The Future of in Cancer

Matthew Lunning D.O.
Associate Professor
OptumHealth Education Medical Director Forum
5/15/19
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Affiliations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td>Amgen; BMS; Celgene; Curis; Juno; Janssen; Pharmacyclics; TG Therapeutics</td>
</tr>
<tr>
<td>Consultancy</td>
<td>AbbVie/Pharmacyclics; Bayer; Cardinal Health; Celgene/Juno; Dava; Janssen; Gilead/Kite; Novartis; Portola; Seattle Genetics; Spectrum; TG Therapeutics; Vanium; Verastem</td>
</tr>
<tr>
<td>Employment</td>
<td>NONE</td>
</tr>
<tr>
<td>Major Stock Holder</td>
<td>NONE</td>
</tr>
<tr>
<td>Speaker Bureau</td>
<td>NONE</td>
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Objectives

1. Discuss the safety, efficacy, and role of chimeric antigen receptor (CAR) T-cell therapy in cancer treatment

2. Outline guideline recommendations for patient selection, administration of treatment, and monitoring and management of toxicities with regard to CAR T-cell therapy

3. Discuss current and future strategies for applying CAR T-cell therapy and managing treatment-related complications
Cancer is Smart!

<table>
<thead>
<tr>
<th>Low Immunogenicity</th>
<th>Tumor Treated as Self Antigen</th>
<th>Antigenic Modulation</th>
<th>Tumor-Induced Immune Suppression</th>
<th>Tumor-Induced Privileged Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>No peptide: MHC ligand; No adhesion molecules; No co-stimulatory molecules</td>
<td>Tumor antigens taken up and presented by APCs in absence of co-stimulation to tolerise T cells</td>
<td>Antibody against tumor cell-surface antigens can induce endocytosis and degradation of the antigen. Immune selection of antigen-loss variants</td>
<td>Factors (e.g., TGF-β) secreted by tumor cells inhibit T cells directly. Induction of regulatory cells by tumors</td>
<td>Factors secreted by tumor cells create a physical barrier to the immune system</td>
</tr>
</tbody>
</table>

![Image](image_url)
Glioblastoma

XRT + Temozolomide

Proportion surviving vs Survival in months

Metastatic Pancreatic Cancer

Conroy T et al. NEJM 2011.
1st Relapsed Acute Lymphoblastic Leukemia

5-year OS = 7%

2P < 0.00001

Time (years)

Percentage

Age <20: 12%
Age 20-34: 7%
Age 35-49: 4%

Age 50+: 3%

Relapsed or Refractory Diffuse Large B-cell Lymphoma

Risk of Disease Equals Potential Reward
Can we Get Smarter?

**Target the Tumor**
- Chemotherapy and AutoHCT
- Monoclonal Antibodies
  - Rituximab and Herceptin
- Antibody-Drug Conjugates
  - Brentuximab
- Tumor Checkpoint Blockade – PD-L1

**Target the Host**
- Vaccination
  - Gardasil (anti-HPV16&18)
  - Sipuleucel-T (anti-PSA)
- Immune Modulators
  - Lenalidomide
- Immune Checkpoint Blockade
  - PD1, CTLA4

**Target Both Tumor & Host**
- Allogeneic HCT
- Bispecific Antibodies
  - Blinatumomab
- CAR T Therapy

CAR-T Working Group
Shifting Gears: What is a CAR T-cell?
Normal T-cell role

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells / APC)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (immune and cancer cells)
T-cells Secrete Cytokines
T-cell Immunology

CD4+ → MHC class 2
CD8+ → MHC class 1

AICD = Activation induced cell death

Building Blocks to CAR-T

CD4+ → MHC class 2
CD8+ → MHC class 1

AICD = Activation induced cell death

Evolution of CAR-T

TAA= Tumor associated antigen

Geyer et al. Cytotherapy 2016
Evolution of CAR-T

TAA = Tumor associated antigen

Geyer et al. Cytotherapy 2016
The Target and Why

All Targets

Pro B → Pre B → Immature B cell → Mature B cell → Activated Memory → Long life plasma cell

BCMA

Manufacturing CAR T-cells
Many Hands

Blood collection

T cell isolation and activation

T cell transduction

T cell expansion

Bead removal

T cell formulation

T cell infusion into preconditioned patient

T cell manufacturing workflow
Many Days

Leukapheresis Collection and Transportation

- Apheresis
- Transport
- Central Manufacturing Facility

Manufacturing Process

- Enrichment
- Activation
- Transduction
- Expansion
- Harvest Cryopreserve

2 days → 1 day → 4-7 days

Lot Release and Transport to Clinical Site

- Lot Release
- Transport
- Infusion

Roberts et al. Leukemia & Lymphoma 2017
Patient level Popcorn
Provider level
WMD

Cancer
Current Role of CAR-T in Cancer
# A Short List

<table>
<thead>
<tr>
<th>Academic Group</th>
<th>Company (Drug)</th>
<th>Co-Stimulatory Domain</th>
<th>Vector Delivery</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPenn</td>
<td>Novartis (Tisagenlecleucel) (CTL019)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>ALL, CLL, DLBCL, FL</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>Juno (JCAR017)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>ALL, CLL, various B-cell malignancies</td>
</tr>
<tr>
<td>NCI (NIH)</td>
<td>Kite, A Gilead Company (Axicabtagene Ciloleucel) (KTE-C19)</td>
<td>CD28</td>
<td>Retroviral</td>
<td>DLBCL ALL, MCL</td>
</tr>
<tr>
<td>MDACC</td>
<td>Ziopharm/Intrexon</td>
<td>CD28 → 4-1BB</td>
<td>Transposon/transposase</td>
<td>B-cell malignancies</td>
</tr>
<tr>
<td>Institute Pasteur</td>
<td>Cellectis/Pfizer (UCART19)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>ALL, CLL, AML, MM</td>
</tr>
<tr>
<td>Baylor</td>
<td>Bellicum (BPX-401)</td>
<td>MyDBB + CD40</td>
<td>Retroviral</td>
<td>Various</td>
</tr>
<tr>
<td>Dartmouth</td>
<td>Cardio3</td>
<td>DAP-10</td>
<td>Retroviral</td>
<td>AML, MDS, MM</td>
</tr>
</tbody>
</table>
WMD

Hyperuricemia
Transfusions

Hyperkalemia

Neutropenia
Infections

DLBCL
CAR T-cell in Rel/Ref DLBCL

<table>
<thead>
<tr>
<th>CAR-T Product</th>
<th>Viral Vector</th>
<th>Costimulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axi-Cel (KiTE/Gilead)</td>
<td>Gamma-retrovirus</td>
<td>CD28</td>
</tr>
<tr>
<td>Tisagenlecleucel (Novartis)</td>
<td>Lentivirus</td>
<td>41BB</td>
</tr>
<tr>
<td>Liso-Cel (JUNO/Celgene)</td>
<td>Lentivirus</td>
<td>41BB</td>
</tr>
</tbody>
</table>
## Efficacy of Axi-Cel ZUMA-1

<table>
<thead>
<tr>
<th></th>
<th>N=101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Follow Up (Months)</td>
<td>27.1</td>
</tr>
<tr>
<td><strong>Best Overall Response Rate (ORR; %)</strong></td>
<td></td>
</tr>
<tr>
<td>Refractory &gt; /+ 2 lines</td>
<td>83%</td>
</tr>
<tr>
<td>Relapse within 12 months post Auto txp</td>
<td>53%</td>
</tr>
<tr>
<td>Double expressers (MYC, BCL2, and BCL6)</td>
<td></td>
</tr>
<tr>
<td>Duration of response (DOR; Months)</td>
<td>72%</td>
</tr>
<tr>
<td>Median Progression Free Survival (PFS; Months)</td>
<td>68%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.8 (4.2 to NE)</td>
</tr>
<tr>
<td></td>
<td>5.9 (95% CI 3.3 to 15)</td>
</tr>
</tbody>
</table>

Neelapu S et al. Lancet Oncol 2019
Duration of Response post Axi-cel (ZUMA-1)

Median duration of response 11.1 months (95% CI 4.2-NE)
Overall Survival of Axi-Cel (ZUMA-1)

Neelapu S et al. Lancet Oncol 2019
## Efficacy Of Tisagenlecleucel (JULIET)

<table>
<thead>
<tr>
<th></th>
<th>N=93</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Follow Up (Months)</td>
<td>14.0</td>
</tr>
<tr>
<td><strong>ORR CR</strong></td>
<td></td>
</tr>
<tr>
<td>Best ORR (%)</td>
<td>52% 40%</td>
</tr>
<tr>
<td>12 months post response (%)</td>
<td></td>
</tr>
<tr>
<td>Relapse free survival</td>
<td>65%</td>
</tr>
<tr>
<td>Relapse free in CR</td>
<td>79%</td>
</tr>
</tbody>
</table>

Shuster S et al. NEJM 2019
Duration of Remission Of Tisagenlecleucel (JULIET)

Shuster S et al. NEJM 2019
Overall Survival of Tisagenlecleucel (JULIET)

Shuster S et al. NEJM 2019
Liso-cel (Not FDA approved)

- Late stage clinical trial (TRANSCEND)
- How is Liso-cel different?
  - Individually formulated CD4 and CD8 suspensions through lentiviral transduction
  - Low ALC requirement
  - Flat dosing
    - 1:1 ratio of CD4:CD8
  - 41BB costimulatory

Abramson J et al. EHA 2018
TRANSCEND: CORE

- DLBCL-NOS
- Transformed FL
- High grade B-cell lymphoma (DH/TH)

- ECOG 0-1
- No ALC minimum

Abramson J et al. EHA 2018
TRANSCEND Cohort/Dose

Core group
- DLBCL-NOS
- Transformed FL
- High grade B-cell lymphoma (DH/TH)
- ECOG 0-1
- No ALC minimum

Dosing Levels
- $5 \times 10^7$ cells single dose (DL1S)
- $5 \times 10^7$ cells double dose (DL1D)
- $1 \times 10^8$ cells single dose (DL2S)

Abramson J et al. EHA 2018
TRANSCEND
Pivotal Cohort

FOCUS ON:

Core + DL2S
Outcomes, unknown results of accrued PIVOTAL cohort

Abramson J et al. EHA 2018
Liso-Cel Efficacy (Transcend)

<table>
<thead>
<tr>
<th>Core &amp; DLS2</th>
<th>N=37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best ORR</td>
<td>80%</td>
</tr>
<tr>
<td>Best CR</td>
<td>55%</td>
</tr>
<tr>
<td>ORR @ 6 months</td>
<td>50%</td>
</tr>
<tr>
<td>CR @ 6 months</td>
<td>50%</td>
</tr>
</tbody>
</table>

Abramson J et al. EHA 2018
Axi-cel Post Approval
Gloves On Vs Gloves Off
Excluded From ZUMA-1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt; 75</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Active DVT/PE</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Prior CD19 or CAR T cell therapy</td>
<td>24 (8)</td>
</tr>
<tr>
<td>GFR &lt; 60</td>
<td>22 (8)</td>
</tr>
<tr>
<td>History of CNS lymphoma</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Symptomatic pleural effusion</td>
<td>11 (4)</td>
</tr>
<tr>
<td>LVEF &lt; 50%</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Prior allogeneic SCT</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>
Let’s Box

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up, months</td>
<td>3.9</td>
<td>15.4</td>
</tr>
<tr>
<td>Day 30 ORR, N (%)</td>
<td>238</td>
<td>191 (80) N/A</td>
</tr>
<tr>
<td>Day 30 CR, N (%)</td>
<td></td>
<td>113 (47) N/A</td>
</tr>
<tr>
<td>Best ORR at Day 90, N (%)</td>
<td>248(^a)</td>
<td>201 (81) 89 (82)</td>
</tr>
<tr>
<td>Best CR at Day 90, N (%)</td>
<td>142 (57)</td>
<td>63 (58)</td>
</tr>
</tbody>
</table>

\(^a\) Median follow-up time for the best ORR was 248 days

Nastoupil L et al. ASH 2018
## Too Sick To Fight?

<table>
<thead>
<tr>
<th>Variables</th>
<th>CR @ 3 month N (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 vs. &gt;60</td>
<td>37 (51) vs. 52 (64)</td>
<td>0.11</td>
</tr>
<tr>
<td>DLBCL vs. PMBCL vs. TFL</td>
<td>59 (58) vs. 4 (40) vs. 26 (63)</td>
<td>0.41</td>
</tr>
<tr>
<td>COO GCB vs. ABC</td>
<td>50 (62) vs. 30 (53)</td>
<td>0.29</td>
</tr>
<tr>
<td>DHL/THL vs. Not</td>
<td>19 (59) vs. 65 (57)</td>
<td>0.77</td>
</tr>
<tr>
<td>IPI 0-2 vs. 3-5</td>
<td>45 (58) vs. 43 (58)</td>
<td>0.96</td>
</tr>
<tr>
<td>Bridging therapy Yes vs. No</td>
<td>40 (53) vs. 49 (64)</td>
<td>0.17</td>
</tr>
<tr>
<td>Tocilizumab Yes vs. No</td>
<td>51 (58) vs. 38 (59)</td>
<td>0.86</td>
</tr>
<tr>
<td>Steroids Yes vs. No</td>
<td>49 (58) vs. 40 (61)</td>
<td>0.71</td>
</tr>
<tr>
<td>ICU Admission Yes vs. No</td>
<td>26 (52) vs. 63 (61)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Nastoupil L et al. ASH 2018
## Fittest Fighters?

<table>
<thead>
<tr>
<th>Variables</th>
<th>CR @ 3 month N (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female vs. male</td>
<td>39 (72) vs. 50 (51)</td>
<td>0.009</td>
</tr>
<tr>
<td>ECOG 0-1 vs. ≥ 2</td>
<td>82 (62) vs. 7 (35)</td>
<td>0.024</td>
</tr>
<tr>
<td>Relapsed vs. primary refractory/refractory</td>
<td>27 (79) vs. 24 (47)/38 (56)</td>
<td>0.011</td>
</tr>
<tr>
<td>Non-bulky vs. bulky (≥ 10cm)</td>
<td>76 (62) vs. 13 (42)</td>
<td>0.040</td>
</tr>
<tr>
<td>Met eligibility for ZUMA-1 vs. not</td>
<td>62 (65) vs. 27 (47)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Nastoupil L et al. ASH 2018
Should We Keep Fighting?

Nastoupil L et al ASH 2018; Neelapu et a. Lancet Oncol 2019
Who Should Get CAR-T?
The Right Disease And Right Situation
Who Can Weather the Fall Out?

Baseline Tests

1. Transthoracic echocardiogram
2. Pulse oximetry
3. CBC, CMP, and DIC panel
4. Lactate dehydrogenase (LDH)
5. Pre-CART disease burden assessment
Selection of a Specific CAR-T
Finding a CAR T Site
ASBMT ➔ ASTCT
Within Our CAR T Site

Case Manager Process and Checklist:
  • Binder specific to each product and diagnosis
  • Overall Checklist
  • Details of each stage of process with screen shots:
    • Eligibility/Consult
    • Evaluation
    • Insurance
    • Collection
    • Enrollment, Ordering, & PO process
    • Chemotherapy
    • Infusion
    • Discharge
    • Long-Term Follow-up
Before the CAR T

- Risk Evaluation and Mitigation Strategy (REMS) training
- CAR T education…education….education
- Tocilizumab supply process and documentation
- Policies for each product (includes Foundation for the Accreditation of Cellular Therapy (FACT) requirements)
  - Includes Wallet Card process and tocilizumab process
- Patient Consents for each product
- Treatment Plans for each product and diagnosis
- Pharmacy iVents
  - Patient specific notes used by pharmacists to communicate information
    - Dose and location of rescue agents
    - Other pertinent patient and product information
  - Crosses inpatient and outpatient care areas
  - Visible to all pharmacists viewing the EMR
- Formal Patient/Caregiver Education
  - Handouts, web-based, 1:1
  - Documentation via Template with teaching points
- On-Call/Triage
  - CAR T trained staff
  - Who to call and when to call
- IT

Courtesy of Kim Schmit-Pokorny
# Our Patient Tracker

<table>
<thead>
<tr>
<th>Date of First Contact</th>
<th>Place on Waitlist</th>
<th>Patient Name</th>
<th>Referred By</th>
<th>Patient City of Residence</th>
<th>Short Disease History</th>
<th>MR Number</th>
<th>Investigator</th>
<th>Case Manager or Research Coordinator</th>
<th>Date of Consult</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/4/2018</td>
<td>1</td>
<td>Test Patient</td>
<td>John Doe</td>
<td>Anywhere, USA</td>
<td>DLBC</td>
<td>123456</td>
<td>Bieman</td>
<td>Tawny</td>
<td>1/4/2018</td>
</tr>
</tbody>
</table>

**Blue = Demographic Information**  
**Green = Study Information**  
**Yellow = Insurance Information**  
**Gold = Treatment Plan Dates**
After Selection of a CAR-T construct
Bridging Therapy

- Insurance
- Need to bridge?
  - Yes or No
- If Yes
  - Prior treatments (R-CHOP; ICE)
- Cell of origin (Hans)
  - GCB—Bendamustine or Gemcitabine
  - Non-GCB—Ibrutinib or Lenalidomide
- Late bridging
  - Steroids
  - Low dose oral Cytoxan, etoposide, prednisone
  - BOOM-BOOM (XRT)
Lymphodepletion

• Cy/Flu vs Benda vs None
  • Known the dose
  • Know when not to use (Tisagenlecleucel)

• Renal
  • Know the CrCl and how you will handle the fludarabine dosing

• Timing
  • Know the current EGOC & volume of disease
  • Know the product is ready
  • Know you have beds
WMD

CRS = Cytokine Release Syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome
## “Old” CRS Grading

<table>
<thead>
<tr>
<th>Grading System</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE version 4.0</td>
<td>Mild reaction; infusion interruption not indicated; intervention not indicated</td>
<td>Therapy or infusion interruption indicated; treatment required; administration of additional antiemetics or supportive care (CRS) required</td>
<td>Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical monitoring (eg, renal impairment, pulmonary infiltrate)</td>
<td>Life-threatening consequence or death; intervention needed</td>
</tr>
<tr>
<td>CTCAE version 5.0</td>
<td>Fever, chills, or constitutional symptoms</td>
<td>Hypotension responding to fluids; Hypotension managed with one pressor; Hypotension requiring &lt; 40% FIO2; Symptoms require and respond to moderate intervention</td>
<td>Hypotension managed with one pressor; Hypotension requiring &gt; 40% FIO2; Symptoms require and respond to aggressive intervention</td>
<td>Life-threatening consequence or death; intervention needed</td>
</tr>
<tr>
<td>Lee criteria</td>
<td>Symptoms are not life-threatening and require no intervention</td>
<td>Hypotension responsive to fluid bolus or low dose of one vasopressor or Grade 2 organ toxicity</td>
<td>Life-threatening complication such as hypotension requiring high-dose vasopressors</td>
<td>Life-threatening symptoms:</td>
</tr>
<tr>
<td>Penn criteria</td>
<td>Mild reaction; Treated with supportive care, such as antipsychotics, antineoplastics, anesthetics</td>
<td>Moderate reaction; Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition</td>
<td>Hospitalization for management of CRS-related symptoms, including neuropsychiatric fever and need for ICU therapy (not including fluid resuscitation for hypotension)</td>
<td>Life-threatening symptoms:</td>
</tr>
<tr>
<td>MSKCC criteria</td>
<td>Mild symptoms requiring observation or supportive care only (eg, antipsychotics, antineoplastics, pain medication)</td>
<td>Hypotension requiring any vasopressors &gt; 24 h</td>
<td>Hypotension requiring any vasopressors ≥24 h</td>
<td>Life-threatening symptoms</td>
</tr>
<tr>
<td>CAPR regimen</td>
<td>Hypotension or dyspnea requiring supplemental oxygen &gt; 40%</td>
<td>Hypotension refractory to high-dose vasopressors or multiple vasopressors</td>
<td>Hypotension refractory to high-dose vasopressors or multiple vasopressors</td>
<td>Life-threatening symptoms</td>
</tr>
<tr>
<td>CAPRIQG criteria</td>
<td>Temperature ≥38°C</td>
<td>Hypotension responding to IV fluids or low dose vasopressor</td>
<td>Hypotension refractory to high-dose vasopressors or multiple vasopressors</td>
<td>Life-threatening symptoms</td>
</tr>
</tbody>
</table>

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Lee D et al. BBMT 2018
## Old Neurotoxicity Grading

<table>
<thead>
<tr>
<th>Grading System</th>
<th>Adverse Event Term</th>
<th>Neurotoxicity Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 CTCAE v5.0</td>
<td>Encephalopathy</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td></td>
</tr>
<tr>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Seizure</td>
<td>Brief partial seizure and no loss of consciousness</td>
<td>Brief generalized seizure</td>
<td>New-onset seizures (partial or generalized); multiple seizures despite medical intervention</td>
<td></td>
</tr>
<tr>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Dyshasia</td>
<td>Awareness of receptive or expressive characteristics; not impairing ability to communicate</td>
<td>Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously</td>
<td>Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly</td>
<td></td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>Tremor</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td></td>
</tr>
<tr>
<td>CARTOX criteria</td>
<td>Headache</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self-care ADL</td>
<td></td>
</tr>
<tr>
<td>[12] Neurologic Assessment Score (CARTOX-10)</td>
<td>Confusion</td>
<td>Mild disorientation</td>
<td>Moderate disorientation; limiting instrumental ADL</td>
<td>Severe disorientation; limiting self-care ADL</td>
<td></td>
</tr>
<tr>
<td>Elevated ICP</td>
<td>Depressed level of consciousness</td>
<td>Decreased level of alertness</td>
<td>Sedation; slow response to stimuli; limiting instrumental ADL</td>
<td>Life-threatening consequences; urgent intervention indicated; difficult to arouse</td>
<td></td>
</tr>
<tr>
<td>Seizures or motor weakness</td>
<td>Cerebral edema</td>
<td>7-9 (mild impairment)</td>
<td>0-2 (severe impairment)</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td></td>
</tr>
<tr>
<td>CARTOX criteria</td>
<td>[12] Neurologic Assessment Score (CARTOX-10)</td>
<td>Elevated ICP</td>
<td>N/A</td>
<td>Patient in critical condition, and/or obtunded and cannot perform assessment of tasks</td>
<td></td>
</tr>
<tr>
<td>Seizures or motor weakness</td>
<td>N/A</td>
<td>N/A</td>
<td>Stage 1-2 papilledema, or CSF opening pressure ≤20 mmHg</td>
<td>Stage 3-5 papilledema, or CSF opening pressure ≥20 mmHg, or cerebral edema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generalized seizures or convulsive or nonconvulsive status epilepticus, or new motor weakness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Reported Toxicity of Axi-Cel (ZUMA-1)

<table>
<thead>
<tr>
<th></th>
<th>CRS</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>93%</td>
<td>64%</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>11%</td>
<td>32%</td>
</tr>
<tr>
<td>Median Time to onset (range) in days</td>
<td>2 (1-12)</td>
<td>5 (1-17)</td>
</tr>
<tr>
<td>Median Time to Resolution</td>
<td>8 days</td>
<td>17 days</td>
</tr>
<tr>
<td>Tocilizumab Usage</td>
<td></td>
<td>43%</td>
</tr>
<tr>
<td>Dexamethasone Usage</td>
<td></td>
<td>27%</td>
</tr>
</tbody>
</table>

Neelapu S et al. NEJM 2018; Neelapu S et al. Lancet Oncol 2019; NT=CTAE 4.03
# Reported Toxicity of Tisagenlecleucel (JULIET)

<table>
<thead>
<tr>
<th></th>
<th>CRS*</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>58%</td>
<td>21%</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>Median Time to onset (range) in days</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Median Time to Resolution</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Tocilizumab Usage</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Dexamethasone Usage</td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

*CRS = UPENN criteria; NT = CTAE 4.03

Shuster S et al. NEJM 2019
# Reported Toxicity of Liso-Cel (TRANSCEND)

<table>
<thead>
<tr>
<th></th>
<th>Core &amp; DL2S or Full</th>
<th>CRS</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td></td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td></td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Median Time to onset (range) in days</td>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Median Time to Resolution</td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tocilizumab Usage (FULL)</td>
<td></td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>Dexamethasone Usage</td>
<td></td>
<td></td>
<td>21%</td>
</tr>
</tbody>
</table>

Abramson J et al. EHA 2018; CRS per Lee D et al; NT=CTAE 4.03; NR=Not reported
“New” CRS Grading:
Starts with Fever

<table>
<thead>
<tr>
<th>CRS Parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever* With Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula(^1) or blow-by</td>
<td>Requiring high-flow nasal cannula(^1), facemask, nonrebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

\(^1\) temperature ≥38°C
ICANS Grading: Starts with ICE

<table>
<thead>
<tr>
<th>Neurotoxicity Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE score*</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0 (patient is unarousable and unable to perform ICE)</td>
</tr>
<tr>
<td>Depressed level of consciousness†</td>
<td>N/A</td>
<td>N/A</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td>Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min); or Repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor findings‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging§</td>
<td>Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing’s triad</td>
</tr>
</tbody>
</table>

ICANS = Immune effector cell-associated neurotoxicity syndrome

Lee D et al. BBMT 2018
Post CAR-T Infusion
Post CAR-T

Early Post CAR-T
- Mini Mental Status Exam (30) or ICE (10)
- CBC/CMP
- DIC panel
- Ferritin
- CRP

Long-term Post CAR-T
- Prophylaxis (Acyclovir, Levofloxacin, Fluconazole)
- Caregiver (24 hours)
- Vaccinations
- No driving for 2 months (research opportunity)
Management of Toxicity: Experience Matters

Grade

Diagram with pendulum and gradient bar indicating grade.
Management of CRS

Fever
Fatigue
Nausea/Vomit
Myalgias
Hypotension

Tocilizumab
Dexamethasone

Grade

Tocilizumab—IL-6 receptor mAB

Hypotension
Resp dysfunction
Renal dysfunction
Liver dysfunction

Abramson ASH 2017; Neelapu ASH 2017; Schuster ASH 2017
Management of CRS

Fever
Fatigue
Nausea/Vomit
Myalgias
Hypotension

Tocilizumab

Dexamethasone

Grade

Hypotension
Resp dysfunction
Renal dysfunction
Liver dysfunction

Abramson J et al. ASH 2017; Neelapu S et al. ASH 2017; Schuster S et al. ASH 2017
Management of ICANS

Shake of the Hand

Tocilizumab  Dexamethasone

?  

Tremor  Agitation  Aphasia  Weakness

Grade

Coma  Seizures  Herniation

ICANS = Immune effector cell-associated neurotoxicity syndrome

Abramson J et al. ASH 2017; Neelapu S et al. ASH 2017; Schuster S et al. ASH 2017
Management of ICANS

- Tremor
- Agitation
- Aphasia
- Weakness

Dexamethasone

*Tocilizumab—if concurrent or going CRS*

Grade

- Coma
- Seizure
- Herniation

Abramson ASH 2017; Neelapu ASH 2017; Schuster ASH 2017
Management of ICANS

Prophylaxis

Tocilizumab

Dexamethasone

X Prophylaxis

? Prophylaxis

Tremor
Agitation
Aphasia
Weakness

Grade

Coma
Seizure
Herniation

Abramson ASH 2017; Neelapu ASH 2017; Schuster ASH 2017
### Late Infectious Toxicities

**B-cell aplasia with hypogammaglobulinemia: Use of IVIG**

<table>
<thead>
<tr>
<th>Patient</th>
<th>SAE Start Time Post Axi-cel Infusion (months)</th>
<th>Grade</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.7</td>
<td>3</td>
<td>Lung infection</td>
</tr>
<tr>
<td>2</td>
<td>16.7</td>
<td>3</td>
<td>Recurrent viral upper respiratory infection</td>
</tr>
<tr>
<td></td>
<td>18.6</td>
<td>3</td>
<td>Rotavirus infection</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
<td>3</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>7.2</td>
<td>4</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>7.2</td>
<td>3</td>
<td>Left lower lobe pneumonia</td>
</tr>
<tr>
<td></td>
<td>7.2</td>
<td>3</td>
<td>Atrial fibrillation with rapid ventricular response</td>
</tr>
<tr>
<td>5</td>
<td>9.1</td>
<td>3</td>
<td>Lung infection</td>
</tr>
<tr>
<td></td>
<td>9.2</td>
<td>3</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>6</td>
<td>7.1</td>
<td>3</td>
<td>Influenza B infection</td>
</tr>
<tr>
<td>7</td>
<td>7.9</td>
<td>3</td>
<td>Infection other - pneumonia</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
<td>1</td>
<td>Muscle weakness right side</td>
</tr>
<tr>
<td></td>
<td>6.7</td>
<td>2</td>
<td>Slurred speech</td>
</tr>
<tr>
<td>9</td>
<td>9.3</td>
<td>3</td>
<td>Heart failure</td>
</tr>
<tr>
<td>10</td>
<td>14.4</td>
<td>3</td>
<td>Community acquired pneumonia</td>
</tr>
</tbody>
</table>

Neelapu S et al. ASH 2017
The Hematologic Double Dip
Future Strategies for CAR-T
CAR-T in 1st Relapse of DLBCL

No significant differences in PFS and OS were observed according to:
- sAA-IPI
- Relapse <12 months
- Primary refractory disease vs relapse ≥12 months
- Type of salvage therapy

PFS rate of 49% (95% CI: 34-62)
3-yr OS rates of 54% (95% CI: 39-68)

PBR Me ASAP?

Polatuzumab* + Bendamustine Rituximab (PBR)

Sehn L et al. ASH 2017

*CD79b ADC
Prediction of Toxicities*

Locke F et al. ASH 2017; *Product Axi-cel
Access, Referrals and other drugs

DLBCL

CART
1. Current clinical trials involving chimeric antigen therapy (CAR) T-cell therapy various hematologic malignancies target the following antigens except:

A. CD19
B. CD20
C. CD22
D. CD28
Question 2

2. Prior to the delivery of cyclophosphamide and fludarabine based lymphodepleting chemotherapy, a change in this may necessitate a dose reduction:

A. Creatinine clearance
B. ECOG performance status
C. Absolute neutrophil count (ANC)
D. Hemoglobin
Question 3

3. In monitoring for cytokine release syndrome (CRS) these factors are taken into consideration except:

A. Temperature  
B. Oxygen saturation  
C. Blood pressure  
D. Pain score
Question 4

4. In the treatment of neurotoxicity related to CAR-T therapy when may it appropriate to consider the use of tocilizumab?

A. At onset of fever  
B. When there established concurrent CRS  
C. At the onset of grade 1 neurotoxicity  
D. At the resolution of grade 1 neurotoxicity
Question 5

Axi-cel is commonly delivered in the outpatient setting?

A. True  
B. False