CAR T-cell Therapy: Where are We Now & Where are We Headed?

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Disclosures

Financial: I currently have or have had the following relevant financial relations to disclose:

– Clinical Trials: Kite Pharma, Celgene, Bluebird Bio, CRISPR, Atara, Immatics, Adaptimmune, Bellicum, Kiadis, Incyte, Takeda, Pharmacyclic

– Consulting: Kite, Pfizer, Atara, Magenta

Off-Label Use: I do not intend to discuss an off-label use of a product during this activity.
What is Adoptive Cell Therapy?

1. **Harvest PBMCs by apheresis**
2. **T cell activation**
3. **Transduction**
4. **TIL cell isolation**
5. **TIL cell expansion**
6. **Infusion**
7. **Host condition chemotherapy**
8. **CART cells**
9. **TCRT cells**
10. **Lymphodepleted cancer patient**

Cancer patient

- Excise tumor mass
- CAR
- Tumor binding domain
- Signaling domains
- TCR
- α
- β
- CDC3
- γεδ
- ζζ

NewYork-Presbyterian
The University Hospital of Columbia and Cornell
What is CAR T Therapy?

Chimeric Antigen Receptor (CAR) genetically modified (“engineered”) T cells. Designed to expand in the patient, recognize tumor cells and destroy them

Usually generated from the patient’s own T cells (“autologous”)

CAR T cells are a “living drug”

CAR T cells are “serial killers”

Persistence ➔ “immune memory”
CAR T Cells - History

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.

F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment

By DENISE GRADY  JULY 12, 2017

Aug. 25, 2011

July 12, 2017
First Approved CAR-T cells

Oct. 17, 2017 – adult lymphoma

Aug. 30, 2017 – ALL up to age 25

May 1, 2018 – adult lymphoma
Leukapheresis: Patient’s white blood cells are collected and shipped to the manufacturing facility

T cell activation/transduction: T cells are genetically transduced with a viral vector encoding the anti-CD19 CAR

Modified T cell expansion: CAR-T cells undergo ex vivo expansion on magnetic, antibody-coated beads

Chemotherapy: The patient receives a preparative lymphodepleting regimen before T-cell infusion (Flu/Cy)

CAR T cell infusion: CAR-T cells are cryopreserved, shipped back to the center, thawed and infused into the patient

Turnaround Time: 12 – 27 days
Collection of T Cells
CAR-T Manufacturing
Targeting with Chimeric Antigen Receptors

Antibody (scFv) to target a specific antigen on cancer cell

Signals for T cell activation, proliferation and survival

Provides 2nd signal for T-cell activation

Antigen binding domain

Hinge region

4-1BB costimulatory domain

CD3-zeta chain signaling domain
Viral vector

T cell

CAR T cell

Anti-CD19 CAR

CD19

Dead CD19+ cell

B-cell lymphoma or leukemia cell
Variety of CAR-T Cell Constructs

- MSKCC-28\(\zeta\) CAR
- MSKCC
- NCI
- Baylor
- SJCRH-4-1BB\(\zeta\) CAR
- CHOP/UP
- FHCRC

Axicabtagene ciloleucel (Yescarta)

Tisagenlecleucel I (Kymria)
Costimulatory Domain Affects Expansion and Persistence

These differences also determine the kinetics of toxicities: CD28 early and rapid; 4-1BB gradual
# CAR T Cells Demonstrate High Response Rates and Durable Complete Responses

<table>
<thead>
<tr>
<th></th>
<th>Aggressive Lymphoma</th>
<th>Acute Lymphoblastic Leukemia</th>
<th>Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>CD19</td>
<td>CD19</td>
<td>BCMA</td>
</tr>
<tr>
<td><strong>Pivotal Clinical Trials</strong></td>
<td>ZUMA-1</td>
<td>ELIANA</td>
<td>KarMMa</td>
</tr>
<tr>
<td></td>
<td>JULIET</td>
<td>ZUMA-3, ZUMA-4</td>
<td>(KITE-585)</td>
</tr>
<tr>
<td></td>
<td>TRANSCEND NHL 001</td>
<td>ROCKET</td>
<td>(JCARH125)</td>
</tr>
<tr>
<td><strong>Response rates</strong></td>
<td>Up to 82%</td>
<td>&gt;95%</td>
<td>Up to 100%</td>
</tr>
<tr>
<td><strong>Complete Remission rates</strong></td>
<td>Up to 58%</td>
<td>Up to 93% (MRD negative)</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Patients in CR more than 1 year</strong></td>
<td>Approx. 40%</td>
<td>Approx. 60%</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Approval Status</strong></td>
<td></td>
<td><img src="logo.png" alt="FDA Approved" /></td>
<td><img src="logo.png" alt="FDA Approved" /></td>
</tr>
</tbody>
</table>
Unmet Need in DLBCL – how effective is 1st line?

Standard R-CHOP cures less than 2/3 of newly diagnosed patients. 5-yr OS after R-CHOP is 58%
Unmet Need in DLBCL – how effective (and feasible) is 2nd line?

Salvage + Auto-HSCT curative in 40% of DLBCL patients at 1st relapse

![Survival Probability Graph](image)

- Red line: Failure from diagnosis <12 months
- Blue line: Failure from diagnosis >=12 months

Statistical significance: p<0.0001
Unmet Need in DLBCL – what happens beyond 2 lines?

**Refractory DLBCL** (Scholar-1 Study)

- Refractory or relapsed within 12 mo from auto-HSCT
- ORR = 26%
- CR rate = 7%
- Median OS = 6.3 mo
- 2-yr OS = 20%
ZUMA-1: Multicenter Trial of KTE-C19 (axi-cel) in Refractory Aggressive NHL

Phase 1
Refractory DLBCL/PMBCL/TFL (cohort of n=6)

Phase 2
Cohort 1
Refractory DLBCL (n=72)
Cohort 2
Refractory PMBCL/TFL (n=20)

Eligibility criteria
Aggressive NHL: DLBCL, PMBCL, TFL
Chemotherapy-refractory disease:
  no response to last chemotherapy or relapse ≤12 mo ASCT
Prior anti-CD20 mAb and anthracycline
ECOG PS 0-1

Primary endpoint
• Phase 2: ORR

Key secondary endpoints
DOR, OS, Safety, Levels of CAR T and Cytokines
ZUMA-1: Phase 2 CONSORT Diagram

Not treated:
- n=5 SAE
- n=1 Product unavailable
- n=2 Non-measureable disease

Enrolled & Leukapheresed (n=111)

Conditioning
Cy 500 mg/m²
Flu 30mg/m² × 3 days

KTE-C19
2 × 10⁶/kg (n=101)

22 sites
99% manufacturing success
91% of enrolled patients dosed
17 day average turnaround time from apheresis to delivery to clinical site

No bridging therapy allowed
# ZUMA-1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DLBCL (n=77)</th>
<th>TFL/PMBC L (n=24)</th>
<th>All Patients (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>58 (25-76)</td>
<td>57 (23-76)</td>
<td>58 (23-76)</td>
</tr>
<tr>
<td>Age ≥65 years, n (%)</td>
<td>17 (22)</td>
<td>7 (29)</td>
<td>24 (24)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>50 (65)</td>
<td>18 (75)</td>
<td>68 (67)</td>
</tr>
<tr>
<td><strong>ECOG performance status 1, n (%)</strong></td>
<td>49 (64)</td>
<td>10 (42)</td>
<td>59 (58)</td>
</tr>
<tr>
<td><strong>Median number of prior therapies (#)</strong></td>
<td>3 (1-7)</td>
<td>4 (2-12)</td>
<td>3 (1-12)</td>
</tr>
<tr>
<td><strong>IPI 3-4, n (%)</strong></td>
<td>37 (48)</td>
<td>11 (46)</td>
<td>48 (48)</td>
</tr>
<tr>
<td><strong>Disease stage III/IV, n (%)</strong></td>
<td>67 (87)</td>
<td>19 (79)</td>
<td>86 (85)</td>
</tr>
<tr>
<td><strong>Refractory subgroup, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to 2\textsuperscript{nd} or later therapy</td>
<td>59 (77)</td>
<td>19 (79)</td>
<td>78 (77)</td>
</tr>
<tr>
<td>Relapse post-ASCT</td>
<td>16 (21)</td>
<td>5 (21)</td>
<td>21 (21)</td>
</tr>
<tr>
<td><strong>CD19-negative, n (%)</strong></td>
<td>7/63 (11)</td>
<td>1/19 (5)</td>
<td>8/82 (10)</td>
</tr>
</tbody>
</table>
CD19 CAR in Adult Lymphoma (axi-cel)

Pivotal phase 1/2 study:
- ZUMA-1 (NCT02348216)

Evaluable patients:
- DLBCL (76%), TFL (16%), PMBCL (8%)

<table>
<thead>
<tr>
<th>Response Rates (N=101)</th>
<th>Local</th>
<th>Central Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>83</td>
<td>72</td>
</tr>
<tr>
<td>CR</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td>PR</td>
<td>25</td>
<td>21</td>
</tr>
</tbody>
</table>

Neelapu et al., NEJM 2017
Response to CAR-T in Lymphoma Patient

52yo male
DLBCL with myc amplification, TP53 mutation
R-EPOCH x 2 -> refractory
DHAP x 2 -> refractory

1/27/19

3/6/19
Response to CAR-T in Lymphoma Patient

52yo male
DLBCL with myc amplification, TP53 mutation
R-EPOCH x 2 -> PD
DHAP x 2 -> PD

1/27/19

3/6/19
Consistent Responses Across Key Covariates

Age
Extranodal
CD19
COO
Toci
Steroids

Neelapu et al., NEJM 2017
Long Duration of Remission (Axi-cel)

Duration of Response in Complete Responders

Median DOR (95% CI), months
- Investigator-Assessed: 11.1 (4.2 – NR)
- Central Review: NR (10.9 – NR)

Neelapu ASH 2018
Unprecedented Survival (Axi-cel)

Median OS (95% CI), months
NR (12.8 – NR)

<table>
<thead>
<tr>
<th>OS Rate</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month</td>
<td>60%</td>
</tr>
<tr>
<td>18-month</td>
<td>53%</td>
</tr>
<tr>
<td>24-month</td>
<td>51%</td>
</tr>
</tbody>
</table>

Patients at Risk
10 199 97 96 93 87 80 78 74 70 69 63 61 60 60 56 54 53 53 53 53 52 51 50 41 32 25 18 12 7 6 1 0

Neelapu ASH 2018
Responses may evolve over time

**Diagram:**
- **Progression-free survival, months (95% CI):**
  - Complete response: NR (NE-NE)
  - Partial response: NR (4.4-NE)
  - Stable disease: 7.3 (3.4-NE)

**Legend:**
- Green line: Complete response
- Red line: Partial response
- Blue line: Stable disease

**Axes:**
- **Y-axis:** Progression-free survival (%)
- **X-axis:** Time (months)

**Source:** Locke et al. *Lancet Oncology* 2019
Predictors of Clinical Benefit
Lessons from ZUMA-1

Reponses by line of therapy

<table>
<thead>
<tr>
<th>Prior Lines of Therapy Before Enrollment on ZUMA-1</th>
<th>1 - 2 (n = 32)</th>
<th>3 (n = 33)</th>
<th>4 (n = 30)</th>
<th>≥ 5 (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>29 (91)</td>
<td>31 (94)</td>
<td>24 (80)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>CR</td>
<td>18 (56)</td>
<td>22 (67)</td>
<td>18 (60)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (34)</td>
<td>9 (27)</td>
<td>6 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Ongoing response at 1 year</td>
<td>15 (47)</td>
<td>12 (36)</td>
<td>15 (50)</td>
<td>3 (23)</td>
</tr>
</tbody>
</table>

Reponses by disease burden

Objective Response and Response at 1 Year

- ORR
- Ongoing response at 1 year

Locke et al. ASCO 2018
CAR-T Cell Expansion Predicts Response

Locke, Neelapu et al. ASCO 2018
CD19 CAR in Adult Lymphoma (tisagen)

• Tisagenlecleucel (Kymriah) is a CD19-targeting CAR-T cell product with a 4-1BB costimulatory domain

• JULIET is a single-arm, open-label, multicenter, global phase 2 trial of tisagenlecleucel in adult patients with R/R DLBCL (NCT02445248)

• Prior single-center phase II in 28 patients (14 DLBCL, 14 FL) – ORR 64%
  • DLBCL – CR 43%
  • FL – CR 71%
  • 86-89% of CR were durable through the median follow up of 28.6 mo
  • No relapses after the first 6 mo
  • As of May 2018, first patients have reached 4 years in CR
  • Severe CRS 18%, severe neurotox 11%. Overall neurotox in third of patients. One death from encephalopathy.
CD19 CAR in Adult Lymphoma (tisagen)

- Eligibility: Adult DLBCL pts; ≥ 2 prior tx lines for DLBCL; PD following or ineligible for autoHSCT; no prior anti-CD19 tx; no active CNS involvement
- N = 165
- 26% received outpatient infusion; 77% of them remained outpatient ≥ 3 days post infusion
- 50 patients not infused (inability to manufacture, n = 12; related to pt status, n = 38)
- 90% of patients received bridging chemotherapy
- Lymphodepleting chemo Flu 25 mg/m2 and Ctx 250 mg/m2 x 3. Alternative regimens allowed.
- 7% received no lymphodepleting chemo
## CD19 CAR in Adult Lymphoma (Kymriah)

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Pts (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>56 (22-76)</td>
</tr>
<tr>
<td>▪ ≥ 65 yrs, %</td>
<td>23</td>
</tr>
<tr>
<td>ECOG PS 0/1, %</td>
<td>55/45</td>
</tr>
<tr>
<td>Histology, %</td>
<td></td>
</tr>
<tr>
<td>▪ DLBCL</td>
<td>80</td>
</tr>
<tr>
<td>▪ Transformed FL</td>
<td>19</td>
</tr>
<tr>
<td>Double/triple hits in CMYC/BCL2/BCL6,* %</td>
<td>15</td>
</tr>
<tr>
<td>Cell of origin, %</td>
<td></td>
</tr>
<tr>
<td>▪ GCB</td>
<td>52</td>
</tr>
<tr>
<td>▪ Non-GCB</td>
<td>42</td>
</tr>
</tbody>
</table>

*CMYC/BCL2, n = 4; CMYC/BCL6, n = 3; CMYC/BCL2/BCL6, n = 8.

### Baseline Characteristics, %

<table>
<thead>
<tr>
<th>Baseline Characteristics, %</th>
<th>Pts (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. prior lines</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>19</td>
</tr>
<tr>
<td>Response to last tx</td>
<td></td>
</tr>
<tr>
<td>▪ Refractory</td>
<td>52</td>
</tr>
<tr>
<td>▪ Relapsed</td>
<td>48</td>
</tr>
<tr>
<td>Prior autoHSCT</td>
<td>47</td>
</tr>
</tbody>
</table>
## CD19 CAR in Adult Lymphoma (tisagen)

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Best ORR (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>54</td>
</tr>
<tr>
<td>▪ CR</td>
<td>40</td>
</tr>
<tr>
<td>▪ PR</td>
<td>14</td>
</tr>
</tbody>
</table>

Median follow up 19 mo (ASH 2018)
CD19 CAR in Adult Lymphoma (tisagen)

64% relapse free at 12 months and 18 months

No relapses beyond 11 months

## Probability of Relapse Free (%)

<table>
<thead>
<tr>
<th>Mos From Onset of Response</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts at Risk, n</td>
<td>43</td>
<td>36</td>
<td>25</td>
<td>18</td>
<td>16</td>
<td>13</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Median DoR: NR

Duration of Response
JCAR017 in R/R DLBCL

- JCAR017 (lisocabtagene maraleucel): CD19-directed CAR T-cells with 4-1BB/CD3ζ signaling domain
- Formulated at a defined 1:1 composition of CD4+ and CD8+ CAR T-cells
- Phase I TRANSCEND NHL 001
## TRANSCEND NHL 001 Exploratory Analysis: Response (EHA 2018)

<table>
<thead>
<tr>
<th>Response, %</th>
<th>FULL All Dose Levels</th>
<th>CORE (DLBCL)</th>
<th>DL1S (at 6 mo)</th>
<th>DL2S (at 6 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHA 2018 Update</td>
<td>n = 88</td>
<td>n = 65</td>
<td>n = 20</td>
<td>n = 14</td>
</tr>
<tr>
<td>▪ ORR</td>
<td>74</td>
<td>80</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>▪ CR</td>
<td>52</td>
<td>55</td>
<td>30</td>
<td>50</td>
</tr>
</tbody>
</table>
CAR T Cell Therapy: Toxicity

No significant infusion reactions

Tumor Lysis Syndrome - rare

Cytokine Release Syndrome (CRS)
  – Common; requires careful monitoring and management

Neurologic Side Effects
  – Changes in mental status, confusion, delirium, mutism. Cerebral edema rare

Cytopenias
  – Generally from chemotherapy regimen. Reversible but frequently prolonged

HLH/MAS – uncommon

Prolonged hypogammaglobulinemia due to B-cell aplasia
Typical Onset and Resolution of CRS and Neurologic Events

May occur within hours but generally appears within days (day 1-14)

Coincides with maximal T-cell expansion

Median time to CRS onset:
- Tisagen – 3 days
- Axi-cel – 2 days
Cytokine Release Syndrome (CRS)

CRS is a condition resulting from the release of cytokines from activated CAR T cells, as well as bystander immune cells. Most patients who respond to CAR T therapy develop CRS.

Blocking IL-6 with a monoclonal antibody (tocilizumab) is effective therapy. Steroids are used for severe CRS.

Patients treated inpatient or requested to be close to the hospital and carry a CAR-T wallet card.

REMS program requires treatment sites to have 2 doses of tocilizumab available on site for each CAR T patient.
Signs and Symptoms of CRS

Diagnosis based on clinical symptoms

- Rash
- Fatigue
- Tachycardia
- Nausea, vomiting, diarrhea
- Myalgia, arthralgia
- Rigors
- High fever
- Abnormal kidney, liver function, coagulopathy
- Hypotension, Shock
- Hypoxia, respiratory failure
- Hemophagocytosis

CRS
Cytokine elevation after CAR-T infusion

Elevation of cytokines and markers of inflammation during CRS in adults with lymphoma

- **Proliferative**
  - IL-15
  - IL-2

- **Inflammatory**
  - IL-6
  - CRP
  - SAA
  - IL-5
  - Ferritin
  - IL-1Ra
  - IL-2Rα

- **Immune-modulating**
  - GM-CSF
  - IFN-γ
  - IL-10

- **Chemokine**
  - IL-8
  - IP-10
  - MCP-1

- **Effector**
  - Granzyme B

*Analytes shown were elevated in ≥50% of patients with ≥2-fold induction above baseline out of a panel of 44 measured*
CRS – Typical Course

![Graph showing the typical course of CRS (Cytokine Release Syndrome) after CAR-T cell infusion. The graph plots various parameters including temperature, heart rate, systolic blood pressure, oxygen saturation, and CRP (C-Reactive Protein) over time. The x-axis represents time from CAR-T cell infusion in days (0 to 9), and the y-axis represents temperature in degrees Celsius. The graph highlights the peak temperature and other parameters changes over the course of CRS.]
CRS Management

Grade 1 CRS
Fever, constitutional symptoms

Grade 2 CRS
Hypotension: responds to fluids or 1 low-dose pressor
Hypoxia: responds to <40% O₂
Organ toxicity: grade 2

Grade 3 CRS
Hypotension: requires multiple or high-dose pressors
Hypoxia: requires ≥40% O₂
Organ toxicity: grade 3 or grade 4 transaminitis

Grade 4 CRS
Mechanical ventilation
Organ toxicity: grade 4 (excluding transaminitis)

Vigilant supportive care
- Antipyretics, analgesics, adequate hydration, blood pressure support
- Broad-spectrum antibiotics

Extensive comorbidities or older age?

NO
Vigilant supportive care

YES

Tocilizumab – primary CRS reversal agent
Refractory CRS – siltuximab, corticosteroids, infliximab, etanercept, anakinra
Response to Tocilizumab

Time Since Infusion, d
Time of Day

Tocilizumab, d+10
CAR-T Neurotoxicity

• Neurotox resembles a toxic/metabolic encephalopathy

• Symptoms include diminished attention, headache, anxiety, aphasia, dysphasia, difficulty in performing complex tasks (handwriting), memory loss, confusion, altered ms

• On ZUMA-1, neurologic toxicities occurred in 87% of patients, including Grade 3 or higher neurologic toxicities in 31% of patients

• 98% of all neurotox occurred within the first 8 weeks following infusion

• The median time to onset was 4 days (range, 1-43 days)

• The median duration was 17 days

• Prolonged encephalopathy lasting up to 173 days was observed

• Serious events including cerebral edema and seizures have occurred
CAR-T Neurotoxicity

Day 0: Baseline

CARTOX-10 Neurological Assessment

- Orientation:
  - To current year: 1
  - To current month: 1
  - To current city: 1
  - To current hospital: 1
  - To current President of the U.S.: 1

- Identification:
  - Correctly identifies three objects; for example ‘point to clock, pen, button’: 1
  - Correctly identifies first object: 1
  - Correctly identifies second object: 1
  - Correctly identifies third object: 1

Day +2: 6/27/18

Writing Section

- My favorite color is green

Counting

- Correctly counts backwards from 100 in tens: 1

Date: 6/27/18 Total = 10 / 10
CAR-T Neurotoxicity
Neurotoxicity Management

• Reassurance
• Close monitoring
• Rule out other causes of neurologic symptoms
• Steroids for grade 2 or higher
• Nonsedating, antiseizure medicines (eg, levetiracetam for Grade 2 or higher)
• Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly
• Patients should not drive for 8 weeks
## Toxicity– Are the products different??

<table>
<thead>
<tr>
<th>CAR-T product</th>
<th>KTE-C19 (Kite)</th>
<th>CTL019 (Novartis)</th>
<th>JCAR017 (Juno)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD28, bulk T</td>
<td>4-1BB, bulk T</td>
<td>4-1BB, CD4/CD8 subsets</td>
</tr>
<tr>
<td>Study populations</td>
<td>DLBCL, TFL, PMBCL (N=101)</td>
<td>DLBCL (N=99)</td>
<td>DLBCL, tFL, FL3B (N=102)</td>
</tr>
</tbody>
</table>

### Any CRS
- 93%
- 58%
- 37%

### ≥ Grade 3 CRS
- Comparisons across trials

### Any NT
- 64%
- 21%
- 23%

### ≥ Grade 3 NT
- Different grading schemas
- Different toxicity management algorithms
- Learning curve from trial to trial

### Grade 5 AEs
- 3 Total
- None (1 death from NT on earlier Ph2)

### Tocilizumab
- 43%
- 15%
- 17%

### Steroids
- 27%
- 11%
- 21%

---

Columbia University Medical Center

NewYork-Presbyterian
The University Hospital of Columbia and Cornell
What should the referring physician know?

**Prolonged cytopenias**

17-27% of patients will still have grade 3-4 cytopenias 3 months after CAR-T infusion.

Transfusions and growth factor support are allowed and recommended.
What should the referring physician know?

Hypogammaglobulinemia

CD19-targeting CAR-T cells destroy healthy B cells in addition to cancer cells.

Monitoring of IgG levels and IVIG repletions are recommended until full recovery.

Most patients will recover B cells and antibody production over time.
CAR-T cells Real World Experience

- N=295 (17 centers). Commercial axi-cel (non-clinical trial patients)
- Median time from leukopheresis to LD chemo – 21.5 days
- Manufacturing failure 2%
- 55% received bridging chemotherapy
- Median age 60 (range 21-83)
- 19% ECOG performance status > 1
CAR-T cells Real World Experience

43% of patients would not have met eligibility for ZUMA-1.

<table>
<thead>
<tr>
<th>Criteria Excluded from ZUMA-1</th>
<th>N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt; 75</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Active DVT/PE</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Prior CD19 or CAR T cell therapy</td>
<td>24 (8)</td>
</tr>
<tr>
<td>GFR &lt; 60</td>
<td>22 (8)</td>
</tr>
<tr>
<td>History of CNS lymphoma</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Symptomatic pleural effusion</td>
<td>11 (4)</td>
</tr>
<tr>
<td>LVEF &lt; 50%</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Prior allogeneic SCT</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>
### CAR-T cells Real World Experience - Safety

<table>
<thead>
<tr>
<th></th>
<th>SOC Axi-cel N = 274 (mITT)</th>
<th>ZUMA-1(^1) N = 108</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades of CRS*, N (%)</td>
<td>240 (92%)</td>
<td>100 (93%)</td>
</tr>
<tr>
<td>Grade ≥ 3 CRS, N (%)</td>
<td>18 (7%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Median time to onset of CRS</td>
<td>3 days</td>
<td>2 days</td>
</tr>
<tr>
<td>All Grades of NT**, N (%)</td>
<td>181 (69%)</td>
<td>70 (65%)</td>
</tr>
<tr>
<td>Grade ≥ 3 NT, N (%)</td>
<td>85 (33%)</td>
<td>33 (31%)</td>
</tr>
<tr>
<td>Median time to onset of NT</td>
<td>6 days</td>
<td>5 days</td>
</tr>
</tbody>
</table>

Treatment-related deaths – 2 (<1%)
# CAR-T cells Real World Experience - Efficacy

<table>
<thead>
<tr>
<th></th>
<th>SOC Axi-cel Evaluable</th>
<th>SOC Axi-Cel</th>
<th>ZUMA-1&lt;sup&gt;1&lt;/sup&gt; N=108</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow up, months</strong></td>
<td></td>
<td>3.9</td>
<td>15.4</td>
</tr>
<tr>
<td><strong>Day 30 ORR, N (%)</strong></td>
<td>238</td>
<td>191 (80)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Day 30 CR, N (%)</strong></td>
<td></td>
<td>113 (47)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Best ORR at Day 90, N (%)</strong></td>
<td>248&lt;sup&gt;a&lt;/sup&gt;</td>
<td>201 (81)</td>
<td>89 (82)</td>
</tr>
<tr>
<td><strong>Best CR at Day 90, N (%)</strong></td>
<td></td>
<td>142 (57)</td>
<td>63 (58)</td>
</tr>
</tbody>
</table>

<sup>a</sup> N=176
CD19 CAR T Cells – Unprecedented Efficacy in Pediatric Leukemia

CR Rate 81%
All CRs are MRD-negative

Maude et al. NEJM 2018
Aggressive Lymphoma - Who is eligible?

Diagnosis:
- Diffuse Large B-cell Lymphoma
- Transformed Follicular Lymphoma
- High Grade B-cell Lymphoma (e.g., Double-hit, Triple-hit)
- Primary Mediastinal B-cell Lymphoma

Prior therapy: Failed at least 2 lines of standard therapies, either including stem-cell transplant or not.

Active CNS disease excluded.

No strict age or organ function criteria. Patients treated up to age 83 in published data.

Discuss individual patients with contact at a certified treatment center.
Pediatric ALL - Who is eligible?

Diagnosis:

B-cell Acute Lymphoblastic Lymphoma

Prior therapy: Failed at least 2 lines of standard therapies, either including stem-cell transplant or not.

FDA Approval granted up to age 25.

Adult ALL treated on clinical trials.

Discuss individual patients with contact at a certified treatment center.
Evolution of CAR-T in Clinical Trials

Evolution of CAR-T in Clinical Trials

Future Developments: Clinical Trials

Total = 469 trials
What’s next on the horizon?

CAR-T targeting B-cell Maturation Antigen (BCMA) in Myeloma

BCMA is uniformly expressed on plasma cells in most multiple myeloma patients.

Ongoing trials with BCMA-targeting CAR-T cells show high response rates and complete remissions in heavily-pretreated patients.

bb2121 data
Median age 65 (range 44 – 75)
median 8 prior lines of therapy
ASCO 2018
# Modifications of CAR-T Cells

<table>
<thead>
<tr>
<th>Variable</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR design</td>
<td>Use of single-chain variable fragment (scFv); source of scFV monoclonal antibody moiety; murine vs. human</td>
</tr>
<tr>
<td></td>
<td>Use of “stalk” segment to extend scFV from cell surface (Ig Fc region, CD8)</td>
</tr>
<tr>
<td></td>
<td>Trans-membrane domain (CD4, CD8, other)</td>
</tr>
<tr>
<td></td>
<td>Costimulatory domains: CD28, 41BB, ICOS, OX40</td>
</tr>
<tr>
<td>CAR target</td>
<td>Lineage-specific antigen, tumor-associated antigen, neovasculature antigen</td>
</tr>
<tr>
<td>Transgenes co-expressed with CAR</td>
<td>None, cytokine, cytokine receptor, chemokine receptor</td>
</tr>
<tr>
<td>Cell target</td>
<td>PBMCs, CD8-enriched, 1:1 ratio, Treg-depleted, memory subpopulations, viral-specific</td>
</tr>
<tr>
<td>T cell growth conditions</td>
<td>Anti-CD3 + IL-2, anti-CD3 + anti-CD28, IL-7, IL-15</td>
</tr>
<tr>
<td>Gene transfer</td>
<td>Viral transduction (γ-retrovirus, lentivirus), non-viral gene transfer (electrotransfer of DNA, mRNA), transposon/transposase DNA plasmids</td>
</tr>
<tr>
<td>Conditioning chemotherapy</td>
<td>None, lymphodepletion, Dose escalation.</td>
</tr>
<tr>
<td>Post-cell boost</td>
<td>None, IL-2, dendritic cells</td>
</tr>
</tbody>
</table>
CAR-T Cell Therapy – Summary

• CAR T cells induce higher rates of durable complete remissions and prolonged survival compared to historical treatments.
• Side effects can be serious but highly manageable with vigilant monitoring and supportive care.
• CAR-T therapy is an option for patients with B-cell ALL or aggressive B-cell NHL who failed 2 lines of therapy.
• Ongoing clinical trials will determine the benefit of using CAR-T cells in earlier lines, in other blood cancers and in solid tumors.
Thank you!

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