A Conversation with the Investigators: Chimeric Antigen Receptor T-Cell Therapy in Hematologic Cancers

Tuesday, July 13, 2021
5:00 PM – 6:00 PM ET

Faculty
Caron Jacobson, MD
David G Maloney, MD, PhD
Nikhil C Munshi, MD

Moderator
Neil Love, MD
Faculty

Caron Jacobson, MD
Assistant Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

Nikhil C Munshi, MD
Kraft Family Chair
Director of Basic and Correlative Science
Jerome Lipper Multiple Myeloma Center
Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

David G Maloney, MD, PhD
Professor, Clinical Research Division
Medical Director, Cellular Immunotherapy
Leonard and Norma Klorfine Endowed Chair for Clinical Research
Fred Hutchinson Cancer Research Center
Professor of Medicine, Division of Oncology
University of Washington
Medical Director
Cellular Immunotherapy and Bezos Family Immunotherapy Clinic
Seattle Cancer Care Alliance
Seattle, Washington
Commercial Support

This activity is supported by educational grants from Bristol-Myers Squibb Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.
Dr Love — Disclosures

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.
<table>
<thead>
<tr>
<th><strong>Consulting Agreements</strong></th>
<th>AbbVie Inc, bluebird bio, Bristol-Myers Squibb Company, Celgene Corporation, Kite, A Gilead Company, Lonza, Novartis, Precision BioSciences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contracted Research</strong></td>
<td>Kite, A Gilead Company, Pfizer Inc, Precision BioSciences</td>
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</table>
# Dr Maloney — Disclosures

<table>
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<tr>
<th>Category</th>
<th>Details</th>
</tr>
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<tr>
<td><strong>Advisory Committee</strong></td>
<td>A2 Biotherapeutics</td>
</tr>
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<td>Amgen Inc, BioLineRx, Bristol-Myers Squibb Company, Celgene Corporation, Genentech, a member of the Roche Group, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Legend Biotech, MorphoSys, Novartis, Umoja Biopharma</td>
</tr>
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<td><strong>Data and Safety Monitoring Board/Committee</strong></td>
<td>BioLineRx</td>
</tr>
<tr>
<td><strong>Rights to Royalties</strong></td>
<td>Fred Hutchinson Cancer Research Center for patents licensed to Juno Therapeutics, a Celgene Company</td>
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Familiarizing Yourself with the Zoom Interface

How to answer poll questions

When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.
Familiarizing Yourself with the Zoom Interface

Expand chat submission box

Drag the white line above the submission box up to create more space for your message.
Familiarizing Yourself with the Zoom Interface

Increase chat font size

Press Command (for Mac) or Control (for PC) and the + symbol. You may do this as many times as you need for readability.
ONCOLOGY TODAY
WITH DR NEIL LOVE

CHIMERIC ANTIGEN RECEPTOR
T-CELL THERAPY IN NON-HODGKIN LYMPHOMA

DR TANYA SIDDQUI
CITY OF HOPE NATIONAL MEDICAL CENTER

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Gail J Roboz, MD
Eytan M Stein, MD

Moderator
Neil Love, MD
Meet The Professor
Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Monday, July 19, 2021
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Daniel P Petrylak, MD
Arlene Siefker-Radtke, MD

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Neil Love, MD
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Thursday, July 22, 2021
5:00 PM – 6:00 PM ET

Faculty
David F McDermott, MD

Moderator
Neil Love, MD
A Conversation with the Investigators: Endometrial and Cervical Cancers

Monday, July 26, 2021
5:00 PM – 6:00 PM ET

Faculty
Mansoor Raza Mirza, MD
David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc

Moderator
Neil Love, MD
What General Medical Oncologists Want to Know About Targeted Therapy for Non-Small Cell Lung Cancer

Tuesday, July 27, 2021
5:00 PM – 6:00 PM ET

Faculty
Professor Solange Peters, MD, PhD
Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator
Neil Love, MD
What General Medical Oncologists Want to Know About Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Wednesday, July 28, 2021
5:00 PM – 6:00 PM ET

Faculty
Mark Awad, MD, PhD
David R Spigel, MD
Heather Wakelee, MD

Moderator
Neil Love, MD
Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.
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Neil Love, MD
CAR T-Cell Therapy: Other Lymphoma Subtypes
Caron Jacobson, MD, MMSc

CD19 CAR T-Cell Therapy for Diffuse Large B Cell Lymphoma (DLBCL)
David G Maloney, MD, PhD

CAR T-Cell Therapy in Multiple Myeloma
Nikhil C Munshi, MD
Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)
- Mechanistic similarities and differences between axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tis-cel) and lisocabtagene maraleucel (liso-cel)
- Efficacy and safety of axi-cel, tis-cel and liso-cel in DLBCL
- Management of class-effect and other toxicities observed with CD19-directed CAR T-cell therapy
- Faculty cases

Module 2: Other Lymphoma Subtypes
- ZUMA-2: Brexucabtagene autoleucel (brex-cel) in relapsed/refractory (R/R) MCL
- ZUMA-5: Axi-cel for R/R follicular lymphoma
- ELARA: Tis-cel in patients with R/R indolent lymphomas
- Early efficacy and safety data with CD19-directed CAR T-cell therapy in patients with R/R CLL
- TRANSCEND CLL 004: Liso-cel in R/R CLL
- Faculty cases

Module 3: Multiple Myeloma (MM)
- KarMMA: Idecabtagene vicleucel (ide-cel) in patients with R/R MM; recent FDA approval
- CARTITUDE-1: Ciltacabtagene autoleucel (cilta-cel) for R/R MM
- Management of class-effect and other toxicities observed with BCMA-targeted CAR T-cell therapy
- Faculty cases
Would you like to receive RTP oncology education audio programs in CD format?

- Yes: 35%
- No: 65%

Premeeting survey: July 2021
If a live CME meeting was currently available for you to participate in person, would you likely attend?

1. Yes
2. Yes, if it is a smaller meeting with social distancing standards in place
3. No
In the past 2 weeks, approximately how many hours did you spend conducting telemedicine visits with patients?

1. 0
2. 1-5 hours
3. 6-10 hours
4. 11-15 hours
5. More than 15 hours
Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)
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- Faculty cases
Approximately how many patients have you referred for chimeric antigen receptor (CAR) T-cell therapy?

- 0: 17%
- 1-3: 54%
- 4-6: 22%
- 7-10: 5%
- 10+: 2%

Median: 1
Range: 0-18

Premeeting survey: July 2021
At what point in the treatment course are you referring patients with multiple regimen-relapsed diffuse large B-cell lymphoma (DLBCL) for consultation regarding CAR T-cell therapy?

- At first relapse: 22%
- At second relapse: 37%
- At third relapse: 37%
- I am not referring patients for CAR T-cell therapy: 5%

Premeeting survey: July 2021
A patient with DLBCL should be in adequate physical condition to undergo ASCT to be a suitable candidate for CAR T-cell therapy.

Premeeting survey: July 2021
Which therapy would you generally recommend first for a patient with DLBCL who experiences disease progression on front-line R-CHOP and is not eligible for high-dose therapy or ASCT?

- Polatuzumab vedotin/BR: 41%
- Tafasitamab/lenalidomide: 27%
- CAR T-cell therapy: 24%
- Selinexor: 2%
- I don’t know: 5%

Premeeting survey: July 2021
Currently approved CAR T-cell therapies for lymphoma differ significantly in which of their following components?

- CD19-binding region: 39%
- Costimulatory domain: 39%
- I’m not sure: 22%

Premeeting survey: July 2021
## Aggressive lymphoma: commercial CD19 CAR T cell products

<table>
<thead>
<tr>
<th>Feature</th>
<th>Tisagenlecleucel</th>
<th>Axi-cel</th>
<th>Liso-cel</th>
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<tbody>
<tr>
<td><strong>Construct</strong></td>
<td>FMC-63 murine scFv 4-1BB co-stimulatory domain</td>
<td>FMC-63 murine scFv CD28 co-stimulatory domain</td>
<td>FMC-63 murine scFv 4-1BB co-stimulatory domain</td>
</tr>
<tr>
<td><strong>Viral transfer</strong></td>
<td>Lentiviral</td>
<td>Gamma retroviral</td>
<td>Lentiviral</td>
</tr>
<tr>
<td><strong>Collection</strong></td>
<td>Resting state apheresis Cryopreserved Bulk cells</td>
<td>Resting state apheresis Fresh only Bulk cells</td>
<td>Resting state apheresis Fresh only Selection CD4 and CD8</td>
</tr>
<tr>
<td><strong>Dose administered</strong></td>
<td>0.6–6.0 ( \times 10^8 ) CAR T cells CoA based on cell recovery</td>
<td>( 2 \times 10^6/kg ) Max. 200 ( \times 10^6 ) No CoA</td>
<td>100 ( \times 10^6 ) (CD4/CD8) in separate vials (1:1) Dose based on recovery</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>DLBCL tFL</td>
<td>DLBCL PMBCL tFL</td>
<td>DLBCL, HGBCL PMBCL tIndolent (FL, CLL, MZL)</td>
</tr>
<tr>
<td><strong>CNS involvement</strong></td>
<td>No</td>
<td>No</td>
<td>Secondary</td>
</tr>
</tbody>
</table>
ZUMA-1: durable responses with axi-cel in patients with R/R DLBCL

Data cut-off date: August 11, 2020.

Three events had no causal relationship (MDS, cardiac arrest), 4 events occurred post subsequent therapy (sepsis, infection, and pulmonary nocardiosis), and 1 event was unknown.

One event was related to conditioning chemotherapy, 2 events had no causal relationship, and 2 events were related to axi-cel.

AE, adverse event; CI, confidence interval; MDS, myelodysplastic syndrome; NE, not estimable; PD, disease progression; RR, relapsed/refractory.

JULIET: sustained benefit of tisagenlecleucel in patients with R/R DLBCL

Data cut-off date: February 20, 2020.
Note: efficacy assessments were taken at Day 28, Month 3, 6, 9, 12, 18, 24, 36, 48, and 60, or as clinically indicated.


- PFS at 24 and 36 months was 33% and 31%, respectively.
- Among responders, 60% were estimated to maintain response at 24 and 36 months.
- With long-term follow-up, no new AEs were detected.
- Severe (Grade 3 or 4) CRS and neurologic events occurred in 23% and 11% of patients, respectively.
- No treatment-related deaths were reported.

Updated long-term data (median follow-up: 40.3 months)

- CR, complete response; PFS, progression-free survival; AE, adverse events

Data cut-off date: February 20, 2020.
Note: efficacy assessments were taken at Day 28, Month 3, 6, 9, 12, 18, 24, 36, 48, and 60, or as clinically indicated.

- Recorded during the first 8 weeks post infusion.
- Lasting > 28 days.
- Penn grading scale.

CR at Month 3 (n/N = 9/37)
CR at Month 6 (n/N = 6/34)
Overall (n/N = 71/115)

Number of relapses in patients with CR at 6 months

- Relapse after 6 months: 3
- Relapse after 12 months: 1

No. at risk

CR at Month 3
CR at Month 6
Overall

Time (months)

PFS (%)
TRANSCEND NHL 001: efficacy and safety of liso-cel in patients with R/R LBCL


**Characteristics**

<table>
<thead>
<tr>
<th>Patients (N = 269)</th>
</tr>
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<tbody>
<tr>
<td>Median age, years (range)</td>
</tr>
<tr>
<td>Double-/triple-hit lymphoma, n (%)</td>
</tr>
<tr>
<td>CNS involvement, n (%)</td>
</tr>
<tr>
<td>Median prior lines of therapy, n (range)</td>
</tr>
<tr>
<td>Chemorefractory, n (%)</td>
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</table>

**Best response**

<table>
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<td>Best ORR, %</td>
</tr>
<tr>
<td>Best CR, %</td>
</tr>
<tr>
<td>12-month DOR, %</td>
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**AEs**

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<tr>
<td>Any CRS, %</td>
</tr>
<tr>
<td>Median time to onset, days</td>
</tr>
<tr>
<td>CRS Grade ≥ 3, %</td>
</tr>
<tr>
<td>Any neurologic event, %</td>
</tr>
<tr>
<td>Neurologic event Grade ≥ 3, %</td>
</tr>
</tbody>
</table>

Data cut-off date: August 12, 2019.

Courtesy of David G Maloney, MD, PhD
# Summary of CD19 CAR T cell therapies for aggressive lymphoma

<table>
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<th>Characteristics</th>
<th>Axi-cel</th>
<th>Tisagenlecleucel</th>
<th>Liso-cel</th>
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<tbody>
<tr>
<td>Lymphodepletion chemotherapy</td>
<td>Cy/Flu 500/30 mg/m² × 3 days</td>
<td>Cy/Flu 250/25 mg/m² × 3 days Bendamustine 90 mg/m² × 2 days</td>
<td>Cy/Flu 300/30 mg/m² × 3 days</td>
</tr>
<tr>
<td>Bridging therapy, %</td>
<td>Not allowed</td>
<td>92%</td>
<td>59%</td>
</tr>
<tr>
<td>Indication</td>
<td>DLBCL, High grade, PMBCL, tFL</td>
<td>DLBCL, High grade, tFL</td>
<td>DLBCL, HGBCL, PMBCL, tFL, tIND</td>
</tr>
<tr>
<td>ORR, %</td>
<td>82</td>
<td>53</td>
<td>73</td>
</tr>
<tr>
<td>CR, %</td>
<td>54</td>
<td>40</td>
<td>53</td>
</tr>
<tr>
<td>CRS overall/Grade 3/4, %</td>
<td>94/13</td>
<td>58/23&lt;sup&gt;a&lt;/sup&gt;</td>
<td>42/2</td>
</tr>
<tr>
<td>Neurologic event overall/Grade 3/4, %</td>
<td>87/28</td>
<td>21/12</td>
<td>30/10</td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>No</td>
<td>Yes (26%)</td>
<td>Yes</td>
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<sup>a</sup> Includes CR 3, 4, or 5 from the grading system.

Courtesy of David G Maloney, MD, PhD
Site and patient requirements for outpatient monitoring in TRANSCEEND NHL 001, OUTREACH, and PILOT trials

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<th>Hospital requirements</th>
<th>Patient and caregiver requirements</th>
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<td>• University or non-university specialty oncology centers</td>
<td>• One designated hospital for CAR T cell patient care</td>
<td>• Caregiver support for the first 30 days after liso-cel infusion</td>
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<td>• HSCT or phase 1 trial capability</td>
<td>• CAR T cell AE management capability</td>
<td>• Stay within 1 hour of site for 30 days</td>
</tr>
<tr>
<td>• Outpatient infusion centera</td>
<td>- Oncology ward, ICU, and ED medically staffed 24/7</td>
<td>• Safety monitoring education to recognize early symptoms of CRS and neurologic events</td>
</tr>
<tr>
<td>• Affiliated leukapheresis center</td>
<td>- Subspecialty care: neurology, cardiology, infectious disease</td>
<td>• Commitment to return to site for immediate medical evaluation</td>
</tr>
<tr>
<td>• Multidisciplinary medical team</td>
<td>• Staff trained to manage CAR T cell toxicities (CRS, neurologic events, serious AEs)</td>
<td></td>
</tr>
<tr>
<td>- Coordinates care between outpatient and inpatient setting</td>
<td>• Tocilizumab available in pharmacy before liso-cel infusion</td>
<td></td>
</tr>
<tr>
<td>- Standard operating procedures for outpatient monitoring and admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 24/7 on-call oncologist</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liso-cel has not yet obtained any regulatory approval outside of the USA and Japan. The safety and efficacy of this agent is still under investigation in other countries/regions. In the USA, liso-cel is indicated for r/r LBCL after two or more lines of therapy, including DLBCL NOS, HGBCL, PMBCL, and FL grade 3b. Prescribing Information may vary depending on local approval in each country or region. aCAR T cell therapy infusion could also be administered in the inpatient facility with subsequent discharge the same day at the end of the observation period. ED, emergency department; ICU, intensive care unit. Bachier C, et al. Outpatient treatment with lisocabtagene maraleucel (liso-cel) across a variety of clinical sites from three ongoing clinical studies in relapsed/refractory large B-cell lymphoma. Poster presented at EHA 2020; abstract EP1212.

Courtesy of David G Maloney, MD, PhD
Safety and efficacy of liso-cel in patients with R/R large B-cell NHL treated in the outpatient setting

<table>
<thead>
<tr>
<th>Best overall response, (^a) n (%)</th>
<th>All outpatients (N = 56)</th>
<th>TRANSCEND NHL 001 (n = 25)</th>
<th>OUTREACH (n = 19)(^b)</th>
<th>PILOT (n = 12)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>47 (84)</td>
<td>20 (80)</td>
<td>16 (84)</td>
<td>11 (92)</td>
</tr>
<tr>
<td>CR</td>
<td>34 (61)</td>
<td>14 (56)</td>
<td>13 (68)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (23)</td>
<td>6 (24)</td>
<td>3 (16)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (5)</td>
<td>2 (8)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>6 (11)</td>
<td>3 (12)</td>
<td>2 (11)</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety, n (%)</th>
<th>All outpatients (N = 59)</th>
<th>TRANSCEND NHL 001 (n = 25)</th>
<th>OUTREACH (n = 22)</th>
<th>PILOT (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS any Grade</td>
<td>21 (36)</td>
<td>12 (48)</td>
<td>9 (41)</td>
<td>0</td>
</tr>
<tr>
<td>CRS Grade ≥ 3</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurological event any Grade</td>
<td>17 (29)</td>
<td>11 (44)</td>
<td>6 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Neurological event Grade ≥ 3</td>
<td>3 (5)</td>
<td>2 (8)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Tocilizumab alone</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Steroid use</td>
<td>2 (3)</td>
<td>2 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tocilizumab and steroid use</td>
<td>4 (7)</td>
<td>1 (4)</td>
<td>3 (14)</td>
<td>0</td>
</tr>
</tbody>
</table>

Liso-cel has not yet obtained any regulatory approval outside of the US and Japan. The safety and efficacy of this agent is still under investigation in other countries/regions. In the US, liso-cel is indicated for r/r LBCL after two or more lines of therapy, including DLBCL NOS, HGBCL, PMBCL and grade 3b FL. Prescribing information may vary depending on local approval in each country or region.

\(^a\) Per 2014 Lugano criteria.

\(^b\) All patients with ≥ 1 efficacy assessment per protocol.

Progression of CAR T cell products to second line of therapy in LBCL?

- Various trials are ongoing

<table>
<thead>
<tr>
<th>Product</th>
<th>ZUMA-7 trial</th>
<th>BELINDA trial</th>
<th>TRANSFORM trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axi-cel</td>
<td>Randomized, open label, phase 3 trial of second-line axi-cel versus standard of care in adult patients with r/r DLBCL</td>
<td>Randomized, open label, phase 3 trial of second-line tisagenlecleucel versus standard of care in adult patients with r/r aggressive B-cell NHL</td>
<td>Randomized, open-label, phase 3 trial of second-line liso-cel versus standard of care in adult patients with high-risk, transplant-eligible r/r aggressive B-cell NHL</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liso-cel</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of David G Maloney, MD, PhD
Phase III ZUMA-7 Trial of Axi-Cel Meets Primary Endpoint
Press Release – June 30, 2021

“The ZUMA-7 trial (NCT03391466) demonstrated superiority of axicabtagene ciloleucel (axi-cel) compared with standard of care (SOC) autologous stem cell transplant (ASCT) after meeting the primary end point of event-free survival (EFS) improvement for patients with relapsed or refractory large B-cell lymphoma (LBCL), according to a press release from the company responsible for manufacturing the chimeric antigen receptor (CAR) T-cell therapy. A statistically significant EFS benefit (HR, 0.398; P <0.0001) was observed as well as improvement in the secondary end point of objective response rate (ORR).

The top-line results of the randomized ZUMA-7 trial paint the picture of a potential paradigm shift in the treatment of large B-cell lymphoma, Frederick L Locke, MD, ZUMA-7 lead principal investigator and co-leader of the Immuno-Oncology Program at Moffitt Cancer Center in Tampa, Florida, said in the press release. Investigators mentioned that these data are still immature and further analyses are planned for the future. The trial was conducted under a Special Protocol Agreement from the FDA where the trial design, end points, and statistical analysis were agreed in advance.”

https://www.cancernetwork.com/view/zuma-7-trial-meets-event-free-survival-end-point-in-large-b-cell-lymphoma
Phase III TRANSFORM Trial of Liso-Cel Meets Primary Endpoint
Press Release – June 10, 2021

“Data from the Phase 3 TRANSFORM trial (NCT03575351) of the chimeric antigen receptor (CAR) T-cell therapy lisocabtagene maraleucel (liso-cel) as second-line therapy for patients with relapsed/refractory large B-cell lymphoma (LBCL) resulted in a statistically significant improvement in the primary end point of event-free survival versus therapy with the standard-of-care comparator arm, according to the company responsible for developing the agent.

Additionally, the toxicity profile observed with liso-cel was consistent with the safety data reported in the TRANSCEND NHL 001 trial (NCT02631044) which led to the FDA approving the CD19-directed therapy for patients with certain types of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL), following 2 or more prior therapies. These data represent the first time a treatment for relapsed/refractory LBCL has demonstrated benefit over high-dose chemotherapy and hematopoietic stem cell transplant (HSCT).

Results regarding the primary end point will be evaluated and shared at an upcoming medical conference as well as with regulatory authorities.”

https://www.cancernetwork.com/view/liso-cel-meets-primary-end-point-of-event-free-survival-improvement-in-phase-3-trial
Perspectives of moving CAR T cell therapy to the first line?

ZUMA-12: a phase 2, multicenter, open-label, single-arm study of axi-cel as part of first-line treatment in patients with high-risk LBCL

Eligibility criteria
- Age ≥ 18 years
- High-risk LBCL
  - HGBCL, with MYC and BLCL2 and/or BCL6 translocations, or
  - LBCL with IPI score ≥ 3 any time before enrollment
- 2 cycles of anti-CD20 plus anthracycline-containing regimen
- Positive interim PET (DS 4 or 5)
- ECOG PS score 0 or 1

Enrollment/leukapheresis

Optional nonchemotherapy bridging therapy

Conditioning chemotherapy + axi-cel infusion

- Conditioning
  - Flu 30 mg/m² i.v. and Cy 500 mg/m² i.v. on Days -5, -4, and -3
- Axi-cel
  - Single i.v. infusion of $2 \times 10^6$ CAR T cells/kg on Day 0

Primary endpoint
- CR

Key secondary endpoints
- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

Courtesy of David G Maloney, MD, PhD
ZUMA-12: interim safety and efficacy results of axi-cel as first-line treatment

Data cut-off date: July 15, 2020.

a In the safety-evaluable set (N = 32), the ORR was 88% and CR rate was 78%.

b Includes all treated patients with centrally confirmed disease type (double-/triple-hit lymphomas) or IPI score ≥ 3 who received ≥ 1 x 10^6 CAR T cells/kg and had ≥ 1 month of follow-up.


Baseline characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range), years</td>
<td>61 (23-86)</td>
</tr>
<tr>
<td>≥ 65 years, n (%)</td>
<td>13 (41)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>23 (72)</td>
</tr>
<tr>
<td>Disease stage III or IV, n (%)</td>
<td>28 (88)</td>
</tr>
<tr>
<td>ECOG PS score ≥ 1, n (%)</td>
<td>21 (66)</td>
</tr>
<tr>
<td>1 prior line of systemic therapy, n (%)</td>
<td>32 (100)</td>
</tr>
<tr>
<td>Double-/triple-hit lymphoma, n (%)</td>
<td>17 (53)</td>
</tr>
<tr>
<td>IPI score ≥ 3, n (%)</td>
<td>23 (72)</td>
</tr>
<tr>
<td>DS 4, n (%)</td>
<td>16 (50)</td>
</tr>
</tbody>
</table>

Safety

<table>
<thead>
<tr>
<th>CRS (N = 32)</th>
<th>Neurologic events (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade, n (%)</td>
<td>32 (100)</td>
</tr>
<tr>
<td>Grade ≥ 3, n (%)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Grade 4, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 5, n (%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Most commonly associated any-Grade symptoms, n (%)

- Pyrexia: 32 (100)
- Chills: 8 (25)
- Hypotension: 8 (25)
- Encephalopathy: 10 (31)
- Confusional state: 9 (28)

ORR and CR in response-evaluable cohort

(N = 27)

85% ORR (n=20)
74% CR (n=20)
15% (n=4)
0% (n=0)

Courtesy of David G Maloney, MD, PhD
Case Presentation - Dr Maloney: A 57-year-old man with refractory Primary Mediastinal B-cell Lymphoma (PMBCL)

57 year old man with refractory PMBCL with massive chest disease as well as nodules in lungs and abdomen. Presented in 12/2015 with neck swelling and early SVC syndrome.

PATH: Biopsy showed PMBCL, CD20 positive 11 x 7 cm mass.

Prior treatments:

- R-EPOCH x 6 with good, but not complete response on PET.
- PD 2 months later- treated with XRT.
- 11/2016 PET showed CR

Relapsed 4/2017, 11 x 10 cm mass, SUV 18.9.

- Bx: PMBCL, CD19 positive
- 5/2017 R-ICE x 1 mixed response
  - Lenolidomide- PD
  - R- Gem/dex - PD

Referred to Fred Hutch IMTX service for clinical trial with JCAR-017 (Lisocabtagene Maraleucel)

- Cells collected
  - Required R-gem/dex bridging

PET pre (see image) 11 x 7.4 cm mass (SUV 16.7), encasing pulmonary vessels

Cy/Flu lymphodepletion
Case Presentation - Dr Maloney: A 57-year-old man with refractory PMBCL (continued)

CAR-T cells infused (outpatient)
  Day 4- Admitted overnight with low grade fever and discharged.
  No significant CRS and no NT.
PET/CT day 30 showed PR that continued to improve.
Month 9 and 12 PET showed CR (see image from 1 year)
Continues in CR to date.
Case Presentation - Dr Maloney: A 57-year-old man with refractory PMBCL (continued)

Pre Lisocabtagene Maraleucel

1 year post Lisocabtagene Maraleucel

Courtesy of David G Maloney, MD, PhD
Case Presentation - Dr Maloney: A 61-year-old man with double-hit DLBCL

5/2017. 61 year old man with double hit DLBCL with widespread abdominal disease. Presented with NS, weight loss, abdominal pain. Stage IVB disease. Negative bone marrow and CNS.

PATH: Double hit (myc/bcl2) DLBCL, CD10 positive, GC like.

Prior treatments:
DA-EPOCH-R x 6 cycles, Dose escalation to dose level 4 with IT MTX x 4
PET PR (Primary refractory)
Rapidly presented with bowel obstruction requiring surgery- Path:DLBCL
R-ICE x 2  PD

Referred to Fred Hutch IMTX service for commercial CAR-T (axicabtagene ciloleucel)
1/2018 cells collected
   Rapidly progressive disease required DA-EPOCH-R with Flu as bridging
PET/CT pre (see image) PD, Deauville score =5
2/28 Cy/flu lymphodepletion and commercial CAR-T infusion
   -CRS grade 2- treated with Toci x 1, dex, 10 mg x 2
   -NT grade 2
Day 30 PET/CT- (see image) CR, Deauville score of 2.

Had some persistent cytopenias that resolved, requires IVIG. Continues in CR to date.

Courtesy of David G Maloney, MD, PhD
Case Presentation - Dr Maloney: A 61-year-old man with double-hit DLBCL (continued)

Pre axicabtagene ciloleucel 1 month Post axicabtagene ciloleucel
Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)
• Mechanistic similarities and differences between axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tis-cel) and lisocabtagene maraleucel (liso-cel)
• Efficacy and safety of axi-cel, tis-cel and liso-cel in DLBCL
• Management of class-effect and other toxicities observed with CD19-directed CAR T-cell therapy
• Faculty cases

Module 2: Other Lymphoma Subtypes
• ZUMA-2: Brexucabtagene autoleucel (brex-cel) in relapsed/refractory (R/R) MCL
• ZUMA-5: Axi-cel for R/R follicular lymphoma
• ELARA: Tis-cel in patients with R/R indolent lymphomas
• Early efficacy and safety data with CD19-directed CAR T-cell therapy in patients with R/R CLL
• TRANSCEND CLL 004: Liso-cel in R/R CLL
• Faculty cases

Module 3: Multiple Myeloma (MM)
• KarMMa: Idecabtagene vicleucel (ide-cel) in patients with R/R MM; recent FDA approval
• CARTITUDE-1: Ciltacabtagene autoleucel (cilta-cel) for R/R MM
• Management of class-effect and other toxicities observed with BCMA-targeted CAR T-cell therapy
• Faculty cases
ZUMA-2: Brexucabtagene autoleucel in MCL


Courtesy of Caron Jacobson, MD
TRANSCEND NHL 001 Outcomes

Palomba et al. ASH 2020;Abstract 118.

Courtesy of Caron Jacobson, MD
ZUMA-5 Outcomes: ORR and CR

- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

Jacobson et al. ASH 2020;Abstract 700.
ZUMA-5 Outcomes: DOR, PFS, OS

Duration of Response

Progression-Free Survival

Overall Survival

Jacobson et al. ASH 2020;Abstract 700.

Courtesy of Caron Jacobson, MD
FDA Approvals in MCL and FL: Who Should be Referred for CAR T-cells?

- FDA label very broad:
  - **Relapsed/refractory MCL** (no restrictions on prior lines of therapy)
  - **Relapsed/refractory FL** after 2 lines of systemic therapy
  - **No upper age limit**
  - **No evidence that tumor must demonstrate CD19+**

- We have learned from aggressive lymphoma that referral timing matters! Best to refer as early as possible!

- For MCL, best to refer when the patient starts a BTK inhibitor or refer all patients with high-risk features

- For FL, there is generally more time and it is challenging to identify high-risk patients but would consider referral for any patient who has relapsed within 24m of initial therapy or who requires 3\(^{rd}\) line therapy

- Same special considerations/lessons from DLBCL remain:
  - i.e. Disease pace and burden, ECOG PS, organ dysfunction, underlying autoimmune and neurologic conditions
  - Refer everyone! Allow CAR T-cell center to assess eligibility as criteria differ between centers

Courtesy of Caron Jacobson, MD
**Tisa-cel in R/R FL: ELARA ORR, DOR, Safety**

### Best Overall Response Rate

<table>
<thead>
<tr>
<th>Response Rate, %</th>
<th>Patients Evaluable for Efficacy(^a) (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>65.4(^a)</td>
</tr>
<tr>
<td>PR</td>
<td>17.3</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>82.7</td>
</tr>
</tbody>
</table>

- Investigator-assessed CR rate was 67.3\(^b\) (ORR 88.5%)
- ORR was consistent across subgroups, including prior SCT, disease status, and high-risk features

### At 10 Months Median Follow-up for Efficacy, Median DOR Not Reached

- Median follow-up for efficacy (n=52): 9.9 months (6.0-15.6)
- Probability for a responding patient to remain in response ≥6 months was 84.4%
- 8 of 18 PRs (44%) converted to CRs; all but 1 occurred between Month 3 and Month 6

- Median time to next antilymphoma treatment was not reached
- 69% (36/52) had ongoing responses at the time of data cutoff

---

Fowler et al. ASH 2020;Abstract 1149.  
Courtesy of Caron Jacobson, MD
**ELARA: PFS and OS**

- Median PFS and median OS were not reached, 95% CI (11-NE) and 95% CI (NE-NE), respectively.
- 6-month PFS was 73.2% (95% CI, 58.2-83.5)

Fowler et al. ASH 2020;Abstract 1149.  

Courtesy of Caron Jacobson, MD
Ongoing Studies

- Mantle-cell lymphoma
  - TRANSCEND NHL 001 (Liso-cel)
  - ZUMA-2 Cohort 2: relapsed MCL pre-BTK inhibition (Brexi-cel)

- Indolent B-NHL
  - ZUMA-5 in marginal zone lymphoma (Axi-cel)
  - ELARA (Tisa-cel)
  - TRANSCEND FL (Liso-cel)

- CLL
  - TRANSCEND CLL 004 (Liso-cel)
  - ZUMA-8 (Brexi-cel)

- Phase 1/2 studies of new products: allo and NK CAR, dual antigen targeting CARs

Courtesy of Caron Jacobson, MD
55 year-old man with relapsed TP53 mutated MCL, blastoid variant, Ki67 80%

- Diagnosed 11/2017 with weight loss and fatigue; CT scans showed LAD and splenomegaly. Biopsy blastoid MCL with a TP53 mutation

- 1/2018-2/2018: cycles 1-3 BR
  - PET with SD

  - PET with SD

- 6/2018-9/2018: acalabrutinib
  - PET with PD

- Received CAR T-cells on a clinical trial on 11/13/2018
  - Course c/b grade 1 CRS and no ICANS. Neither Toci nor dex were given
  - Discharged home on day +8
Case Presentation – Dr Jacobson: A 55-Year-Old Man with Refractory Mantle-Cell Lymphoma (continued)

Pre-treatment 1 month 1 year 2 years

Courtesy of Caron Jacobson, MD
Case Presentation – Dr Jacobson: A 58-Year-Old Woman with Refractory Follicular Lymphoma

58 year-old woman with multiply relapsed and refractory FL

- Diagnosed 7/2011 with asymptomatic LAD and observed for 3 years off treatment
- 3/2014-8/2014 cycles 1-6 BR due to paraneoplastic rash with CR
- 2/2019: recurrence of rash prompting CT scans that showed low volume recurrent disease, confirmed on biopsy
- 6/2019-9/2019: O-CVP x4 with PD, rebiopsy c/w FL (CD20 negative)
- 10/2019-12/2019: clinical trial of combination immunotherapy with PD
- 1/2020-8/2020: lenalidomide with initial PR but then PD
- 8/2020-10/2020: copanlisib with mixed response but ultimate PD in marrow and spleen; bone marrow biopsy c/w FL (still CD20 negative)
- 10/2020-11/2020: dose reduced ICE with PD
- 12/2020-1/2021: polatuzumab with SD but c/b cytopenias, bleeding and DIC
- 2/2021-4/2021: venetoclax with SD by marrow and imaging but good clinical response

Courtesy of Caron Jacobson, MD
58 year-old woman with multiply relapsed and refractory FL

- Diagnosed 7/2011 with asymptomatic LAD and observed for 3 years off treatment
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- 2/2021-4/2021: venetoclax with SD by marrow and imaging but good clinical response

Treated with CD19 CAR T-cells on 4/21/2021

Course complicated by grade 1-2 CRS (fevers and mild transaminitis) treated with tocilizumab

Discharged home on day +10

Courtesy of Caron Jacobson, MD
Case Presentation – Dr Jacobson: A 58-Year-Old Woman with Refractory Follicular Lymphoma (continued)

[Imaging studies showing medical imaging results]

Courtesy of Caron Jacobson, MD
**Agenda**

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- Mechanistic similarities and differences between axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tis-cel) and lisocabtagene maraleucel (liso-cel)
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- Management of class-effect and other toxicities observed with BCMA-targeted CAR T-cell therapy
- Faculty cases
At what point in the treatment course are you referring patients with multiple regimen-relapsed multiple myeloma (MM) for consultation regarding CAR T-cell therapy?

- At first relapse: 15%
- At second relapse: 15%
- At third relapse: 54%
- I am not referring patients for CAR T-cell therapy: 17%

Premeeting survey: July 2021
Which of the following agents would you generally use first for a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMA-directed CAR T-cell therapy</td>
<td>35%</td>
</tr>
<tr>
<td>Selinexor</td>
<td>33%</td>
</tr>
<tr>
<td>Belantamab mafodotin</td>
<td>24%</td>
</tr>
<tr>
<td>Isatuximab</td>
<td>7%</td>
</tr>
</tbody>
</table>

Premeeting survey: July 2021
Indirect comparison of the efficacy data from the KarMMa and CARTITUDE-1 studies in patients with R/R MM suggests which of the following regarding ide-cel and ciltacabtagene autoleucel (cilta-cel)?

- Cilta-cel and ide-cel have equal efficacy: 24%
- Cilta-cel has greater efficacy than ide-cel: 27%
- Ide-cel has greater efficacy than cilta-cel: 2%
- I’m not sure: 46%

Premeeting survey: July 2021
Treatment with cilta-cel has been associated with which of the following?

Non-immune effector cell-associated neurotoxicity syndrome (ICANS) neurologic movement disorders: 56%

Increased risk of viral infections: 2%

I’m not sure: 41%

Premeeting survey: July 2021
B-Cell Maturation Antigen (BCMA)  
A Promising Target in Multiple Myeloma

• BCMA is member of the TNF receptor superfamily
  • Expressed nearly universally on MM cells
  • Expression largely restricted to plasma cells and some mature B cells

• BCMA support survival of long-lived PCs, Ig Class switch and antibody production

• Promotes proliferation, survival and associated with immunosuppressive BM microenvironment.

BCMA is a promising target in multiple myeloma, as it supports the survival of long-lived plasma cells (PCs) and promotes antibody production. BCMA is a member of the TNF receptor superfamily, expressed universally on myeloma cells and primarily on plasma cells and mature B cells. Its support of long-lived PCs is associated with proliferation, survival, and an immunosuppressive bone marrow (BM) microenvironment. The Akt and NFκB signaling pathways, as well as JNK and Elk1, are activated upon BCMA binding to APRIL, BAFF, or sBCMA. This leads to growth and survival of long-lived PC or MM cells. 

![Diagram of B-cell development and BCMA signaling](Diagram)
# The phase 2 pivotal KarMMA study assessed the efficacy and safety of idecabtagene vicleucel (ide-cel; bb2121)

## Ide-cel CAR design

<table>
<thead>
<tr>
<th>MND</th>
<th>SP</th>
<th>Anti-BCMA scFv</th>
<th>CD8</th>
<th>4-1BB</th>
<th>CD3 ζ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promoter</td>
<td>Tumor-binding domain</td>
<td>Linker</td>
<td>Signaling domains</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- RRMM
- ≥ 3 prior regimens
- Previously exposed to: IMiD®, proteasome inhibitor, Anti-CD38 antibody
- Refractory to last prior therapy per IMWG

### Study status as of 14 January 2020

- Screened N = 158
- Leukapheresed N = 140
- Treated N = 128 (Target dose CAR T cells)
  - 150 × 10⁶: n = 4
  - 300 × 10⁶: n = 70
  - 450 × 10⁶: n = 54
- Median follow-up (months)
  - Total: 13.3

### Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since initial diagnosis</td>
<td>6 (1−18)</td>
</tr>
<tr>
<td>No. of prior anti-myeloma regimens</td>
<td>6 (3–16)</td>
</tr>
<tr>
<td>Prior autologous SCT</td>
<td>1 94, &gt; 1 34</td>
</tr>
<tr>
<td>Any bridging therapies for MM</td>
<td>88</td>
</tr>
<tr>
<td>Refractory status</td>
<td>Anti-CD38 Ab-refractory 94, Triple-refractory 84</td>
</tr>
</tbody>
</table>

### Data cut-off: 21 December 2020

<table>
<thead>
<tr>
<th>Treatment Dose</th>
<th>ORR 50%</th>
<th>ORR 69%</th>
<th>ORR 81%</th>
<th>ORR 73%</th>
</tr>
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<tbody>
<tr>
<td>150 × 10⁶ (n=4)</td>
<td>25</td>
<td>29</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>300 × 10⁶ (n=70)</td>
<td>40</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>450 × 10⁶ (n=54)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ide-cel treated (N=128)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**EudraCT: 2017-002245-29**
**ClinicalTrials.gov: NCT03361748**

Courtesy of Nikhil C Munshi, MD
**Ide-cel efficacy (KarMMa): longer follow-up (median 24.8 months)**

Patients treated at $450 \times 10^6$ cells target dose had an ORR of 81% and a CR/sCR of 39%.

### TOXICITIES

- **CRS** - 84%, with 5% grade 3-5
- Time to CRS 1 (1-12) day; Duration - 5 (1-63) days
- Neurotoxicity - 18% of all patients treated with ide-cel
  - No grade 4 or 5 NT occurred
  - All neurotoxicity was proximal to CRS

### Median PFS and OS in all ide-cel treated patients

- Median PFS was 8.6 months and median OS was 24.8 months in all ide-cel treated patients.
- Median time to first response of 1.0 month (range 0.5-8.8); median time to CR of 2.8 months (range 1.0-15.8).
- 79% of patients in CR were MRD negative.

### Median MRD-negative and ≥CR

<table>
<thead>
<tr>
<th>Target dose, CAR T cells</th>
<th>150 x 10^6 (n = 4)</th>
<th>300 x 10^6 (n = 70)</th>
<th>450 x 10^6 (n = 54)</th>
<th>Total (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-negative and ≥CR, n (%) [95% CI]</td>
<td>1 (25) [0.6-80.6]</td>
<td>17 (24) [14.8-36.0]</td>
<td>15 (28) [16.5-41.6]</td>
<td>33 (26) [18.5-34.3]</td>
</tr>
<tr>
<td>MRD-negative and ≥VGPR, n (%) [95% CI]</td>
<td>2 (50) [6.8-93.2]</td>
<td>22 (31) [20.9-43.6]</td>
<td>26 (48) [34.4-62.2]</td>
<td>50 (39) [30.6-48.1]</td>
</tr>
</tbody>
</table>

### Median PFS increased with higher target dose and greater depth of response

TOXICITIES

- **CRS** - 84%, with 5% grade 3-5
- Time to CRS 1 (1-12) day; Duration - 5 (1-63) days
- Neurotoxicity - 18% of all patients treated with ide-cel
  - No grade 4 or 5 NT occurred
  - All neurotoxicity was proximal to CRS
KarMMa Trial of Ide-cel in R/R MM: Response rate by subgroup

- ORR was ≥ 65% and CR rate was ≥ 20% across all high-risk subgroups except R-ISS disease stage III
- Presence of extramedullary disease and baseline tumor burden did not substantially affect ORR
- Among high-risk subgroups treated with the highest target dose of 450 × 10^6 CAR+ T cells, ORR and CR rate were ≥ 75% and ≥ 19%, respectively, across all subgroups except R-ISS disease stage III

Data cutoff date: 14 Jan 2020.
CR, complete response; ORR, overall response rate; PR, partial response; R-ISS, revised International Staging System; sCR, stringent CR; VGPR, very good PR.
*Sum of CR/sCR, VGPR, and PR rates may differ from the ORR rate due to rounding.


Courtesy of Nikhil C Munshi, MD
### KarMMa: Summary of adverse events in high-risk subgroups

- No new safety signals were identified in the subgroups examined.
- Across all high-risk subgroups, the incidence of CRS was comparable with that of the overall ide-cel treated population.
- Median time to onset of CRS was 1 day in all subgroups and in the overall ide-cel treated population; median duration of CRS ranged from 5 to 7 days.

Data cutoff date: 14 Jan 2020.

CRS, cytokine release syndrome; R-ISS, revised International Staging System; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

<table>
<thead>
<tr>
<th></th>
<th>Extramedullary disease (n = 50)</th>
<th>High-risk cytogenetics (n = 45)</th>
<th>High tumor burden (n = 65)</th>
<th>Received bridging therapy (n = 112)</th>
<th>R-ISS disease stage III (n = 21)</th>
<th>&gt; 1 prior regimens/year (n = 60)</th>
<th>All ide-cel treated (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade TEAE</td>
<td>50 (100)</td>
<td>45 (100)</td>
<td>65 (100)</td>
<td>112 (100)</td>
<td>21 (100)</td>
<td>60 (100)</td>
<td>128 (100)</td>
</tr>
<tr>
<td>Grade 3/4 TEAE</td>
<td>50 (100)</td>
<td>45 (100)</td>
<td>64 (99)</td>
<td>111 (99)</td>
<td>21 (100)</td>
<td>60 (100)</td>
<td>127 (99)</td>
</tr>
<tr>
<td>SAE</td>
<td>36 (72)</td>
<td>32 (71)</td>
<td>50 (77)</td>
<td>78 (70)</td>
<td>15 (71)</td>
<td>41 (68)</td>
<td>86 (67)</td>
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<tr>
<td>≥ 1 CRS event</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Max. grade (Lee criteria), a,b</td>
<td>41 (82)</td>
<td>41 (91)</td>
<td>57 (88)</td>
<td>94 (84)</td>
<td>16 (76)</td>
<td>49 (82)</td>
<td>107 (84)</td>
</tr>
<tr>
<td>1</td>
<td>24 (48)</td>
<td>21 (47)</td>
<td>31 (48)</td>
<td>55 (49)</td>
<td>8 (38)</td>
<td>27 (45)</td>
<td>61 (48)</td>
</tr>
<tr>
<td>2</td>
<td>14 (28)</td>
<td>18 (40)</td>
<td>23 (35)</td>
<td>32 (29)</td>
<td>7 (33)</td>
<td>20 (33)</td>
<td>39 (31)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>3 (5)</td>
<td>7 (6)</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>


Courtesy of Nikhil C Munshi, MD

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a Sum of percentages may differ from the total due to rounding. b CRS graded according to Lee criteria (Lee DW, et al. Blood. 2014;124:188-195).
## Ide-Cel Studies

<table>
<thead>
<tr>
<th></th>
<th>Ide-cel KarMMa-1 N = 128</th>
<th>Ide-cel KarMMa-1-450x10^6 dose N = 54</th>
<th>Ide-Cel CRB-401 N = 62</th>
<th>Ide-cel CRB-401 450x10^6 dose N = 38</th>
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</thead>
<tbody>
<tr>
<td><strong>RESPONSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>73%</td>
<td>82%</td>
<td>75.8 %</td>
<td>89.5 %</td>
</tr>
<tr>
<td>CR</td>
<td>33%</td>
<td>39%</td>
<td>38.7%</td>
<td>36.8 %</td>
</tr>
<tr>
<td><strong>RESPONSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median f/p</td>
<td>13.3 mo</td>
<td>12.4 mo</td>
<td>18.1 mo</td>
<td>NA</td>
</tr>
<tr>
<td>Median DOR</td>
<td>10.7 mo</td>
<td>Not reported</td>
<td>10.3 mo</td>
<td>10.0 mo</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.8 mo</td>
<td>12.1 mo</td>
<td>8.8 Mmo.</td>
<td>9.0 Mo</td>
</tr>
<tr>
<td>Median OS</td>
<td>19.4 mo</td>
<td>NA</td>
<td>34.2 mo.</td>
<td>34.2 mo.</td>
</tr>
<tr>
<td><strong>CYTOKINE RELEASE SYNDROME</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades (≥3 ) %</td>
<td>84% (6%)</td>
<td>96% (6%)</td>
<td>76% (6.5%)</td>
<td>92% (7.9%)</td>
</tr>
<tr>
<td><strong>NEUROTOXICITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades (≥3 ) %</td>
<td>18% (3%)</td>
<td>20% (6%)</td>
<td>43% (3.2%)</td>
<td>52.6% (5.2%)</td>
</tr>
</tbody>
</table>

Courtesy of Nikhil C Munshi, MD
CARTITUDE-1: a phase1b/2 trial of cilta-cel (JNJ-4528) BCMA CAR T cell therapy

**Patient characteristics (N = 97)\(^1\)**

- Years since initial diagnosis, median (range): 5.9 (1.6−18.2)
- No. of prior lines of therapy, median (range): 6 (3−18)
- Prior autologous SCT, n (%): 87 (89.7)
- Any bridging therapies for MM, n (%): 73 (75)
- Refractory status, n (%):
  - Triple-refractory: 85 (87.6)
  - Penta-refractory: 41 (42.3)

**Eligibility criteria**

- PD MM with 3 prior therapies or double-refractory
- Prior PI, IMiD, and anti-CD38 mAb
- Measurable disease

---

**OVERALL RESPONSE**

- N=97
- ORR: 97.9%
- 80.4% sCR
- 94.8% ≥VGPR
- 14.4% PR
- 3.1% VGPR

**Median administered dose:**
0.71x10^6 (0.51−0.95x10^6) CAR+ viable T cells/kg

Courtesy of Nikhil C Munshi, MD
CARTITUDE-1: Progression-free survival with cilta-cel

**PFS All Pts and by sCR**

- **Total CRS**: -94.8%
- **Time to CRS**: 7 (1-12) days
- **Duration**: 4 (1-97) days

**Neurotoxicities**

- **Total CAR T cell neurotoxicities**
  - Any grade: 20 patients (20.6%)
  - Grade ≥3: 10 patients (10.3%)
- **Other neurotoxicities**: Occurring after resolution of CRS and/or ICANS - 12.4%
  - 9.3% grade ≥3
  - 5 AEs including movement and/or neurocognitive changes; 7 including nerve palsy, peripheral motor neuropathy
- **Mitigating measures**

**Toxicities**

- **Total CRS**: -94.8%
- **Time to CRS**: 7 (1-12) days
- **Duration**: 4 (1-97) days

**Medians not reached**

- **Median duration of response**: 21.8 months
- **At 12 months**: 73% of responders have not progressed or died
- **Median DOR**: not reached in patients with sCR
- **Median time to first response**: 1.0 month (range 0.9-10.7); median time to CR of 2.6 months (range 0.9-15.2)
- **Of 16 evaluable patients in CR were MRD negative**:
  - 81% were MRD- at $10^{-5}$ or $10^{-6}$; 69% were MRD- at $10^{-6}$

*Courtesy of Nikhil C Munshi, MD*
Select Ongoing Trials of CAR T-Cell Therapies in MM

<table>
<thead>
<tr>
<th>Trial Name or NCT#</th>
<th>Phase</th>
<th>Agent</th>
<th>Target</th>
<th>Setting</th>
<th>Estimated 1° completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>KarMMa-3</td>
<td>III</td>
<td>Ide-cel</td>
<td>BCMA</td>
<td>R/R (3 or 4 prior lines)</td>
<td>May 2022</td>
</tr>
<tr>
<td>CARTITUDE-4</td>
<td>III</td>
<td>Cilta-cel</td>
<td>BCMA</td>
<td>R/R (1-3 prior lines)</td>
<td>April 2026</td>
</tr>
<tr>
<td>CARTITUDE-5</td>
<td>III</td>
<td>Cilta-cel</td>
<td>BCMA</td>
<td>NDMM not undergoing HSCT</td>
<td>June 2026</td>
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<tr>
<td>CARTITUDE-2</td>
<td>II</td>
<td>Cilta-cel</td>
<td>BCMA</td>
<td>R/R (1-3 prior lines)</td>
<td>April 2022</td>
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<tr>
<td>NCT03448978</td>
<td>I/II</td>
<td>Descartes-08</td>
<td>CD8/BCMA</td>
<td>R/R (≥2 prior lines)</td>
<td>December 2021</td>
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<tr>
<td>NCT04499339</td>
<td>I/II</td>
<td>SLAM7 CAR-T</td>
<td>SLAM7</td>
<td>R/R (≥2 prior lines)</td>
<td>March 2024</td>
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<tr>
<td>NCT04555551</td>
<td>I</td>
<td>MCARH109</td>
<td>GPRC5D</td>
<td>R/R (≥3 prior lines)</td>
<td>August 2023</td>
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<tr>
<td>KarMMa-4</td>
<td>I</td>
<td>Ide-cel</td>
<td>BCMA</td>
<td>NDMM</td>
<td>January 2025</td>
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<td>NCT03274219</td>
<td>I</td>
<td>bb21217</td>
<td>BCMA</td>
<td>R/R (≥3 prior lines)</td>
<td>October 2025</td>
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<tr>
<td>MELANI-01</td>
<td>I</td>
<td>UCART</td>
<td>CS1</td>
<td>R/R (≥2 prior lines)</td>
<td>December 2021</td>
</tr>
<tr>
<td>LUMMICAR STUDY 2</td>
<td>I</td>
<td>CT053</td>
<td>CD137/BCMA</td>
<td>R/R</td>
<td>August 2021</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov; Accessed June 2021

Courtesy of Nikhil C Munshi, MD
CARTITUDE-2: Initial Results with Cilta-Cel in Progressive MM

- As of Jan 2021 data cut-off, median follow-up was 5.8 months, median age 60 years; 65% were male
- One patient was treated in an outpatient setting
- All patients were exposed to PI, IMiD, and dexamethasone, 95% to alkylating agents, and 65% to daratumumab

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since diagnosis, median (range)</td>
<td>3.5 (0.7–8.0)</td>
</tr>
<tr>
<td>Prior lines of therapy, median (range)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Previous autologous stem cell transplantation, n (%)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Triple-class exposed, n (%)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Triple-class refractory, n (%)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Penta-drug exposed, n (%)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Penta-drug refractory, n (%)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Refractory status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Refractory to last line of therapy, n (%)</td>
<td>19 (95)</td>
</tr>
</tbody>
</table>

**Efficacy**

- Median time to first response: 1.0 month
- Median time to best response: 1.9 months
- Median duration of response: not reached
- All patients (n=4) with MRD-evaluable samples at the 10^{-5} threshold were MRD negative at data cut-off

**Safety**

- Cilta-cel safety profile was manageable, including in the patient treated in an outpatient setting
- No movement and neurocognitive treatment-emergent AEs were observed in patients of Cohort A

Presented By: Mounzer Agha, UPMC Hillman Cancer Center, Pittsburgh, PA, USA

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Courtesy of Nikhil C Munshi, MD
Case Presentation - Dr Munshi: A 65-year-old woman with multiple myeloma

- 65 year old lady with IgG kappa multiple myeloma, BM plasma cells 45% with ISS stage I with a 1q amplification and 13q deletion diagnosed in 2016.
- Induction therapy with KRD. Excellent response but developed PE and on Rivaroxaban
- 09/2016 – HDT and ASCT – Maintenance with weekly Bortezomib + Lenalidomide
- 01/2018 – Progression on PET/CT – Started on DaraPD
- 04/2018 – A localized head mass – changed to DaraPVD
- 06/2018 – Progression on PET/CT – KCD
- 10/2018 – anti-BCMA CAR T-cell therapy

Courtesy of Nikhil C Munshi, MD
Case Presentation – Dr Munshi: A 65-year-old woman with multiple myeloma

- Cytokine release syndrome Day +1 with fevers and fluid-responsive hypotension (grade 2 CRS) on day +2,
- Resolved with a single dose of tocilizumab.
- She was treated with empiric ceftazidime for neutropenic fever.

Kappa FLC (mg/L)

<table>
<thead>
<tr>
<th>Date</th>
<th>436.7</th>
<th>1.9</th>
<th>40.2</th>
<th>72.9</th>
<th>125.2</th>
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<tr>
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<td></td>
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<td>07/2020</td>
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<tr>
<td>12/2019</td>
<td></td>
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<tr>
<td>02/2020</td>
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<tr>
<td>03/2020</td>
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</tr>
</tbody>
</table>

COVID Pandemic

Patient gets COVID-19

Courtesy of Nikhil C Munshi, MD
Case Presentation - Dr Munshi: A 63-year-old man with t(11;14) myeloma

- 63 year old man. Very healthy. He has run a number of Boston marathons; however, April 2017, while running the Boston marathon he felt extremely exhausted and almost had a syncopal attack.

- Dx Myeloma with t(11;14)

- Complex cytogenetics – 7 with complex karyotype including an unbalanced t(11;14)(q13;q32), monosomy 13, and loss of 17p.

- 43,X−Y, −1,add(3)(q27),del(4)(p14p16),add(6)(q25),add(7)(p22),13,der(14)t(11;14)(q13;q32),der(15)t(1;15)(q12;q26.1),i(17)(q10)[7]/46,XY[13]

Courtesy of Nikhil C Munshi, MD
Case Presentation - Dr Munshi: A 63-year-old man with t(11;14) myeloma (continued)

- 07/2017 - RVDx6 followed by HDT and ASCT – PR and RD maintenance
- 02/2018 - relapsed - Daratumumab with PD
- 05/2018 - Venetoclax with carfilzomib and Dex.
- 07/2019 - progressive disease – eligible for CAR-T protocol
  Following lymphodepletion CAR-T infusion was postponed due to high grade fever with High CRP.
  Fever eventually considered due to aggressive myeloma
  He did develop CRS and required one infusion of Toci
Case Presentation - Dr Munshi: A 63-year-old man with t(11;14) myeloma (cont)

- Started on Elotuzumab, Thalidomide and Dex
- Excellent response sustained over 15 months

Ref. Range
11/2019

<table>
<thead>
<tr>
<th>Lambda FLC(mg/L)</th>
<th>7/02/19</th>
<th>7/19/19</th>
<th>8/2019</th>
<th>9/2019</th>
<th>10/2019</th>
</tr>
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<td>10,079.8</td>
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<td>24.9</td>
<td>11.8</td>
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<td>117.7 (H)</td>
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7/10/2019
CAR-T Infusion

07/03/2019 08/08/2019

Courtesy of Nikhil C Munshi, MD
Faculty Case Appendix
Case Presentation - Dr Maloney: A 50-year-old man with non-GCB type, double-hit DLBCL

PATH: DLBCL, non GCB type, not double hit, CD19 positive

Prior treatments:
- R-CHOP x 6 through 10/2017.
- PET: good response but slight FDG uptake in cervical nodes that progressed 1 mo
- R-ICE x 2 and referred to Fred Hutch BMT program for Autologous HCT.
- Staging: showed new cervical and inguinal LN and referred to IMTX.

Cells collected for axicabtagene ciloleucel.
Bridging not required.
PET/CT (see scan) showed minimal cervical and inguinal LN
Cy/Flu lymphodepletion.
Admitted for CAR-T infusion 3/21
  - Day 6- grade 3 NT with global aphasia
  - Day 7- CRS grade 2
  - Toci x 1, Dex (10 mg) x 9 with resolution.
  - Discharged back to outpatient on Day +12.
Day 30 PET/CT showed CR- (see image) Deauville score 2.
Remains in CR to date.
Case Presentation - Dr Maloney: A 50-year-old man with non-GCB type, double-hit DLBCL (continued)

Pre axicabtagene ciloleucel

Post axicabtagene ciloleucel

Courtesy of David G Maloney, MD, PhD
Case Presentation – Dr Jacobson: A 66-Year-Old Man with Refractory Chronic Lymphocytic Leukemia

66 year-old man with refractory del17p CLL c/b Richter’s transformation

• Diagnosed 8/2018 with abdominal pain, bulky LAD, cytopenias and a lymphocytosis; flow c/w CLL; IGVH unmutated; FISH with del17p
• 8/2018-11/2018: ibrutinib monotherapy with PD
• 12/2018-2/2019: venetoclax with SD
• 2/2019-4/2019: venetoclax and ibrutinib with no response

• Enrolled to receive CAR T-cells on a clinical trial when optional LN biopsy revealed evidence of Richter’s transformation
• 6/10/19: received CAR T-cells under a single patient compassionate use IND
  • Course c/b grade 3 CRS (hypotension requiring pressors) but no ICANS. Toci and dex were given for CRS
  • Discharged home on day +13

Courtesy of Caron Jacobson, MD
Case Presentation – Dr Jacobson: A 66-Year-Old Man with Refractory Chronic Lymphocytic Leukemia (continued)

66 year-old man with refractory del17p CLL c/b Richter’s transformation

- Diagnosed 8/2018 with abdominal pain, bulky LAD, cytopenias and a lymphocytosis; flow c/w CLL; IGVH unmutated; FISH with del17p
- 12/2018-2/2019: venetoclax with SD
- Enrolled to receive CAR T-cells on a clinical trial when optional LN biopsy revealed evidence of Richter’s transformation
- 6/10/19: received CAR T-cells under a single-patient compassionate-use IND
  - Course c/b grade 3 CRS (hypotension requiring pressors) but no ICANS. Toci and dex were given for CRS
  - Discharged home on day +13

Day 30 bone marrow and CT assessment consistent with a CR in the marrow and a PR by CT

At 24 months, CBCD remains within normal limits and CT scans show further decrease in LAD c/w an ongoing PR

Courtesy of Caron Jacobson, MD
Case Presentation - Dr Munshi: A patient with multiple myeloma

5/8/2015  Initial Diagnosis
IgG Kappa Multiple myeloma

5/12/2015 - 9/8/2016  RVD -> RD maintenance
10/2016 - 1/2017  Carfilzomib+Pomalidomide+Dexamethasone
1/23/2017 - 4/5/2017  Daratumumab+Pomalidomide+Dexamethasone
4/5/2017 - 8/2017  Elotuzumab+Pomalidomide+Dexamethasone
8/2017 - 8/30/2017  Radiation - XRT to Pancreas
8/2017 - 12/23/2017  Carfilzomib+Pomalidomide+Dexamethasone

Courtesy of Nikhil C Munshi, MD
Case Presentation - Dr Munshi: A patient with multiple myeloma (continued)

Response to Retreatment

|        |        |        |        |        |        |        |        |        |
|--------|--------|--------|--------|--------|--------|--------|--------|
| 1st Resp | 2nd Resp | 1st PFS | 2nd PFS | 1st CRS | 2nd CRS | 1st Dose | 2nd Dose | 1st CRP-Day | 2nd CRP-Day | 1st Ferritin | 2nd Ferritin |
| 2       | SD     | VGPR   | 6 mos   | 12mos   | None   | 1- D4   | 150     | 45 - D6     | 216 - D6     | 23         | 1693        |

Free Kappa LC ng/mL

1st CAR-T Infusion

2nd CAR-T Infusion

01/2018 08/08/2019

Courtesy of Nikhil C Munshi, MD
A Conversation with the Investigators: Acute Myeloid Leukemia and Myelodysplastic Syndromes

Wednesday, July 14, 2021
5:00 PM – 6:00 PM ET

Faculty
Courtney D DiNardo, MD, MSCE
Gail J Roboz, MD
Eytan M Stein, MD

Moderator
Neil Love, MD
Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.