FLASCO Fall 2023 Session
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Saturday October 21, 2023

CAR T Innovations
Practice Changing Updates
Cytotoxic T Cells

Diagram showing the interaction between an antigen-presenting cell and a T cell, highlighting the T-cell receptor, major histocompatibility complex, B7-1, CD28, and co-stimulatory signal.
The Chimera (Greek mythology) – a fire-breathing hybrid creature merged from a lion, a goat, and a snake.

The CAR T-Cell is the merged form of cytotoxic T cell and antibodies.
# Pivotal Anti-CD19 CAR T-cell Trials

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1(^{[1,2]})</th>
<th>JULIET(^{[3]})</th>
<th>TRANSCEND NHL 001(^{[4]})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAR T-cell agent</strong></td>
<td>Axicabtagene ciloleucel</td>
<td>Tisagenlecleucel</td>
<td>Lisocabtagene maraleucel</td>
</tr>
<tr>
<td><strong>Study phase</strong></td>
<td>II</td>
<td>II</td>
<td>I/II</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>DLBCL NOS, TFL, PMBCL</td>
<td>DLBCL NOS, TFL</td>
<td>DLBCL, Transformed iNHL, PMB CL</td>
</tr>
<tr>
<td><strong>Patients apheresed/ treated, n</strong></td>
<td>111/101</td>
<td>165/111</td>
<td>344/269*</td>
</tr>
<tr>
<td><strong>Bridging therapy</strong></td>
<td>None allowed</td>
<td>92%</td>
<td>59%</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>82%</td>
<td>52%</td>
<td>73%</td>
</tr>
<tr>
<td><strong>CR, %</strong></td>
<td>54%</td>
<td>40%</td>
<td>53%</td>
</tr>
</tbody>
</table>

*256 included in the efficacy-evaluable set.
Timeline of CAR T Therapy FDA Approvals

2017
- Tisagenlecleucel 08/2017

2018
- Axicabtagene ciloleucel 10/2017
- Tisagenlecleucel 05/2018

2020
- Lisocabtagene maraleucel 02/2021

2021
- Brexucabtagene autoleucel 07/2020
- Axicabtagene ciloleucel 03/2021
- Idecabtagene vicleucel 03/2021

2022
- Ciltacabtagene autoleucel 02/2022

Barriers to CAR T

Patients

- Access issues for at-risk patients
- Reimbursement

Screening per eligibility criteria of CAR-T therapy

- Restriction of CAR-T therapy to specialized medical centers

Apheresis

- Limited resources for manufacturing
- Limited production slots in manufacturing centers and subsequent CAR-T availability in clinic
- Ven-to-vein time resulting in the need for bridging therapy

Manufacturing of autologous CAR-T from patients’ cells

CAR-T therapy administration

- Requirement that patients remain within specified radius of CAR-T treatment center
- Lost wages for caregivers owing to time commitments required for patient monitoring

Postinfusion assessments and safety monitoring

DOI: 10.1200/OP.22.00315 JCO Oncology Practice 18, no. 12 (December 01, 2022) 800-807.
CAR T Challenges

- Manufacturing time, costs, and complex logistics
- Patient/disease factors:
  - T cell fitness and persistence
  - Tumor immune escape (CD19 antigen loss)
- Toxicity and safety
The CAR T-Cell Process

Cancer.gov
In the JULIET, TRASCEND-NHL-001, and ZUMA-1 trials, 31%, 15%, and 9% of patients, respectively, had leukapheresis but did not receive CAR-T therapy.

“Financial toxicity” – cost can go upwards of $500k per dose

Manufacturing failures

Solutions: Reduced manufacturing times and cost, off the shelf CAR T or NK cells, decentralized manufacturing
“Off the shelf” Engineered Cellular Products: Allogeneic Therapies

Advantages
- “Off-the-shelf”, readily available
- More cost-effective
- Scale to larger numbers
- Expand access to therapy (ie, leukopenic patients)
- Healthy donor cells = more T cell fitness

Disadvantages
- Risk of graft vs host disease (GvHD)
- Host allorejection
- Limited data available
Allogeneic CAR T Cells: Current Trials of Interest

- Phase 1 ALPHA/ALPHA 2 for ALLO-501 and ALLO-501A
- An off-the-shelf, anti-CD19 allogeneic CAR T cell product.
  - ALLO-501 is similar to ALLO-501A except for the inclusion of a rituximab off switch.
- Manageable safety profile, tolerability with no DLTs and preliminary efficacy in CAR T naïve pts.
ALPHA/ALPHA 2 Phase I Updates

- Update on 12 of 33 CAR T naïve pts with r/r LBCL received a 3 day Flu/Cy lymphodepletion + 90 mg of Allo-647 + single dose of ALLO-501 or ALLO-501A

<table>
<thead>
<tr>
<th>Baseline Characteristics for Patients Treated With Selected Phase 2 Regimen (N=12)</th>
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<tbody>
<tr>
<td>Age, median</td>
</tr>
<tr>
<td>Stage IV disease</td>
</tr>
<tr>
<td>ECOG PS of 1</td>
</tr>
<tr>
<td>Baseline LDH &gt; ULN</td>
</tr>
<tr>
<td>IPI score &gt;2</td>
</tr>
<tr>
<td>Germinal center subtype</td>
</tr>
<tr>
<td>Double or triple hit</td>
</tr>
<tr>
<td>Median # prior regimens</td>
</tr>
<tr>
<td>Prior transplant</td>
</tr>
<tr>
<td>Extramedal disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events of Interest</th>
<th>All r/r CAR T-naïve LBCL (N=33)</th>
<th>Patients Treated With Phase 2 Selected Regimen (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Gr n (%)</td>
<td>8 (24)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Gr23 n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>13 (39)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>GvHD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IRR</td>
<td>16 (49)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Infection</td>
<td>19 (58)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Prolonged Gr23 Cytopenia</td>
<td>-</td>
<td>4 (12)</td>
</tr>
</tbody>
</table>

CRS = cerebral edema syndrome; GvHD = graft-versus-host disease; ICANS = immune effector cell-associated neurotoxicity syndrome; IRR = infusion-related reactions; LDH = lactate dehydrogenase; IPI = international prognostic index. Locke, et al. Phase 1 Results with Anti-CD19 Allogeneic CAR T ALLO-501/501A in Relapsed/Refractory Large B-Cell Lymphoma (r/r LBCL). Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 2517-2517.
ALPHA/ALPHA 2 Phase I Updates

- Efficacy results (ASCO 2023: Locke, et al) of Phase 2 regimen:
  - ORR 67% (8/12), CR 58% (7/12)
  - All patients followed through month 6:
    - 5 patients sustained CR
    - 4 of 5 remain in CR at data cut off April 20, 2023
    - Median duration of response of 23.1 months, 3 remain in remission at 24+ months with the longest at 31+ months

- Phase 2 ALPHA2 trial enrolling
- ALPHA 3 ongoing to study ALLO-501/501A in earlier line DLBCL

Locke, et al. Phase 1 Results with Anti-CD19 Allogeneic CAR T ALLO-501/501A in Relapsed/Refractory Large B-Cell Lymphoma (r/r LBCL). *Journal of Clinical Oncology* 41, no. 16_suppl (June 01, 2023) 2517-2517.
Rapid CAR T manufacturing

- YTB323 - A novel autologous CD19-directed CAR T-cell therapy expressing the same validated CAR as tisa-cel, manufactured using a next generation platform (“T-Charge”) in <2 days.
- Pre-clinical data in mice showed enhanced expansion and antitumor activity at doses 25-fold lower than tisa-cel.
- Preliminary phase I data reported Sept 2023 (AACR): YTB323 showed promising overall safety.

Rapid CAR T manufacturing

YTB323 Safety & Efficacy

- **Phase I trial**
  - 20 pts with r/r DLBCL received YTB323 at DL1 (n=4) or DL2 (n=16)
    - Doses 10 to 50 times lower than the typical tisa-cel dose

- **Results:**
  - CRS: any grade, 35%; grade ≥ 3, 6%
  - Neurotoxicity: any grade 25%; grade ≥ 3, 6%
  - Low/comparable rates of infection and cytopenias
  - 2 deaths at DL1, 3 deaths at DL2 – none treatment related
  - ORR: 75% for DL1, 80% for DL2
  - At month 3, one (25%) patient at DL1 and 11 (73%) at DL2 achieved a complete response (CR).

CAR T Challenges

- Manufacturing time, costs, and complex logistics

- Patient/disease factors:
  - T cell fitness and persistence
  - Tumor immune escape (CD19 antigen loss)

- Toxicity and safety
Patient and Disease Factors

- Progression of disease
- Poor harvesting
- T-cell fitness
  - Quality of cells impacted from disease or prior therapies
- Antigen loss/escape
- Tumor microenvironment
T-Cell Fitness

- Impacted by age, chronic infection, disease burden, and prior treatments
- Lower proportion of naive memory T-cells in the CAR product have been associated with lack of durable response
- Approaches:
  - CAR T in earlier lines of therapy, early lymphopheresis
## CAR T-cells in 2\textsuperscript{nd} line r/r LBCL

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-7</th>
<th>TRANSFORM</th>
<th>BELINDA</th>
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</thead>
<tbody>
<tr>
<td><strong>Product</strong></td>
<td>Axi-cel</td>
<td>Liso-cel</td>
<td>Tisa-cel</td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>83 v 50</td>
<td>165</td>
<td>46 v 43</td>
</tr>
<tr>
<td><strong>CR (%)</strong></td>
<td>65 v 32</td>
<td>74 v 43</td>
<td>28 v 28</td>
</tr>
<tr>
<td><strong>mEFS (months)</strong></td>
<td>8.3 v 2.0</td>
<td>NR v 2.4</td>
<td>3.0 v 3.0</td>
</tr>
<tr>
<td><strong>EFS (%)</strong></td>
<td>24m: 41 v 16</td>
<td>18m est: 51 v 19</td>
<td>10m: 19 vs 20</td>
</tr>
<tr>
<td><strong>mPFS (months)</strong></td>
<td>14.7 v 3.7</td>
<td>NR v 6.2</td>
<td>NR</td>
</tr>
<tr>
<td><strong>mOS</strong></td>
<td>NR v 35.1</td>
<td>NR v 29.9</td>
<td>NR</td>
</tr>
</tbody>
</table>

Locke et al NEJM 2022; 386:641, Abramson et al Blood 2023; 141:1675, Bishop et al NEJM 2022; 386:637
Slide adapted from Caron Jacobson, MD ASCO 2023 presentation
ZUMA-7 Updates

- High-risk population of 352 pts randomized to treatment
  - 94% received axi-cel
  - 36% SOC (HDC + ASCT)
- OS benefit of 54.6% vs 46%
  - 57% in SOC arm still went on to receive 3L + CAR T

Taking it another step further…

- ALYCANTE – phase 2 trial looking at axi-cel in r/r DLBCL as 2\textsuperscript{nd} line in transplant- ineligible pts
  - 62 patients
  - CMR of 71% at 3 months
  - mPFS 11.8 months (median f/u 12 months)

- Results support axi-cel as 2\textsuperscript{nd} line in ASCT-ineligible pts with r/r DLBCL

Tumor Immune Escape

- 2/3 of pts relapse after CD19-directed CAR T cell therapy
  - Antigen loss is a common mechanism
  - Downregulation of CD19 receptor

- Proposed solutions
  - Single targeted CAR construct against other B-cell lymphoma antigens
  - Multi-targeted CARs
Multi-targeted CAR T-cell Approaches

Shah, N. et al. Front. Onc. 9:146, 2019
Bispecific CAR T Therapy

- DALY2-US Trial - Phase 2 randomized trial of bispecific ANTI-CD20/19 CAR T (Zamtocabtagene autoleucel)
  - 22 pts with r/r DLBCL after ≥2L, ineligible for HDC +ASCT
    - 28% previously treated with anti-CD19 or anti-CD79 agents
  - No bridging chemo allowed
  - Manufactured in 12 day process (vein-to-vein 14 days), infused fresh

- Results: 18 of 22 (82%) with response
  - 46% with CR, 36% with PR
  - Post-progression biopsy available in 5 pts – no isolated CD19 loss, 1 dual target loss

Tumor Microenvironment
Generations of CAR T Cells
Next Generation CAR T-cells

- 4th/next generation
  - Cytokine secreting CARs deposit interleukins into the target, in turn attracting an innate cell response and remodeling the TME
  - “Armored” CARs
    - via PD1 pathway in hematology: MC-19PD1 CAR-T in r/r B Cell Lymphoma (NCT03932955) - no results available
- Switchable CAR T-cells
- Universal CAR T-cells
CAR T Challenges

- Manufacturing time, costs, and complex logistics
- Patient/disease factors:
  - T cell fitness and persistence
  - Tumor immune escape (CD19 antigen loss)
- Toxicity and safety
CAR T-related toxicities

Bonifant et al. Molecular Therapy 2016;(3):16011
Cytokine Release Syndrome (CRS)

- Most common toxicity resulting from the release of cytokines from activated CAR T cells, as well as bystander immune cells.
- Usually within the first 7 days
- Hallmark = fever
- Key manifestations: fever, chills, hypotension, tachycardia, hypoxia

IEC-Associated Neurotoxicity syndrome (ICANS)

- Second most common toxicity
- Pathophysiology not well understood
- Can occur with or without CRS
- Common: confusion/delirium, aphasia, weakness, headaches, tremor, altered level of consciousness
- Rare: motor weakness, seizures, cerebral edema

Graded using ASTCT Consensus grading scale (Lee, et al 2018)
Toxicity Management

Cytokine Release Syndrome (CRS)
- Supportive care, rule out infection
- Tocilizumab (IL-6 receptor antagonist)
  - FDA approved
  - Effective, not directly cytotoxic
  - Most respond to 1 or 2 doses
- Steroids are used for severe CRS

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- Mainstay of treatment is corticosteroids at escalating doses
- Grade 3 ICANS remains high in real world experiences
- Need for more effective strategies
ICANS Pathophysiology

- Not well understood
- Optimal management of severe or refractory ICANS remains ill-defined
- Anti-cytokine therapy as therapeutic option
  - Tocilizumab has limited CNS penetration
    - Not effective for ICANS with potential negative influence
  - Alternative agents:
    - IL-1 (Anakinra), IL-6 (Siltuximab)
Recombinant IL-1 receptor antagonist competitively inhibits IL-1 receptor signaling and therefore blocks downstream production of inflammatory cytokines including IL-6.

Higher levels of IL-1a are seen in serum and CSF of severe ICANS

In murine models, anakinra effectively treated both CRS and ICANS
## Phase II Trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Disease</th>
<th>Anakinra indication</th>
<th>Dosing via SQ inj</th>
<th>n</th>
<th>Adjunctive therapies</th>
<th>Grading criteria</th>
<th>Rate of ICANS</th>
<th>Severe CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park, et al 2021</td>
<td>LBCL or MCL</td>
<td>Prophylaxis</td>
<td>100 mg q12h on Day 2 to Day 10+ or earlier if 2 fevers</td>
<td>n=31</td>
<td>yes</td>
<td>ASTCT</td>
<td>D30, 2/31 (6%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Frigault, et al 2021</td>
<td>r/r LBCL</td>
<td>Prophylaxis</td>
<td>200 mg 4 hours prior to infusion and qd x 7 days</td>
<td>n=6</td>
<td>--</td>
<td>Lee 2013</td>
<td>D28, 2/6 grade 3</td>
<td>0</td>
</tr>
</tbody>
</table>
Anakinra prophylaxis

- Phase 2 trial in r/r LBCL and MCL patients treated with commercial anti-CD19 directed CAR T
- Cohort 1: SubQ injection of anakinra from day 2 until at least day 10 post-CAR T-cell infusion
  - n=31, 74% received axi-cel, 13% received brexi-cel, 4% tisa-cel
  - ICANS, all grade = 19%
    - Severe (grade ≥ 3) ICANS = 9.7%. No grade 4 or 5.
  - CRS, all grade = 74% (19 pts)
    - Severe CRS = 6.4%
- ORR 77%, CR 65%

Park, et al. Nature Medicine 03 July 2023
Anakinra for refractory toxicities

- Retrospective review by Gazeau, et al (2023)
  - 43 pts - 37 with NHL, 5 with ALL, and 1 with MM
  - Commercial product (n=7) or investigational (n=6)
  - Grade 2 refractory CRS (n=3) or ICANS (n=40)
  - Two anakinra dosage groups were retrospectively defined as:
    - "high dose" (>200mg/day IV) and "low dose" (100-200mg/day SC or IV)
- Conclusions:
  - High-dose anakinra (up to 12 mg/kg/day) for refractory CRS or ICANS was safe.
  - Higher dose may be associated with faster CRS/ICANS resolution and was independently associated with lower TRM

- TRM at day 28 and day 60 was 7% and 23%, respectively
- Day 28 TRM was 47% in the low dose cohort (n=15) and 0% in the high dose cohort (n=23)
Take Home Points

- Novel manufacturing processes are being evaluated to decrease vein-to-vein time and increase CAR efficacy & persistence
- Favorable results showing benefit for use of CAR T as earlier therapy, especially in high risk patients
- CAR T-cell therapy viable option for ASCT-ineligible patients
- Anakinra for prophylaxis or refractory toxicity management without reducing treatment efficacy
What’s on the CAR T horizon?

- Allogeneic CARs – NK, iPSCs
- Earlier lines – Zuma-23: phase 3 axi-cel in 1st line
- Novel CAR T targets
- Dual binding CARs
- Universal CARs
- New CAR constructs for solid tumors
- On/Off Switches
Chimera vs CAR T-cell

Thank You!

Questions?