ADVANCES IN CAR T-CELL THERAPY

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DISCLOSURES
Advances in CAR T-cell Therapy

Iris Isufi, MD, has affiliations with Astra Zeneca, Celgene, Kite Pharmaceuticals and Novartis (Consultant).
Objectives

• Why CAR T-cell (chimeric antigen receptor T-cell) therapy shows promise for blood cancers
• Approved and emerging CAR T-cell therapies
• Side effects of CAR T-cell therapy: what to expect
• The future of CAR T-cell therapy for blood cancer patients

Multiple Mechanisms of Modulating Immune System to Treat Cancer

• Monoclonal antibodies or antibody drug conjugates
• Dual antigen re-targeting proteins
• Immune checkpoint antibodies
• Chimeric antigen receptor T cells

What is CAR T-cell therapy?

CAR T-cell therapy is a type of cancer therapy that uses a patient’s own modified white blood cells to kill cancer cells.

CAR T-Cells are at The Intersection of Three Innovative Technologies

**Cellular therapy**
Using the patient's own T-cells as therapy

**Gene therapy**
Insertion of genes into a patient's cells, thereby causing these cells to produce a new therapeutic protein (CAR)

**Immunotherapy**
Harnessing the patient's own immune system (T-cells) to treat his/her disease
Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy

The emergence of CAR-T therapy, like most scientific advances, reflects the incremental insights of hundreds of scientists over decades. Indeed, the story of CAR-T therapy says as much about the methodical nature of scientific progress as it does about the passions that sustain it.

Lisa Rosenbaum, M.D.

N Engl J Med 377;14 nejm.org October 5, 2017

From Manufacturing of CAR T-Cells to Infusion
Structure of T-Cell Receptors and CAR Modified T-cells


CAR T Cells Traffic to Tumor and Proliferate Extensively after Infusion

Ideal CAR Target

• Tumor specific antigen (Ag)
  • Required for tumor pathogenicity (ability to cause disease)
  • Critical for survival, such that loss of that Ag comes at really high cost for the cancer
• Highy expressed on all tumor cells (cancer stem cells?)
  • Cell surface molecule
• Absent from normal tissue (or where normal tissue is dispensable)
• Absent from T cells (to avoid self killing)

CD19 as a Target of B-Cell Malignancies

CD19 expression is generally restricted to B cells and B-cell precursors and, importantly, is expressed by most B-cell malignancies, and represents a rational target for therapy
Evolution in CAR Design

First-generation CAR
- mAB scFv
- TM domain
- Hinge
- CD3ζ or FCRγ
- One co-stimulatory domain (CD28, 4-1BB, OX-40)

Second-generation CAR
- TM domain
- Hinge
- CD3ζ or FCRγ
- Two co-stimulatory domains (CD28, 4-1BB, OX-40)

Third-generation CAR

Data source: CellTrials.org

Total Registered CAR-T Trials Worldwide

- Industry is Taking Over CAR T-Cell Development

Data source: CellTrials.org
### Selected Approved or Late-Stage CAR T Therapies

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Company</th>
<th>Indication</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisagenlecleucel (CTL-019)</td>
<td>Novartis</td>
<td>Childhood B-cell ALL (≤25)</td>
<td>CD19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult DLBCL, transformed FL (tFL)</td>
<td></td>
</tr>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>Gilead Sciences (Kite Pharma)</td>
<td>DLBCL, tFL and PMBCL</td>
<td>CD19</td>
</tr>
<tr>
<td>(KTE-C19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brexucabtagene autoleucel</td>
<td>Gilead Sciences (Kite Pharma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(KTE-X19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisocabtagene maraleucel</td>
<td>Celgene (Juno Therapeutics)</td>
<td>B-NHL</td>
<td>CD19</td>
</tr>
<tr>
<td>(JCAR 017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idecabtagene vicleucel</td>
<td>Bluebird bio/Celgene</td>
<td>Multiple myeloma</td>
<td>BCMA</td>
</tr>
<tr>
<td>(bb2121)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Phase III**

- Lisocabtagene maraleucel (JCAR 017)
- Idecabtagene vicleucel (bb2121)

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### CAR T- Cell Therapy in B-Cell Acute Lymphoblastic Leukemia (B-ALL)

[Image of CAR T-cell therapy]
Pediatric Relapsed/Refractory (R/R) B-ALL: ELIANA Study Design

- ELIANA (NCT02435849) is a phase 2, open-label, single-arm study in pediatric and young adult patients with r/r B-cell ALL\(^1\)\(^-\)\(^2\)

<table>
<thead>
<tr>
<th>Pretreatment phase</th>
<th>Pretreatment phase</th>
<th>Pretreatment phase</th>
<th>Pretreatment phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening phase</td>
<td>Screening phase</td>
<td>Screening phase</td>
<td>Screening phase</td>
</tr>
<tr>
<td>Apheresis and</td>
<td>Tisagenlecleucel</td>
<td>Enrollment</td>
<td>Tisagenlecleucel</td>
</tr>
<tr>
<td>cryopreservation</td>
<td>manufacturing</td>
<td>Tisagenlecleucel</td>
<td>manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>infusion</td>
<td>infusion</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

*To be completed 2 to 14 days prior to Tisagenlecleucel infusion.


ELIANA Study in B-ALL

- Single arm, open-label, multi-center, global phase 2 study
  - 107 pts screened, 88 enrolled, 68 treated
- Dose of Tisagenlecleucel: 2-5 x 10^6 CAR-T cells/kg
  - Conditioning chemo: Flu 30 mg/m2 x 4 days + Cy 500 mg/m2 x 2 days
- Response rates: Complete Remission/Complete Remission with incomplete hematologic recovery **CR/CRi: 81%** (CR 60% + CRi 21%)
- **Tisagenlecleucel approved for treatment of patients up to age 25 with B-ALL that is refractory or in 2\(^{nd}\) or later relapse**

ELIANA: Patient Demographics and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (N = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>11 (3-23)</td>
</tr>
<tr>
<td>Prior stem cell transplant, n (%)</td>
<td>46 (61)</td>
</tr>
<tr>
<td>Previous line of therapies, median (range), n</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>Disease status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Chemo-refractory or relapsed</td>
<td>69 (92)</td>
</tr>
<tr>
<td>Morphologic blast count in bone marrow, median (range), %</td>
<td>74 (5-99)</td>
</tr>
</tbody>
</table>

Duration of Remission: ELIANA

Relapse-Free Survival

6-month RFS\(^a\)
75% (95% CI, 57-87)
9- and 12- month RFS\(^a\)
64% (95% CI, 42-87)

Patients (N = 52)  Number of events (n = 11) Median follow-up, 4.8 mo
Median DOR, not reached
**Overall Survival: ELIANA**

![Graph showing overall survival](image)

- 6-month OS: 89% (95% CI, 77-94)
- 9- and 12-month OS: 79% (95% CI, 63-89)

**Patients (N = 68)**

**Number of events (n = 11)**

**Median follow-up, 6.2 mo**

**Median OS, 16.6 mo**

*Bueschner J, *EHA* 2017, Abstract S476*

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**ELIANA: Overall safety of Tisagenlecleucel**

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Time (N = 75)</th>
<th>≤8 Wk after Infusion (N = 75)</th>
<th>&gt;8 Wk to 1 Yr after Infusion (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event of any grade</td>
<td>75 (100)</td>
<td>74 (99)</td>
<td>65 (93)</td>
</tr>
<tr>
<td>Suspected to be related to tisagenlecleucel</td>
<td>71 (95)</td>
<td>69 (92)</td>
<td>30 (43)</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
<td>66 (88)</td>
<td>62 (83)</td>
<td>31 (44)</td>
</tr>
<tr>
<td>Suspected to be related to tisagenlecleucel</td>
<td>55 (73)</td>
<td>52 (69)</td>
<td>12 (17)</td>
</tr>
</tbody>
</table>

Outcomes with CART19 Therapy in Children and Adults with Relapsed/Refractory B-ALL

<table>
<thead>
<tr>
<th>Reference</th>
<th>CAR</th>
<th>Population</th>
<th>Response</th>
</tr>
</thead>
</table>
| Maude et al. NEJM 2018     | PENN 4-1BB| ALL (peds/adults) N=71      | CR: 81%  
6mo EFS & OS: 73% & 90%  
12mo EFS & OS: 59% & 76%  
n11% proceeded to alloHSCT after CAR T cells |
| Park J et al. ASCO 2017, Abstract 7008 | MSKCC CD28 | ALL (adults) N=53              | CR: 84.6%  
MRD-CR rate: 66.6%  
39% proceeded to alloHSCT after CAR T cells. |
| Turtle et al. JCI 2016     | Seattle 4-1BB Defined CD4/CD8 composition | ALL (adults) N=30      | CR: 93%  
MRD-CR rate: 86%  
1 pt proceeded to alloHSCT after CAR T cells |
| Lee et al. Lancet 2015     | NCI CD28  | ALL (peds/adults) N=21       | CR: 67% |

CAR-T 19 Associated Toxicities

Professional illustration by Patrick Lane, ScYEEnce Studios
CAR-T 19 Associated Toxicities

- Cytokine Release syndrome (CRS)
  - Fevers, flu-like syndrome, low blood pressure, difficulty breathing

- Neurologic changes (NT, CRES, ICANS)
  - Headaches, tremors, mental status changes, difficulty speaking, rarely seizures (normal MRI)

- Organ toxicity (liver, kidneys)

- Off tumor/On target: B cell aplasia
  - Prolonged; Cases requiring IVIG repletion

- Toxicities are usually manageable and reversible

Mechanism of Cytokine Release Syndrome (CRS)

Neurologic Toxicity with CAR T-Cells

- Symptoms and signs: headaches, tremors, somnolence, speech difficulty, confusion, paralysis of limbs, rarely seizures, etc.
  - 1\textsuperscript{st} phase (Days 0-5) – symptoms may appear with other CRS symptoms
  - 2\textsuperscript{nd} phase (After day 5) – starts after CRS symptoms have subsided
- Neurotoxicity typically lasts 2-4 days but may vary in duration from few hours to few weeks. \textit{It is generally reversible.}
  - Corticosteroids treatment of choice in managing neurotoxicity.
  - Seizure prophylaxis is recommended with levetiracetam (750 mg oral/IV q 12 hrs) from day 0 to day 30.
Mechanism of Neurotoxicity

- Pathophysiology remains unclear:
  - Diffusion of cytokines into central nervous system
  - Trafficking of T cells into central nervous system
- CSF is usually positive for CAR T cells
- MRI of brain is usually negative
  - Reversible white matter changes and cerebral edema have been rarely observed
- EEG is either non-focal with generalized slowing or might show non-convulsive seizure pattern


Tools for Grading Neurotoxicity

<table>
<thead>
<tr>
<th>Encephalopathy Assessment Tools for Grading of ICANS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTOX-10</td>
</tr>
<tr>
<td>Orientation: orientation to year, month, city, hospital, president/prime minister of country of residence:</td>
</tr>
<tr>
<td>5 points</td>
</tr>
<tr>
<td>Naming: ability to name 3 objects (eg, point to clock, pen,</td>
</tr>
<tr>
<td>button): 3 points</td>
</tr>
<tr>
<td>Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point</td>
</tr>
<tr>
<td>Attention: ability to count backwards from 100 by 10: 1 point</td>
</tr>
</tbody>
</table>

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.

Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

B-Cell Aplasia Following CAR-T

- All patients with a response to treatment had B-cell aplasia.
- The median time to B-cell recovery was not reached.
- The probability of maintenance of B-cell aplasia at 6 months after infusion was 83% (95% CI, 69 to 91).

CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- Diffuse Large B-Cell Lymphoma (DLBCL)
- Mantle Cell Lymphoma (MCL)
- Follicular Lymphoma
- Marginal Zone Lymphoma

Relative Incidence of the Most Prevalent NHL Subtypes in the United States

T-cell lymphomas constitute < 15% of all NHL cases.
Treatment of Aggressive DLBCL

1. First Line: Chemotherapy (R-CHOP or R-EPOCH) + Anti-CD20 monoclonal antibody (Rituximab)

2. Common 2nd line regimens if disease comes back: R-ICE, R-DHAP, R-GemOx*

   *These regimens may induce remission but response is generally short-lived due to lymphoma stem cells that are resistant to “standard doses” of chemotherapy

3. Autologous stem cell transplant (ASCT)

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Autologous Stem Cell Transplant (ASCT)

- If a patient’s lymphoma goes into remission with 2nd line treatment, ASCT is used to maintain the remission.
- During 2nd line treatment, a patient’s healthy blood-producing cells are obtained and frozen.
- After completing 2nd line chemotherapy, patient receives a “high dose chemotherapy” regimen, followed by infusion of their own healthy blood-producing cells.
  - This helps prevent toxicity of the “high dose chemotherapy.”
Autologous Stem Cell Transplant

• Must be in remission
• Stem cells derived from patient
• High dose chemotherapy
• Stem cell infusion
• Bone marrow recovers in 1.5-3 weeks
• Adverse effects in ~ 3-7%

Treatment Challenges

• What if lymphoma comes back after an autologous stem cell transplant?
• What if lymphoma will not go into remission in order to proceed to an autologous stem cell transplant?
Three Large Multicenter CAR T Studies for DLBCL

- **Zuma-1 (Kite/Gilead) Axicabtagene Ciloleucel** -> First FDA approval October 2017
  - Treatment of adult patients with [*relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy*, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBC), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (transformed follicular lymphoma, or tFL)].

- **Juliet (Novartis) Tisagenlecleucel** -> FDA approval May 2018
  - Treatment of adult patients with [*relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy* including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.]

- **Transcend NHL 001 (Juno/Celgene) Lisocabtagene maraleucel**

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Three Major Anti-CD19 CAR T-cell Products for Lymphoid Malignancies

<table>
<thead>
<tr>
<th>Construct</th>
<th>Axicabtagene Ciloleucel ZUMA-1</th>
<th>Tisagenlecleucel JULIET</th>
<th>Lisocabtagene Maraleucel TRANSCEND NHL-001</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell Manufacturing</td>
<td>Retroviral vector Bulk T-cells</td>
<td>Lentiviral Vector Bulk T-cells</td>
<td>Lentiviral Vector CD4/CD8 1:1 ratio</td>
</tr>
<tr>
<td>Dose</td>
<td>$2 \times 10^9$/kg (max $2 \times 10^9$)</td>
<td>$0.6 \text{ to } 6.0 \times 10^9$</td>
<td>DL1: $0.5 \times 10^9$, DL2: $1.0 \times 10^9$</td>
</tr>
<tr>
<td>Bridging Therapy</td>
<td>None allowed in pivotal trial but often used in standard practice</td>
<td>93%</td>
<td>72%</td>
</tr>
<tr>
<td>Lymphodepletion</td>
<td>Flu/Cy 500/30 x 3d</td>
<td>Flu/Cy 250/25 x 3d, or BR</td>
<td>Flu/Cy 300/30 x 3d</td>
</tr>
<tr>
<td>Treatment Locale</td>
<td>Inpatient Only</td>
<td>Inpatient and Outpatient*</td>
<td>Inpatient and Outpatient*</td>
</tr>
<tr>
<td>Approval Status</td>
<td>FDA approved for DLBCL, high-grade B-cell lymphoma, transformed FL, primary mediastinal B-cell lymphoma</td>
<td>FDA approved for pediatric ALL, DLBCL, high-grade B-cell lymphoma, transformed FL</td>
<td>Not yet FDA approved</td>
</tr>
</tbody>
</table>

* Outpatient therapy requires careful patient selection and is center dependent based on outpatient resources

# CART 19 Therapy Outcomes in R/R LBCL

<table>
<thead>
<tr>
<th></th>
<th>Zuma-1 (Axicabtagene Ciloleucel)</th>
<th>Juliet (Tisagenlecleucel)</th>
<th>Transcend NHL 001 (Lisocabtagene Maraleucel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts leukapheresed, n</td>
<td>111, 108 infused</td>
<td>141, 111 infused</td>
<td>102, 70 infused</td>
</tr>
<tr>
<td>Histologies</td>
<td>Cohort 1: DLBCL</td>
<td>DLBCL/tFL</td>
<td>DLBCL, PMBCL, tFL, FL3b (CORE)</td>
</tr>
<tr>
<td></td>
<td>Cohort 2: PMBCL, tFL</td>
<td></td>
<td>TMZL, MCL, Richter’s</td>
</tr>
<tr>
<td>Efficacy in R/R DLBCL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best OOR</td>
<td>42%</td>
<td>52%</td>
<td>73%</td>
</tr>
<tr>
<td>Best CRR</td>
<td>40%</td>
<td>40%</td>
<td>53%</td>
</tr>
<tr>
<td>6 month CRR</td>
<td>40%</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>12-mo PFS</td>
<td></td>
<td>83% in CR/PR pts at 3mo</td>
<td></td>
</tr>
</tbody>
</table>


## Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory LBCL

Kaplan–Meier Estimates of the Duration of Response, Progression-free Survival, and Overall Survival.

Tisagenlecleucel in Adult Relapsed or Refractory DLBCL

A Overview of Response

- Duration of Response, Progression-free Survival, and Overall Survival


B Progression-free Survival

- Median Follow-up: 12.0 mos (95% CI: 11.2-16.7)

- Probability of Continued Response (%)
  - Median: NR (95% CI: NR-NR)
  - Median: NR (95% CI: 8.6 mos -NR)
  - Median: 1.9 mos (95% CI: 1.1-2.1)

C Progression-free Survival among Patients with a Response

- CR
- PR
- Total

D Overall Survival

Lisocabtagene Maraleucel in Adult R/R LBCL

Efficacy-Evaluable Patients (N = 256)

- ORR (95% CI): 73 (67-78)
- CR rate (95% CI): 53 (47-59)
- Time to first CR or PR, median mos (range): 1.0 (0.7-8.9)
- DoR at 6 mos, % (95% CI): 60.4 (52.6-67.3)
- DoR at 12 mos, % (95% CI): 54.7 (46.7-62.0)

Median Follow-up: 12.0 mos (95% CI: 11.2-16.7)

Medians:
- NR (95% CI: NR-NR)
- NR (95% CI: 8.6 mos -NR)
- 1.9 mos (95% CI: 1.1-2.1)

Why Doesn’t CAR T-Cell Therapy Always Work?

- Leukemia relapse after CAR T-cells could be classified into 2 distinct types:
  - Loss of the CD19 target antigen on the surface of leukemia cells
  - Loss of CD19 CAR T-cells in blood (short persistence)


Strategies to Avoid Antigen-Loss Relapses

- **Single CART** — CAR T cells of same specificity (i.e. CD19)
- **Pooled CART** — 1:1 mixture of single–specificity CART: each cell remains able to recognize only one target (i.e. one with specificity for CD19, and one with specificity for CD22)
- **Dual (or bi-) CART** — every T cell bears 2 distinct CAR structures able to recognize 2 different targets (i.e. one for CD19 and one for CD22)
- **Tandem CART** — every T cell bears 1 CAR structure where 2 scFvs are built in series and are able to recognize 2 different targets

Evolution of CAR Design

- Programmable system: universal receptor expressed on T cells and a tumor-targeting scFv adaptor molecule
- Targets multiple tumor antigens using different zipFvs
- SUPRA CARs can be finely regulated via multiple mechanisms to limit overactivation
- Variables manipulated: (1) the affinity between leucine zipper pairs, (2) the affinity between tumor antigen and scFv, (3) the concentration of zipFv, and (4) the expression level of zipCAR
- Effect on IFN-γ production by primary CD4+ T cells expressing RR zipCAR

Why “humanize” CARs?

1. Immune rejection – loss of CAR cells (pedi- and adult B-ALL)
2. Superior efficacy? durability of response
3. Humanized CAR-T can rescue ~ 50% kids with B-ALL previously treated with murine CAR-T and relapsed (Shannon Maude, ASH 2017)

Number of trials utilizing humanized/fully human CAR constructs (binding domain/signaling domain. Data source: CellTrials.org)

Autologous CAR-T Cells vs Allogeneic CAR-T Cells

**Patient Derived Limitations**
- Cost
- Harvest and Manufacturing Failures
- Product Variability and Quality Control
- Disease Progression During Manufacture
- Contamination with Tumor cells
- Cancer Associated T-cell Dysfunction

**Donor derived**
- Previous HSCT donor
- Virus-specific CAR-T cells
- Gene-edited healthy donor CAR-T cells

**Donor Derived Advantages**
- Easier and cost-effective manufacturing
- Reduced time to CAR-T infusion
- Potential to treat all eligible patients on demand within days, no need for bridging
- Increase probability of healthy CAR-T cell generation
- Convenience of repeat dosing

**Donor Derived Barriers**
- Graft Versus Host Disease (gene editing techniques do not reach 100% knockout)
- Rejection of CAR-T Cells (less persistence)
- Off Target Cleavage with Gene Editing

### What’s Else is Exciting in LBCL CAR-T?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSFORM (NCT03575351)</td>
<td>III</td>
<td>Lisocabtagene maraleucel vs SoC</td>
<td>Transplant-eligible R/R aggressive B-cell NHL</td>
</tr>
<tr>
<td>BELINDA (NCT03568461)</td>
<td>III</td>
<td>Tisagenlecleucel vs SoC</td>
<td>R/R aggressive B-cell NHL</td>
</tr>
<tr>
<td>ZUMA-12 (NCT03761056)</td>
<td>II</td>
<td>Axicabtagene ciloleucel</td>
<td>High-risk large B-cell lymphoma; no prior treatment (1st line)</td>
</tr>
<tr>
<td>TRANSCEND-PILOT (NCT03483103)</td>
<td>II</td>
<td>Lisocabtagene maraleucel</td>
<td>R/R aggressive B-cell NHL after first-line immunochemotherapy, ineligible for ASCT</td>
</tr>
<tr>
<td>MB-CART2019.1 (NCT03870945)</td>
<td>I</td>
<td>Bispecific tandem CAR T construct against CD19 and CD20</td>
<td>R/R B-NHL without curative treatment option, or in 2nd line, non-transplant eligible DLBCL patients</td>
</tr>
<tr>
<td>ALEXANDER (NCT03287817)</td>
<td>I</td>
<td>AUTO3, the first CD19/22 dual targeting with pembrolizumab</td>
<td>R/R DLBCL</td>
</tr>
<tr>
<td>ALPHA (NCT03939026)</td>
<td></td>
<td>ALLO-501 and ALLO-647 anti CD19</td>
<td>R/R large B-cell or follicular lymphoma</td>
</tr>
</tbody>
</table>

### CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- **Diffuse Large B-Cell Lymphoma (DLBCL)**
- **Mantle Cell Lymphoma (MCL)**
- Follicular Lymphoma
- Marginal Zone Lymphoma

![Peripheral blood film in mantle cell lymphoma showing pleomorphic cells](image-url)
Phase II ZUMA-2 Trial of KTE-X19 CAR T-Cell Therapy in Relapsed/Refractory Mantle Cell Lymphoma (MCL)

- Mantle cell lymphoma is an uncommon, aggressive B-cell NHL subtype with hallmark chromosomal translocation t(11;14)(q13;q32)
- KTE-X19: autologous CD19-targeted CAR T-cell therapy comprising a CD3ζ T-cell activation domain and a costimulatory CD28 domain
- The phase II ZUMA-2 study sought to evaluate efficacy and safety of KTE-X19 in patients with relapsed/refractory MCL
- First CAR T-cell therapy, brexucabtagene autoleucel, FDA approved in 2020 for treatment of adults with R/R MCL


ZUMA-2: Study Design

- Multicenter, global phase II trial

<table>
<thead>
<tr>
<th>Patients with relapsed/refractory mantle cell lymphoma; 1-5 prior therapies; ≥ 1 measurable lesion; ECOG PS 0-1 (N = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optional Bridging Therapy</td>
</tr>
<tr>
<td>Dexamethasone 20-40 mg/d x 1-4 d, or Ibrutinib 560 mg/d, or Acalabrutinib 100 mg BID (n = 25)</td>
</tr>
<tr>
<td>Conditioning Chemotherapy</td>
</tr>
<tr>
<td>Fludarabine 30 mg/m² + Cyclophosphamide 500 mg/m² Days -5, -4, -3 (n = 69)</td>
</tr>
<tr>
<td>CAR T-Cells</td>
</tr>
<tr>
<td>KTE-X19 2 x 10⁶ cells/kg, Day 0 (n = 68)</td>
</tr>
</tbody>
</table>

Primary endpoint: ORR (IRRC-assessed per Lugano classification)
Secondary endpoints: DoR, PFS, OS, safety, ORR (investigator assessed), QoL (EQ-5D), CAR T-cell levels in blood and cytokines in serum

- KTE-X19 was successfully manufactured in 96% of patients and administered to 92% of patients
- Median time from leukapheresis to KTE-X19 delivery was 16 days

ZUMA-2: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>65 (38-79)</td>
</tr>
<tr>
<td>≥ 65 yrs, n (%)</td>
<td>39 (57)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>57 (84)</td>
</tr>
<tr>
<td>Stage IV, n (%)</td>
<td>58 (85)</td>
</tr>
<tr>
<td>ECOG PS 0-1, n (%)</td>
<td>68 (100)</td>
</tr>
<tr>
<td>Int/high-risk MIPI, n (%)</td>
<td>38 (56)</td>
</tr>
<tr>
<td>Ki-67 index ≥ 50%, n/N (%)</td>
<td>34/49 (69)</td>
</tr>
<tr>
<td>TP53 mutation, n/N (%)</td>
<td>6/36 (17)</td>
</tr>
<tr>
<td>Bone marrow involvement, n (%)</td>
<td>37 (54)</td>
</tr>
<tr>
<td>Extranodal disease, n (%)</td>
<td>38 (56)</td>
</tr>
<tr>
<td>MCL morphology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Classical</td>
<td>40 (59)</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Blastoid</td>
<td>17 (25)</td>
</tr>
</tbody>
</table>


ZUMA-2: Objective Response, Duration of Response, Progression-free Survival, and Overall Survival

- ORR of 93% (CR: 67%)
- Median DoR: not reached (95% CI: 8.6-NE)
  - 57% of all responders and 78% of those with a CR remained in remission
- Median f/u for initial 28 patients treated: 27 mos (range: 25.3-32.3)
  - 43% remained in remission without additional treatment
- ORR consistent across subgroups

CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- Diffuse Large B-Cell Lymphoma (DLBCL)
- Mantle Cell Lymphoma (MCL)
- Follicular Lymphoma
- Marginal Zone Lymphoma

UPenn CAR-T-cells (CTL019) in R/R CD19+ B-Cell NHLs

- Single-center trial at University of Pennsylvania; CTL019 construct: α-CD19-4-1BB-CD3ζ

CD19+ R/R DLBCL with no curative treatment options or R/R FL with PD < 2 yrs after 2nd therapy; prognosis < 2 yrs; < CR with previous therapy (N = 28)

- Primary endpoint: ORR at 3 mos
- Secondary endpoints: PFS, RD, OS

Schuster. NEJM. 2017;377:2545. NCT02030834

Slide credit: clinicaloptions.com
UPenn CTL019 in Follicular Lymphoma: 4-Yr Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled, N</td>
<td>16</td>
</tr>
<tr>
<td>Infused, n</td>
<td>14</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>59 (43-72)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Prior Rx, median n (range)</td>
<td>5 (2-10)</td>
</tr>
<tr>
<td>Advanced stage, n (%)</td>
<td>14 (88)</td>
</tr>
<tr>
<td>ECOG PS, median (range)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Prior HCT, n (%)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Bridging therapy, n (%)</td>
<td>10 (71)</td>
</tr>
</tbody>
</table>

- Best ORR: 78%; CR, 71% (10/14); PR, 7% (1/14)
- Median PFS: 32 mos (95% CI: 3.5-NE); 60% progression free at 49 mos
- OS: 64% alive at 49 mos

Response Duration

- 60% in remission at 49 mos
- Median RD not reached (95% CI: 9.5-NE)

12 mos post CTL019

Patients at Risk, n

- 11
- 8
- 6
- 0

CAR T-Cell Therapy in Chronic Lymphocytic Leukemia (CLL)

Increased numbers of mature lymphocytes in peripheral blood


Slide credit: clinicaloptions.com
Improving CLL Therapy with CAR T-cells


Feasibility and efficacy of JCAR014 CD19-targeted CAR T cells with concurrent ibrutinib* for CLL after ibrutinib failure

<table>
<thead>
<tr>
<th>Patient Characteristics (n=36)</th>
<th>Ibr Cohort (n=17)</th>
<th>No-Ibr Cohort (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of prior therapies</td>
<td>5 (4,7)</td>
<td>5 (4,6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Prior progression on Ibrutinib</td>
<td>16 (94%)</td>
<td>18 (95%)</td>
<td>1.00</td>
</tr>
<tr>
<td>CRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (24%)</td>
<td>2 (11%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Any grade</td>
<td>13 (76%)</td>
<td>17 (89%)</td>
<td>0.39</td>
</tr>
<tr>
<td>CRS grade 0-2</td>
<td>17 (100%)</td>
<td>14 (74%)</td>
<td>0.05</td>
</tr>
<tr>
<td>CRS grade 3-5</td>
<td>0 (0%)</td>
<td>5 (26%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (71%)</td>
<td>11 (58%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Any Grade</td>
<td>5 (29%)</td>
<td>8 (42%)</td>
<td>0.50</td>
</tr>
<tr>
<td>OR at 4 wks 2008 iwCLL</td>
<td>14 (88%)</td>
<td>10 (56%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Nodal response at 4 wks CR/PR</td>
<td>10 (83%)</td>
<td>10 (59%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* Ibrutinib was scheduled to begin ≥2 weeks before leukapheresis and continue for ≥3 months after CAR T-cell infusion.

Gauthier et al., Blood, 2018
CAR-T and Ibrutinib in CLL: Sequential or simultaneous?

- CD19 CAR T-cell therapy with concurrent ibrutinib is well tolerated.
- The 4-week ORR using 2018 International Workshop on CLL (iwCLL) criteria is higher with Ibrutinib combination, and more patients achieve a minimal residual disease (MRD)-negative marrow response by IGH sequencing.
- The 1-year overall survival and progression-free survival (PFS) probabilities are higher higher with Ibrutinib combination.
- Compared with CLL patients treated with CAR T cells without ibrutinib, CAR T cells with concurrent ibrutinib were associated with lower CRS severity and lower serum concentrations of CRS-associated cytokines, despite equivalent in vivo CAR T-cell expansion.

CAR T- Cell Therapy in Multiple Myeloma (MM)

B-cell Maturation Antigen (BCMA)

- Functions to maintain long-lived plasma cell homeostasis
  - Essential in regulating B-cell maturation and differentiation
- Highly expressed on malignant plasma cells in MM
  - Increased expression associated with progression of disease
- BCMA shed from the surface of plasma cells leads to soluble BCMA (sBCMA) detectable in circulation
  - Higher concentrations of sBCMA associated with poorer outcomes
    - Low level expression on healthy differentiated B-cells; no other normal cells/tissues express BCMA


B-Cell Maturation Antigen (BCMA)-Based Immunotherapies

Phase I NCI BCMA CAR

- Single-center, open-label phase I trial in patients with R/R MM, N=16
- CD28 costimulatory domain, gamma-retroviral vector, dose levels: 0.3, 1, 3, and 9 ×10^6 CAR T-cells/kg
- Lymphodepletion: Flu 30 mg/m² and Cy 300 mg/m² daily on days −5 to −3

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Results</th>
<th>Adverse Events and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median lines of prior therapy</td>
<td>9.5</td>
<td>PR or better</td>
</tr>
<tr>
<td>High risk cytogenetics</td>
<td>40%</td>
<td>Median EFS</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>33%</td>
<td>DoR &gt;1 year</td>
</tr>
<tr>
<td>Refractory to last treatment</td>
<td>63%</td>
<td>DoR &gt; 6 months</td>
</tr>
</tbody>
</table>

Baseline Characteristics: Flu 30 mg/m² and Cy 300 mg/m² daily on days −5 to −3


Phase I Data: BCMA-Directed CAR T Cells in Multiple Myeloma

<table>
<thead>
<tr>
<th>BB2121 (BLUEBIRD) Idecagtagene vicleucel</th>
<th>LCAR-B38M (LEGEND)</th>
<th>JCARH125 (JUNO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>33</td>
<td>57</td>
</tr>
<tr>
<td># Prior Tx</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>CART Dose</td>
<td>50-800 x 106</td>
<td>0.07-2.1 x 106/kg</td>
</tr>
<tr>
<td>ORR</td>
<td>85%</td>
<td>88%</td>
</tr>
<tr>
<td>CR</td>
<td>45%</td>
<td>74%</td>
</tr>
<tr>
<td>CRS All Grades (Grade 3/4)</td>
<td>76% (6%)</td>
<td>89% (7%)</td>
</tr>
<tr>
<td>Med Onset of CRS</td>
<td>2d</td>
<td>9d</td>
</tr>
<tr>
<td>Neurotox All Grades (Grade 3/4)</td>
<td>42% (3%)</td>
<td>2% (0%)</td>
</tr>
<tr>
<td>Med PFS</td>
<td>11.8 months</td>
<td>15 months</td>
</tr>
</tbody>
</table>

Future Directions of Most Advanced CAR T Products in Multiple Myeloma

- Race to FDA Approval in the USA
  - Global Pivotal Trial (KarMMa) of Idecabtagene vicleucel just completed enrollment
  - Legend/Janssen enrolling on pivotal trial of LCAR-B38M or JNJ-68284528

- Use Beyond the Refractory Setting
  - Trials in earlier phase of disease
    - KarMMa 3 – randomized Phase 3 of bb2121 vs SOC in pts with 2-4 priors
    - KarMMa 2 – cohort of pts with early relapse 9 (with or without ASCT), bb2121 as 2nd line
  - Trials in conjunction with ASCT/Consolidation in MRD
    - KarMMa2 – Cohort 2C upfront in pts with inadequate response to ASCT
  - Dual antigen targeting to mitigate Ag escape
    - UPenn/Novartis (BCMA CART with or without CART19) [NCT03549442] – in pts responding to 1st or 2nd line therapy for high-risk MM

Investigational Allogeneic CAR T-cells in Hematologic Malignancies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Planned N</th>
<th>Primary Endpoints</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02746952 (CALM)</td>
<td>I</td>
<td>30</td>
<td>DLT, Safety</td>
<td>UCART19, anti-CD19 allogeneic CAR T-cell in adult R/R ALL</td>
</tr>
<tr>
<td>NCT02808442 (PALL)</td>
<td>I</td>
<td>18</td>
<td>Safety</td>
<td>UCART19, anti-CD19 allogeneic CAR T-cell in pediatric R/R ALL</td>
</tr>
<tr>
<td>NCT03939026 (ALPHA)</td>
<td>I/II</td>
<td>24</td>
<td>DLT, ORR</td>
<td>ALLO-501, anti-CD19 allogeneic CAR T-cell in R/R LBCL or FL</td>
</tr>
<tr>
<td>NCT03190278 (AMELI-01)</td>
<td>I</td>
<td>59</td>
<td>DLT, Safety</td>
<td>UCART123, anti-CD123 allogeneic CAR T-cell in R/R AML</td>
</tr>
<tr>
<td>NCT04093596 (UNIVERSAL)</td>
<td>I</td>
<td>90</td>
<td>DLT</td>
<td>ALLO-715, anti-BCMA allogeneic CAR T-cell in R/R MM</td>
</tr>
<tr>
<td>NCT04142619 (MELANI-01)</td>
<td>I</td>
<td>18</td>
<td>Safety</td>
<td>UCARTCS1A, anti-CS1 allogeneic CAR T-cell in R/R MM</td>
</tr>
<tr>
<td>NCT03971799</td>
<td>I/II</td>
<td>34</td>
<td>DLT, ORR</td>
<td>CD33CART, anti-CD33 allogeneic CAR T-cell in R/R AML</td>
</tr>
</tbody>
</table>

Conclusions

• CD19 CAR T-cells are the most successful and best known CAR therapy providing durable responses in pediatric/young adult B-cell ALL, adult LBCL and MCL

• Unique toxicities of CRS and neurotoxicity may occur
  - Strategies for uniform grading to be used across clinical trials and the post-approval clinical setting recently published

• Clinical trials evaluating the use of CAR T-cells alone or in combination with other agents, in other malignancies, and versus standard of care therapies are ongoing

• Allogeneic CAR T-cell therapy may overcome barriers to current FDA approved products

Q&A SESSION

Advances in CAR T-cell Therapy

• Ask a question by phone:
  – Press star (*) then the number 1 on your keypad.

• Ask a question by web:
  – Click “Ask a question”
  – Type your question
  – Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.
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Augmented Reality CAR T-Cell Therapy Process
Use your smartphone, tablet, or other mobile device to see the CAR T-cell therapy process in action, please visit www.LLS.org/CART.

Patient Podcast
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org.
The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: www.LLS.org/Finances

To order free materials: www.LLS.org/Booklets

THANK YOU

We have one goal: A world without blood cancers