Iris Isufi, MD
Co-Director, Adult CAR T-Cell Therapy Program
Yale Cancer Center/Smilow Cancer Hospital
Assistant Professor, Medicine
Yale University School of Medicine
New Haven, CT

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

A T-Cell Receptor

TARGET CELL

HLA

Tumor antigen

T-Cell Receptor

CD3 CD3

B Chimeric Antigen Receptor

TARGET CELL

Tumor-specific antigen

scFvs

Targeting element

Transmembrane domain

CD28 or 4-1BB (costimulatory domain)

CD3ζ

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
• Highly 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

Second-generation CAR

Third-generation CAR

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

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><strong>Marketed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 (KTE-C19)</td>
<td>Gilead Sciences (Kite Pharma)</td>
<td>DLBCL, tFL and PMBCL</td>
<td>CD19</td>
</tr>
<tr>
<td>Brexucabtagene autoleucel (KTE-X19)</td>
<td>Gilead Sciences (Kite Pharma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase III</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisocabtagene maraleucel (JCAR 017)</td>
<td>Celgene (Juno Therapeutics)</td>
<td>B-NHL</td>
<td>CD19</td>
</tr>
<tr>
<td>Idecabtagene vicleucel (bb2121)</td>
<td>Bluebird bio/Celgene</td>
<td>Multiple myeloma</td>
<td>BCMA</td>
</tr>
</tbody>
</table>

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

![Image of lymphoblastic leukemia cells]

Atlas of Genetics and Cytogenetics in Oncology and Hematology
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

**Study Design**

- **Screening Apheresis and cryopreservation**
- **Tisagenlecleucel manufacturing**
- **Enrollment**
- **Lymphodepleting chemotherapy**
- **Tisagenlecleucel infusion**
- **Primary safety and efficacy follow-up**
- **Survival and long-term safety follow-up**

**Pretreatment phase**

**Screening phase**

**Treatment and follow-up phase**

**Survival and long-term safety follow-up**

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**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/m^2 x 4days + Cy 500 mg/m^2 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 2nd or later relapse**

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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

Buechner et al. EHA 2017, Abstract S476
**Overall Survival: ELIANA**

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

**Patients at risk**

| Time (months) | n = 68 | 64 | 61 | 57 | 54 | 47 | 43 | 36 | 31 | 28 | 22 | 17 | 15 | 13 | 9 | 6 | 3 | 2 | 1 | 0 |
|---------------|--------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Probability (%) |       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

- Median follow-up, 6.2 mo (max, 17.6 mo)
- Median OS, 16.6 mo

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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>
<tbody>
<tr>
<td>Maude et al. NEJM 2018</td>
<td>PENN 4-1BB</td>
<td>ALL (peds/adults) N=71</td>
<td>CR: 81% 6mo EFS &amp; OS: 73% &amp; 90% 12mo EFS &amp; OS: 59% &amp; 76% 11% proceeded to alloHSCT after CAR T cells</td>
</tr>
<tr>
<td>Park J et al. ASCO 2017, Abstract 7008</td>
<td>MSKCC CD28</td>
<td>ALL (adults) N=53</td>
<td>CR: 84.6% MRD-CR rate: 66.6% 39% proceeded to alloHSCT after CAR T cells</td>
</tr>
<tr>
<td>Turtle et al. JCI 2016</td>
<td>Seattle 4-1BB Defined CD4/CD8 composition</td>
<td>ALL (adults) N=30</td>
<td>CR=93% MRD-CR rate: 86% 1 pt proceeded to alloHSCT after CAR T cells</td>
</tr>
<tr>
<td>Lee et al. Lancet 2015</td>
<td>NCI CD28</td>
<td>ALL (peds/adults) N=21</td>
<td>CR=67%</td>
</tr>
</tbody>
</table>

CAR-T 19 Associated Toxicities

- **Neurological:**
  - Seizures
  - Changes in level of consciousness
  - Coma
  - Delirium
  - Dizziness
  - Vomiting
  - Nausea
  - Headache

- **Hypertension:**
  - Transient hypertension
  - Hypertensive crisis

- **Hematological:**
  - Neutropenia
  - Profound neutropenia
  - Thrombocytopenia
  - Profound thrombocytopenia
  - Elevated D-Dimer
  - Hypofibrinogenemia
  - Disseminated intravascular coagulation
  - Hemorrhagic lymphohematous/ocular

- **Cardiovascular:**
  - Tachycardia
  - Wide-QRS tachycardia
  - Hypotension
  - Hypertension
  - Pericardial effusion
  - Left ventricular systolic dysfunction
  - Right ventricular dysfunction
  - QT prolongation

- **Pulmonary:**
  - Acute lung injury
  - Acute respiratory distress syndrome
  - Hypoxemia

- **Renal:**
  - Acute kidney injury
  - Hypokalemia
  - Hyperkalemia
  - Hypernatremia

- **Gastrointestinal:**
  - Anorexia
  - Nausea
  - Vomiting

- **Musculoskeletal:**
  - Soreness
  - Myalgia
  - Weakness

*Professional illustration by Patrick Lane, ScEYEnce 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)

**Inhibitory Action of Tocilizumab in IL-6 Signaling**

Norihiro Nishimoto, Toru Mima, in *Rheumatoid Arthritis*, 2009

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**Neurologic Toxicity with CAR T-Cells**

- Symptoms and signs: headaches, tremors, somnolence, speech difficulty, confusion, paralysis of limbs, rarely seizures, etc.
  - 1st phase (Days 0-5) – symptoms may appear with other CRS symptoms
  - 2nd 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. *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>CARTOX-10 [12]</th>
<th>ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orientation:</strong> orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points</td>
<td></td>
</tr>
<tr>
<td><strong>Naming:</strong> ability to name 3 objects (eg, point to clock, pen, button): 3 points</td>
<td></td>
</tr>
<tr>
<td><strong>Writing:</strong> ability to write a standard sentence (eg, &quot;Our national bird is the bald eagle&quot;): 1 point</td>
<td></td>
</tr>
<tr>
<td><strong>Attention:</strong> ability to count backwards from 100 by 10: 1 point</td>
<td></td>
</tr>
</tbody>
</table>

**Orientation:** orientation to year, month, city, hospital: 4 points

**Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points

**Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point

**Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point

**Attention:** ability to count backwards from 100 by 10: 1 point

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.


doi: https://doi.org/10.1016/j.bbmt.2018.12.758
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)

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

Abramson, Palomba et al. ICML 2017

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

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene Ciloleucel-ZUMA-1</th>
<th>Tisagenlecleucel JULIET</th>
<th>Lisocabtagene Maraleucel TRANSCEND NHL-001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Construct</td>
<td>antiCD19-CD28-CD3z</td>
<td>antiCD19-41BB-CD3z</td>
<td>antiCD19-41BB-CD3z</td>
</tr>
<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 x 10⁶/kg (max 2 x 10⁸)</td>
<td>0.6 to 6.0 x 10⁸</td>
<td>DL1: 0.5 x 10⁹, DL2: 1.0 x 10⁹</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) TMZL, MCL, Richter’s</td>
</tr>
<tr>
<td>Efficacy in R/R DLBCL</td>
<td>Best OOR 42%</td>
<td>Best CRR 52%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>Best CRR 40%</td>
<td>40%</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>6 month CRR 40%</td>
<td>30%</td>
<td>33% R/R DLBCL DL1, 46% DL2</td>
</tr>
<tr>
<td>12-mo PFS</td>
<td>83% in CR/PR pts at 3mo</td>
<td></td>
<td>83%</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


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

Lisocabtagene Maraleucel in Adult R/R LBCL

Efficacy-Evaluable Patients (N = 256)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>73 (67-78)</td>
</tr>
<tr>
<td>CR rate (95% CI)</td>
<td>53 (47-59)</td>
</tr>
<tr>
<td>Time to first CR or PR, median mos (range)</td>
<td>1.0 (0.7-8.9)</td>
</tr>
<tr>
<td>DoR at 6 mos, % (95% CI)</td>
<td>60.4 (52.6-67.3)</td>
</tr>
<tr>
<td>DoR at 12 mos, % (95% CI)</td>
<td>54.7 (46.7-62.0)</td>
</tr>
</tbody>
</table>

Mediation Follow-up: 12.0 mos (95% CI: 11.2-16.7) + Censored

Median: NR (95% CI: NR-NR)

Median: NR (95% CI: 8.6 mos -NR)

Median: 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

#### First generation CAR
- 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

Source: [Image: Peripheral blood film in mantle cell lymphoma showing pleomorphic cells](https://source.com)
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
  
  Patients with relapsed/refractory mantle cell lymphoma; 1-5 prior therapies; ≥1 measurable lesion; ECOG PS 0-1 (N = 74)

  Optional Bridging Therapy
  - Dexamethasone 20-40 mg/d x 1-4 d, or Ibrutinib 560 mg/d, or Acalabrutinib 100 mg BID (n = 25)

  Conditioning Chemotherapy
  - Fludarabine 30 mg/m² + Cyclophosphamide 500 mg/m² Days -5,-4,-3 (n = 69)

  CAR T-Cells
  - KTE-X19 2 x 10⁶ cells/kg, Day 0 (n = 68)

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

**TRANSCEND NHL 001 (MCL Cohort): Study Design**

- Multicenter, nonrandomized, open-label phase I study of Liso-cel, a CD19-directed CAR T-cell therapy with defined composition of CD8+ and CD4+ T-cell components administered separately at equal target doses

**Enrollment and leukapheresis**

Patients with MCL after ≥ 2 lines of therapy*; ECOG PS of 0/1 (N = 44)

- **Lymphodepletion**
  - Fludarabine 30 mg/m² + Cyclophosphamide 300 mg/m² x 3 days

- **Liso-cel** 2-7 days after FLU/CY (n = 32)

- **Follow-up**
  - On-study: 24 mos
  - Long term: up to 15 yrs

**Primary endpoints:**
- AEs, DLTs, ORR by IRC

**Secondary endpoints:**
- CR rate by IRC, DoR, PFS, OS, cellular kinetics, HRQoL, no. ICU days

*Prior BTK inhibitor, alkylating agent, and anti-CD20 agent. Original protocol did not require prior treatment, allowed enrollment of R/R patients with ≥ 1 line of prior MCL therapy and ECOG PS of 2. Prior autologous or allogeneic HSCT allowed. 1 additional patient received nonconforming product where either CD8 or CD4 cell component did not meet requirement to be considered liso-cel.


---

**TRANSCEND NHL 001 (MCL Cohort): Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liso-cel (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM involvement at infusion,* n (%)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Median prior therapies, n (range)</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>≥ 3 prior therapies, n (%)</td>
<td>22 (69)</td>
</tr>
<tr>
<td>Prior HSCT, n (%)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Allogeneic/autologous</td>
<td>3 (9)/10 (31)</td>
</tr>
<tr>
<td>Refractory, n (%)</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Prior BTK inhibitor, n (%)</td>
<td>28 (88)</td>
</tr>
<tr>
<td>Prior ibrutinib</td>
<td>24 (75)</td>
</tr>
<tr>
<td>Refractory to prior ibrutinib</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Prior venetoclax, n (%)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Refractory to prior venetoclax</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Bridging therapy, n (%)</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Systemic treatment only</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>Radiotherapy only</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Systemic therapy and radiotherapy</td>
<td>4 (12.5)</td>
</tr>
</tbody>
</table>

**Characteristic                        | Liso-cel (N = 32) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>67 (36-80)</td>
</tr>
<tr>
<td>≥ 65 yrs of age, n (%)</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>27 (84)</td>
</tr>
<tr>
<td>ECOG PS 0/1 at screening, n (%)</td>
<td>16 (50)/16 (50)</td>
</tr>
<tr>
<td>Blastoid morphology, n (%)</td>
<td>13 (41)</td>
</tr>
<tr>
<td>Ki67 ≥ 30%, n (%)</td>
<td>23 (72)</td>
</tr>
<tr>
<td>TP53 mutations, n (%)</td>
<td>7 (22)</td>
</tr>
<tr>
<td>SDP ≥ 50 cm² prior to LDC,* n (%)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>LDH &gt; ULN prior to LDC, n (%)</td>
<td>16 (50)</td>
</tr>
<tr>
<td>CRP ≥ 20 mg/L at baseline,† n (%)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Secondary CNS lymphoma at time of liso-cel administration, n (%)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

*By BM aspirate or biopsy.
†Best response of PR, SD, or PD to last systemic or transplant treatment with curative intent.
‡Best response of PD.

**TRANSCEND NHL 001 (MCL Cohort): Response**

- Median on-study follow-up: 5.9 mos (range: 0.4-24.8)
- Median time to first CR or PR: 0.95 mos (range: 0.9-2.0)

### Response by Subgroup, %

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67 ≥ 30% (n = 23)</td>
<td>83</td>
<td>65</td>
</tr>
<tr>
<td>Blastoid morphology (n = 13)</td>
<td>77</td>
<td>54</td>
</tr>
<tr>
<td>TP53 mutations (n = 7)</td>
<td>100</td>
<td>57</td>
</tr>
</tbody>
</table>

*Based on n = 32 treated; n = 1 not evaluable, not shown.

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**TRANSCEND NHL 001 (MCL Cohort): Response Over Time**

- Median DoR: not reached
- Median follow-up: 3.9 mos (range: 0-21.3)

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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

ASH Image Bank – American Society of Hematology

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)

Screening, enrollment, leukapheresis
Lymphodepletion
CTL019 manufacturing
CTL019 infusion (1 x 10^8 - 5 x 10^8 CTL019 cells)

± Bridging chemotherapy*

Mar 2014
Initial results reported
Feb 2019
Long-term outcomes analyzed

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

Schuster. NEJM. 2017;377:2545. NCT02030834

*When needed.
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)

Patients Risk, n: 62

ZUMA-5: Phase II Trial of Axicabtagene Ciloleucel (Axi-Cel) in High-Risk R/R Indolent NHL

Patients with high risk* indolent FL or MZL after ≥ 2 prior lines of CIT; ECOG PS 0/1; no CNS involvement or transformed disease (planned N = 160; n = 96 for efficacy analysis†)

*High risk: with POD24, relapse post ASCT, or PD within 6 mos of second-line CIT or beyond.
†n = 80 with FL and ≥ 9 mos of f/u; n = 16 with MZL and ≥ 1 mo of f/u. Axi-cel: CD19-directed CAR T-cell therapy.

- Manageable toxicity profile with axi-cel; early onset of adverse events, generally reversible
### ZUMA-5: Axicabtagene Ciloleucel in iNHL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FL n = 80</th>
<th>MZL n = 16</th>
<th>All Patients N = 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>62 (34 – 79)</td>
<td>67 (52 – 77)</td>
<td>63 (34 – 79)</td>
</tr>
<tr>
<td>≥ 65 years, n (%)</td>
<td>29 (36)</td>
<td>11 (69)</td>
<td>40 (42)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>43 (54)</td>
<td>4 (25)</td>
<td>47 (49)</td>
</tr>
<tr>
<td>ECOG PS 1, n (%)</td>
<td>33 (41)</td>
<td>6 (38)</td>
<td>39 (41)</td>
</tr>
<tr>
<td>Stage IV disease, n (%)</td>
<td>37 (46)</td>
<td>13 (81)</td>
<td>50 (52)</td>
</tr>
<tr>
<td>≥ 3 FLIPI, n (%)</td>
<td>38 (48)</td>
<td>11 (69)</td>
<td>49 (51)</td>
</tr>
<tr>
<td>High tumor bulk (GELF criteria), n (%) h</td>
<td>40 (50)</td>
<td>7 (44)</td>
<td>47 (49)</td>
</tr>
<tr>
<td>Median no. of prior therapies (range)</td>
<td>3 (2 - 9)</td>
<td>3 (2 - 8)</td>
<td>3 (2 - 9)</td>
</tr>
<tr>
<td>≥ 3, n (%)</td>
<td>56 (70)</td>
<td>11 (69)</td>
<td>67 (70)</td>
</tr>
<tr>
<td>Prior PI3Ki therapy, n (%)</td>
<td>26 (33)</td>
<td>6 (38)</td>
<td>32 (33)</td>
</tr>
<tr>
<td>Refractory disease, n (%) h</td>
<td>59 (74)</td>
<td>11 (69)</td>
<td>70 (73)</td>
</tr>
<tr>
<td>POD24 from first anti-CD20 mAb-containing therapy, n (%) c</td>
<td>45 (56)</td>
<td>7 (44)</td>
<td>52 (54)</td>
</tr>
<tr>
<td>Prior autologous SCT, n (%)</td>
<td>19 (24)</td>
<td>3 (19)</td>
<td>22 (23)</td>
</tr>
</tbody>
</table>


### ZUMA-5: Axicabtagene Ciloleucel in iNHL

- The median time to first response was 1 month (range, 0.8 – 3.1)
- Of the 80 patients with FL, 10 (13%) had an initial response of PR at Week 4 and later converted to CR

ZUMA-5: PFS and OS with Axicabtagene Ciloleucel in iNHL

- With a median follow-up of 15.3 months, median PFS was 23.5 months (95% CI, 22.8 – NE) in all patients, and the median OS was not reached
  - The 12-month OS rate was 94.3% (95% CI, 86.8 – 97.6) for all patients


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

Increased numbers of mature lymphocytes in peripheral blood
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.

TRANSCEND JCAR017 CLL 004: Study Design

- Multicenter, open-label phase I/II study
- Patients with relapsed/refractory CLL/SLL; failed or ineligible for BTK inhibitors; high-risk disease with ≥ 2 failed prior therapies or standard-risk disease with ≥ 3 failed prior therapies; ECOG PS 0/1 (N = 23)
- Exploratory endpoints: antitumor activity and pharmacokinetic profile

TRANSCEND JCAR17 CLL 004: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Patients (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any high-risk features, n (%)</td>
<td></td>
</tr>
<tr>
<td>▪ del(17p)</td>
<td>19 (83)</td>
</tr>
<tr>
<td>▪ TP53 mutation</td>
<td>8 (35)</td>
</tr>
<tr>
<td>▪ Complex karyotype*</td>
<td>14 (61)</td>
</tr>
<tr>
<td></td>
<td>11 (48)</td>
</tr>
<tr>
<td>Median number of prior therapies (range)</td>
<td>5 (2-11)</td>
</tr>
<tr>
<td>Prior ibrutinib, n (%)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Ibrutinib refractory/relapsed, n (%)</td>
<td>21 (91)</td>
</tr>
<tr>
<td>BTK inhibitor progression and failed venetoclax,† n (%)</td>
<td>9 (39)</td>
</tr>
</tbody>
</table>

*≥ 3 chromosomal abnormalities. †Discontinuation due to PD or less than PR after ≥ 3 mos of therapy.


TRANSCEND JCAR17 CLL 004: Responses and MRD

Best Overall Response

<table>
<thead>
<tr>
<th>Category</th>
<th>Best Overall Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N = 22)</td>
<td>81.5% (18/22) (95% CI: 59.7-94.8)</td>
</tr>
<tr>
<td>Failed BTK Inhibitor and Venetoclax (n = 9)</td>
<td>89% (8/9) (95% CI: 51.8-99.7)</td>
</tr>
</tbody>
</table>

Undetectable MRD (10^-4) at Any Timepoint

- Blood, flow: 75% (n = 15) (95% CI: 54.3-89.3)
- Bone marrow, NGS: 65% (n = 13)

Median follow-up: 11 mos
TRANSCEND JCAR17 CLL 004 Ibrutinib Combination Cohort

• Analysis of phase I combination cohort of multicenter, open-label, multicohort phase I/II study
  - Primary endpoints: safety and recommended dose determination
  - Exploratory endpoints: antitumor activity and cellular kinetic profile

Patients with R/R CLL/SLL who:
- Progressed on ibrutinib OR
- Had high-risk features* and received ibrutinib for ≥ 6 mos with < CR OR
- Had BTK or PLCg2 mutations OR
- Had prior ibrutinib and no contraindication to restarting ibrutinib
  (N = 19)

Leukapheresis performed at enrollment to manufacture liso-cel and bridging therapy allowed between enrollment and lymphodepletion; liso-cel manufacturing success rate was 100%.

*DL1: 50 x 10^6 CAR T-cells; DL2: 100 x 10^6 CAR T-cells. *Complex cytogenetic abnormalities, del (17p), TP53 mutated, or unmutated IGHV.

73 mos follow-up on study and long-term follow-up up to 15 yrs

TRANSCEND CLL 004 Combination Cohort: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Patients (n = 19)</th>
<th>Liso-cel DL1 or DL2 + Ibrutinib (n = 4)</th>
<th>Liso-cel DL2 + Ibrutinib (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any high-risk features, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• del(17p)</td>
<td>18 (95)</td>
<td>4 (100)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>• TP53 mutation</td>
<td>8 (42)</td>
<td>2 (50)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>• Complex karyotype*</td>
<td>6 (32)</td>
<td>1 (25)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Median no. prior therapies (range)</td>
<td>4 (1-10)</td>
<td>4.5 (1-5)</td>
<td>3 (2-10)</td>
</tr>
<tr>
<td>• Prior ibrutinib, n (%)</td>
<td>19 (100)</td>
<td>4 (100)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>• Ibrutinib relapsed/refractory, n (%)</td>
<td>19 (100)</td>
<td>4 (100)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>• Prior BTKi and venetoclax, n (%)</td>
<td>11 (58)</td>
<td>2 (50)</td>
<td>9 (60)</td>
</tr>
</tbody>
</table>

≥ 3 chromosomal abnormalities.

TRANSCEND CLL 004 Combination Cohort: Efficacy

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Total Patients (n = 19)</th>
<th>Liso-cel DL1 + Ibrutinib (n = 4)</th>
<th>Liso-cel DL2 + Ibrutinib (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRi</td>
<td>18 (95)</td>
<td>3 (75)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>PR</td>
<td>12 (63)</td>
<td>2 (50)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Undetectable MRD ≤ 10^4, n (%)</td>
<td>6 (32)</td>
<td>1 (25)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>PB by flow cytometry</td>
<td>17 (89)</td>
<td>3 (75)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>BM by NGS</td>
<td>15 (79)</td>
<td>3 (75)</td>
<td>12 (80)</td>
</tr>
</tbody>
</table>

- Median follow-up: 10 mos
- All 18 responders achieved a response by day 30 after liso-cel; all 17 patients who achieved undetectable MRD in PB did so by Day 30
- Among 18 patients with ≥ 6 mos of follow-up, 16 maintained or improved response from Day 30


Slide credit: clinicaloptions.com

TRANSCEND CLL 004 Combination Cohort: Conclusions

- Liso-cel plus ibrutinib was generally well tolerated in heavily pretreated patients with R/R CLL/SLL in preliminary analysis of the phase I TRANSCEND CLL 004 trial, with low rates of grade 3 CRS/NEs and no grade 4/5 events
- Liso-cel plus ibrutinib treatment associated with rapid responses, high ORRs, and high rates of patients achieving undetectable MRD
  - ORR: 95% in overall patient population
  - Undetectable MRD in overall patient population: 89% in blood, 79% in bone marrow
- Study ongoing and actively enrolling patients


Slide credit: clinicaloptions.com
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**

![Diagram](image)


---

**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 $\times 10^6$ CAR T-cells/kg
- Lymphodepletion: Flu 30 mg/m^2 and Cy 300 mg/m^2 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>

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

<table>
<thead>
<tr>
<th></th>
<th>BB2121 (BLUEBIRD)</th>
<th>LCAR-B38M (LEGEND)</th>
<th>JCARH125 (JUNO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>33</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td># Prior Tx</td>
<td>7</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>CART Dose</td>
<td>50-800 x 10⁶</td>
<td>0.07-2.1 x 10⁶/kg</td>
<td>50-450 x 10⁶</td>
</tr>
<tr>
<td>ORR</td>
<td>85%</td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>CR</td>
<td>45%</td>
<td>74%</td>
<td>27%</td>
</tr>
<tr>
<td>CRS All Grades (Grade 3/4)</td>
<td>76% (6%)</td>
<td>89% (7%)</td>
<td>80% (9%)</td>
</tr>
<tr>
<td>Med Onset of CRS</td>
<td>2d</td>
<td>9d</td>
<td>3d</td>
</tr>
<tr>
<td>Neurotox All Grades (Grade 3/4)</td>
<td>42% (3%)</td>
<td>2% (0%)</td>
<td>25% (7%)</td>
</tr>
<tr>
<td>Med PFS</td>
<td>11.8 months</td>
<td>15 months</td>
<td>-</td>
</tr>
</tbody>
</table>


### Pivotal Phase II KarMMa trial of Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T-cell therapy, in R/R MM

<table>
<thead>
<tr>
<th>Dose, × 10⁶ CAR+ T cells</th>
<th>150 (n=4)</th>
<th>300 (n=70)</th>
<th>450 (n=54)</th>
<th>Total (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>2 (50)</td>
<td>48 (69)</td>
<td>44 (82)</td>
<td>94 (73)</td>
</tr>
<tr>
<td>CR/sCR, n (%)</td>
<td>1 (25)</td>
<td>20 (29)</td>
<td>19 (35)</td>
<td>40 (31)</td>
</tr>
<tr>
<td>Median DoR*, mo</td>
<td>9.9</td>
<td>11.3</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Median PFS*, mo</td>
<td>5.8</td>
<td>11.3</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>CRS overall / Gr ≥3, n (%)</td>
<td>2 (50) / 0</td>
<td>53 (76) / 4 (6)</td>
<td>52 (96) / 3 (6)</td>
<td>107 (84) / 7 (5)</td>
</tr>
<tr>
<td>Median onset / duration, d</td>
<td>7 / 5</td>
<td>2 / 4</td>
<td>1 / 7</td>
<td>1 / 5</td>
</tr>
<tr>
<td>NT overall / Gr ≥3, n (%)</td>
<td>0 / 0</td>
<td>12 (17) / 1 (1)</td>
<td>11 (20) / 3 (6)</td>
<td>23 (18) / 4 (3)</td>
</tr>
<tr>
<td>Median onset / duration, d</td>
<td>NA</td>
<td>3 / 3</td>
<td>2 / 5</td>
<td>2 / 3</td>
</tr>
</tbody>
</table>

Munshi NC ASCO20 Abstr 8503
Phase 1/2 CARTITUDE-1 (UPDATED)

- Open-label phase 1/2 trial of JNJ-4528 in R/R MM, N=29
- Pts received ≥3 prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and received an anti-CD38 antibody.
- Lymphodepletion: Flu 30 mg/m2 and Cy 300 mg/m2 daily x 3 days
- As of 17 Jan 2020, median follow-up is 9 mo (3–17)

<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>5 (3-18)</td>
<td>ORR 100%</td>
</tr>
<tr>
<td>Triple refractory to a PI, IMiD, and anti-CD38 antibody</td>
<td>86%</td>
<td>sCR 22 (76%)</td>
</tr>
<tr>
<td>Penta-refractory to 2 IMiDs, 2 PIs, and Daratumumab</td>
<td>31%</td>
<td>VGPR 6 (21%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PR 1 (3%)</td>
</tr>
</tbody>
</table>

Berdeja JG et al. JCO 2020 38:15_suppl, 8505-8505

Phase 1/2 CARTITUDE-1 (UPDATED)

- Median time to ≥CR was 2 months (range 1–9).
- 26/29 pts are progression-free, with 6-mo progression-free survival rate of 93% and longest response ongoing at 15 mo.
- All 16 pts (14 sCR, 2 VGPR) evaluable at 6 months were minimal residual disease negative at 10⁻⁵ or 10⁻⁶.
- At 6-mo individual follow-up, 22/28 pts had JNJ-4528 CAR+ T cells below the level of quantification (2 cells/µL) in peripheral blood, suggesting CAR-T persistence in peripheral blood did not seem to correlate with deepening of response.
- **Conclusions:** JNJ-4528 treatment led to responses in all pts. These responses were early, deep, and durable at a low dose of CAR-T cells with 26/29 (90%) pts progression free at median 9-mo follow-up. CRS was manageable in most pts, supporting outpatient dosing.
Universal: An Allogeneic First-in-Human Study of the Anti-BCMA ALLO-715 and the Anti-CD52 ALLO-647 in Relapsed/Refractory Multiple Myeloma

• Autologous anti-BCMA CAR T-cell therapy proven efficacious
  • Access limited by logistics, wait time, and bridging treatment
• Allogeneic anti-BCMA CAR T-cell or “off-the-shelf” therapy options avoids some challenges
  • Simplified, scalable manufacturing process with less product variability
  • Patients can be treated within days, resulting in less treatment delays or need for bridging therapy, with option for convenient repeat dosing
• Phase I UNIVERSAL study is the first in-human trial of allogeneic anti-BCMA CAR T-cell therapy; enrolled heavily pretreated patients with R/R MM


First-in-Human Phase I Trial (UNIVERSAL): Study Design

• Multicenter, open-label, dose-escalation phase I study

- Adults with R/R MM; ≥ 3 previous therapies (including IMiD, PI, anti-CD38); refractory to last therapy; ECOG PS 0/1; no donor specific Abs; no bridging therapy permitted (N = 35)*

  *4 patients ineligible due to organ failure from PD; 31 patients evaluated in safety analysis; 26 patients reached assessment point and included in efficacy analysis.

  - Primary endpoint: safety and tolerability
  - Secondary endpoints: lymphodepletion regimen and recommended ALLO-715 phase II dose; anti-tumor activity (ORR, DoR, PFS, MRD); ALLO-715 cellular kinetics; ALLO-647 PK data
First-in-Human Phase I Trial (UNIVERSAL): Baseline Characteristics

- Median time from enrollment to start of treatment: 5 days
- Median follow-up: 3.2 mos

<table>
<thead>
<tr>
<th>CAR T-Cell Dose</th>
<th>Lymphodepletion Regimen, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FCA + Low-Dose ALLO-647</td>
</tr>
<tr>
<td>40 x 10^6 cells</td>
<td>3</td>
</tr>
<tr>
<td>160 x 10^6 cells</td>
<td>4</td>
</tr>
<tr>
<td>320 x 10^6 cells</td>
<td>6</td>
</tr>
<tr>
<td>480 x 10^6 cells</td>
<td>3</td>
</tr>
</tbody>
</table>

First-in-Human Phase I Trial (UNIVERSAL): Response Rate

- 60% of patients in FCA plus 320 x 10^6 dose of ALLO-715 cohort responded to treatment; 40% achieved ≥ VGPR[1]
- 5/6 patients assessed with ≥ VGPR had negative MRD status[1]
Future Directions of Most Advanced CAR T Products in Multiple Myeloma

- Race to FDA Approval in the USA
  - Global Pivotal Trial (KarMMa) of Idecamtagene 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>


DLT: Dose limiting toxicity
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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Chat live online:
www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: infocenter@LLS.org
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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