the median duration of remission was 17.6 months and 14.5 months in all patients.
Revised adverse event (AE) management for CRS and NEs: earlier steroid use for NEs and tocilizumab only for CRS


<table>
<thead>
<tr>
<th>Event</th>
<th>Original AE Management (n=14)</th>
<th>Revised AE Management (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade ≥3 Neurologic Events, n (%)</strong></td>
<td>9 (64)</td>
<td>1 (11)</td>
</tr>
<tr>
<td><strong>Grade ≥3 Cytokine Release Syndrome, n (%)</strong></td>
<td>4 (29)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Duration of events, days</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Time to onset, days</td>
<td>4.5</td>
<td>6</td>
</tr>
<tr>
<td>Grade 5 events</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1 x 10^6 CAR T cells/kg
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ZUMA 2 – MANTLE CELL LYMPHOMA (MCL)

- Of 74 patients treated:
  - 85% objective response rate
  - 59% CR
  - 16% PR
  - 17 patients with continuing response with median follow-up, 12.3 months

16 deaths on trial:
- 14 due to disease progression
- 1 due to organizing pneumonia
- 2 due to bacterial blood infection

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<tbody>
<tr>
<td>All grades</td>
<td>91%</td>
<td>63%</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>15%</td>
<td>31%</td>
</tr>
<tr>
<td>Time to onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Median (Range)]</td>
<td>2 days (1-13d)</td>
<td>7 days (1-32d)</td>
</tr>
<tr>
<td>Time to resolution</td>
<td>11 days</td>
<td>12 days</td>
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4. Questions
Overall response rate: 92%
CR Rate 80%
Duration of Response – responses maintained in >50% of patients at 17+ months of follow up
3 patient deaths on trial:
1 due to CRS
2 others not thought to be CAR T cell related (Aortic Dissection, Fungal infection)

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<tbody>
<tr>
<td>All grades</td>
<td>84%</td>
<td>77%</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>8%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Time to onset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Median (Range)]</td>
<td>4 days (1-12 days)</td>
<td>6 days (1-79 days)</td>
</tr>
<tr>
<td><strong>Time to resolution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Median)</td>
<td>7 days</td>
<td>16 days</td>
</tr>
</tbody>
</table>

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KARMMA – MM CAR T-CELL

- ORR 94% (at 13.3 months median follow up)
- CR rate 33%
  - 79% MRD negative
- VGPR 52%
- PFS 8.8 months
- OS 19.4 months
- Estimated duration of response 10.7 months
KARMA– CART IN MM

44 patient deaths on trial:
- 27 due to MM progression
- 4 due to CAR T related complications (CRS, infections, bleeding)
- 13 from other causes

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<tbody>
<tr>
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<td>84%</td>
<td>18%</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>

| Time to onset          | CRS     | NE      |
| [Median (Range)]       |         |         |
| 1 days (1-12 days)     | 2 days  | 3 days  |