Chimeric Antigen Receptor (CAR) T-Cells for the Treatment of B-Cell Malignancies: Navigating the Road to Remission

Jilan Kubusek, PharmD, BCPS, BCOP
Clinical Pharmacist,
Hematology/Oncology/BMT
Mayo Clinic Hospital, Rochester
Learning Objectives

• Review the different approaches of immuno-oncology focusing on CAR-T and its place in therapy
• Describe the process of CAR-T therapy and review preliminary data for the treatment of B-cell malignancies
• Discuss the etiology and off-label treatment of the complications of CAR-T therapy of cytokine release syndrome (CRS) and neurotoxicity
Hallmarks of Cancer

- Resist cell death
- Enable replicative immortality
- Induce angiogenesis
- Activate invasion and metastasis
- Capacity to sustain proliferative signaling
- Avoid growth suppressors

Hanahan D. Cell. 2000; 100: 57-70
Cancer Treatment

• Conventional Chemotherapy
  – Targets fast growing cells
  – Classified by their mechanism of cytoxic kill

• Targeted therapies
  – Targets tumor cell markers
  – Monoclonal antibodies (mabs)
    • Induces complement dependent and antibody mediated cellular death
  – Small molecule inhibitors (nibs)
    • Block signaling pathways preventing cellular proliferation
Concepts in immuno-oncology

- Focuses on cancer as a systemic disease
  - Interaction between the host’s immunosurveillance and the cancer’s microenvironment
- Ability to avoid immune destruction
- Potential for chronic inflammation which promotes tumor growth rather than elimination

Hanahan D. Cell. 2011; 100: 57-70
Phases of Immunosurveillance

**Elimination**
- Immunogenic tumor
- Immunocompetent host
- Tumor elimination

**Equilibrium**
- Tumor regrowth
- Repeated activation of the immune system
- Incomplete tumor elimination

**Escape**
- Tumor growth with loss of immunogenicity
- Increased immunosuppressive cells in the microenvironment
- Unregulated tumor growth

Finn OJ. Ann Oncol. 2012; 23 (8): viii6-viii9
Approaches in Immuno-Oncology

• Cancer Vaccines
  – Sipuleucil-T, Bacillus Calmette-Guérin (BCG)

• Cytokine Therapy
  – Interleukins (ILs), Interferons (IFNs)

• Check point antibodies
  – PD-1, PDL-1 and CTLA-4 inhibitors
    – Ipilimumab, nilovumab, pembrolizumab

• Immune Cell therapy
  – Tumor infiltrating lymphocytes (TILs)
  – Chimeric Antigen Receptor (CAR) T-Cells
Question 1.

Which of the following agents would be considered immunotherapy?

A. Eroltinib, an EGFR tyrosine kinase inhibitor
B. Cyclophosphamide, an alkylating agent
C. Pembrolizumab, a PD-1 inhibitor
D. Methotrexate, an anti-folate antimetabolite
E. CAR T-Cells
F. A & D
G. C & E
Chimeric Antigen Receptor T-Cell:
The living drug
Chimeric Antigen Receptor T-Cells

- CAR T-cells are autologous T-cells genetically modified to express a chimeric antigen receptor (CAR)
- CAR is a recombinant receptor construct
  - Antibody-derived extracellular single chain variable fragment (scFv)
  - Linked to intracellular T-cell signaling domains of the T-cell receptor
CD-19 CAR T-Cells

- Antibodies designed to a specific tumor marker
  - CD19 found in B-cell malignancies
- Redirects T-cell specificity to the attack the tumor in an HLA-independent manner
- Induces remission in relapsed and refractory B-cell malignancies
Schema of CAR T manufacturing and administration

- **Patient**
  - PBMC collected for genetic modification
  - Patient receives lymphocyte-depleting chemotherapy
  - Anti-CD19 CAR cells returned to patient

- **Ex vivo cell processing**
  - T-cell activation
  - Transduction with gammaretroviral vector encoding CAR gene
  - T-cell proliferation

Lymphodepletion (Conditioning)

- Conditioning regimens consist of high-dose chemotherapy directed at lymphodepletion
- Lymphodepletion may enhance CAR T-cell responses
  - Eradication of regulatory T-cells
  - Elimination of immune cells that may compete for cytokines
  - Enhance antigen-presenting cell activation
- Most common regimen is Cyclophosphamide (Cy) 60mg/kg x 2days +/- Fludarabine 25mg/m2 (Flu) x 3 days

Park JH. Blood. 2016; 127(26):3312-3320
In-vivo Expansion and Persistence

• CAR-T cells are capable of migrating through tissues (including CNS) and targeting tumor cell antigens
• Upon stimulation they amplify resulting in secretion of cytokines and in-vivo expansion to engage in tumor destruction
• Establish a specific and lasting memory can lead to continual immunosurveillance of tumor regrowth
RR in CD 19 CAR T-cells in ALL

<table>
<thead>
<tr>
<th>Institution</th>
<th>Pt Population</th>
<th>Conditioning</th>
<th>Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>Ped ALL (n=53)</td>
<td>Investigator’s Choice</td>
<td>CR: 50/53 <strong>(94%)</strong> MRD- 45/50 RFS at 12mo: 45% OS at 12mo: 78%</td>
</tr>
<tr>
<td>NCI</td>
<td>Ped ALL (n=20)</td>
<td>Flu/Cy</td>
<td>CR: 14/20 <strong>(70%)</strong> MRD- 12/14 LFS: 79% (4.8 mo in MRD-CR) OS: 52% at 7.8 mo (all)</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Adult ALL (n=46)</td>
<td>Cy or Flu/Cy</td>
<td>CR: 37/45 <strong>(82%)</strong> MRD- 30/36) OS: 65% all at 6 mo OS: 80% MRD- at 6mo</td>
</tr>
<tr>
<td>FHCRC</td>
<td>Adult ALL (n=29)</td>
<td>Cy or Flu/Cy</td>
<td>CR: 10/12 <strong>(83%)</strong> (Cy); 14/14 <strong>(100%)</strong> (Fly/Cy)</td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult ALL (n=12)</td>
<td>Investigator’s Choice</td>
<td>CR: 8/9 <strong>(89%)</strong> (all MRD-)</td>
</tr>
</tbody>
</table>

CHOP, Children’s Hospital of Philadelphia; NCI, National Cancer Institute; MSKCC, Memorial Sloan Kettering Cancer Center; FHCRC, Fred Hutchinson Cancer Research Center; UPenn, University of Penn, MRD, minimal residual disease; LFS, Leukemia-Free Survival; RFS, Relapse-Free Survival; CR, Complete Remission; OS, Overall Survival

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<th>Institution</th>
<th>Pt Population</th>
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<th>Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>Adult CLL &amp; B-NHL (n=8)</td>
<td>Flu/Cy</td>
<td>ORR: 6/8 (75%) CLL 3/4; FL 2/3 CR: 1/8 (12.5%) CLL PR: 5/8</td>
</tr>
<tr>
<td>NCI</td>
<td>Adult B-NHL (n=15)</td>
<td>Flu/Cy</td>
<td>CR: 4/7 (57%) refractory DLBC 4/6 (67%) indolent BCL</td>
</tr>
<tr>
<td>FHCRC</td>
<td>Adult B-NHL (n=28) CLL (n=6)</td>
<td>Cy ± Etoposide or Cy±Flu</td>
<td>ORR: B-NHL Cy: 6/12 (50%) CR= 1; PR =5) Flu/Cy: 8/12 (67%)CR=5; PR=3 ORR: CLL 5/6 (83.3%) CR=3; PR=2</td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult CLL (n=14)</td>
<td>Investigator’s Choice</td>
<td>ORR: 8/14 (57%) MRD- CR=4 PR=4 Median PFS=7mo; OS=29mo</td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult CLL (n=26)</td>
<td>Investigator’s Choice</td>
<td>ORR: 9/23 (39%) CR=5, PR=4</td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult B-NHL (n=24)</td>
<td>Investigator’s Choice</td>
<td>ORR: 15/22 (68%) DLBCL 7/13; FL 7/7; MCL 1/2 PFS: 62% 11.7mo</td>
</tr>
</tbody>
</table>

NCI, National Cancer Institute; FHCRC, Fred Hutchinson Cancer Research Cancer; UPenn, University of Penn, CLL, Chronic Lymphocytic Leukemia; PR, Partial Response; FL, Follicular Lymphoma B-NHL, B-cell Non-Hodgkin’s Lymphoma, CR, Complete Remission; ORR, Overall Response Rate; PFS, Progression Free Survival
Question 2

Which of the following statements best describes CAR T-cell therapy?

A. CAR T-cell therapy is indicated for first-line therapy for newly diagnosed CLL and ALL
B. T-cells are taken from a healthy patient, modified to be directed at specific tumor, and then infused into a patient with cancer
C. The primary goal of conditioning therapy is to eradicate the existing tumor prior to CAR T-cell infusion
D. CAR T-cells are autologous T-cells genetically modified for tumor specificity which have shown to induce remission in relapsed B-Cell malignancies
Cytokine Release Syndrome

- Stimulation and In-vivo expansion
  - Amplification of T-cells $\rightarrow$ secretion of cytokines
- Cytokines elevation of IL-6, IFN-γ, TNF, IL-2, IL-2-receptor-α IL-8, IL-10
- Occurs within 1-5 days and resolves ~1-3 wks
- Precedes peak T-cell levels ~10 d (7-17 d)

# Clinical Signs and Symptoms of CRS

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, hypoxemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Elevated D-dimer, hypofibrinogenemia ± bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, hyperbilirubinemia</td>
</tr>
</tbody>
</table>
### CRS Grading System

<table>
<thead>
<tr>
<th>Institution</th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>Mild reaction; infusion interruption or intervention not indicated</td>
<td>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medication indicated ≤24 hrs</td>
</tr>
<tr>
<td>UPenn</td>
<td>Mild reaction; treated with supportive care</td>
<td>Moderate: requiring IV therapies; some signs of organ dysfunction related to CRS; hospitalization for management of CRS-related symptoms including fevers with associated neutropenia</td>
</tr>
</tbody>
</table>
# CRS Grading System

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
</table>
| Severe symptoms including any 1 or more of the following:  
  • Drop in blood pressure ≥20% from baseline, not responsive to fluid within 24h  
  • Grade 3 respiratory dysfunction  
  • Grade 3 respiratory dysfunction  
  • Grade 3 creatinine indicative of renal dysfunction;  
  • Grade 3 neurological dysfunction | Life-threatening consequences;  
  • Vasopressors or ventilator support indicated |
| More severe reaction:  
  • Hospitalization required for management of symptoms related to organ dysfunction including  
    • Grade 4 liver function test  
    • Grade 3 creatinine elevation related to CRS  
    • includes hypotension treated with IV fluids or low-dose vasopressors | Life-threatening complications:  
  • Hypotension requiring high-dose vasopressors  
  • Hypoxia requiring mechanical ventilation |
## Incidence of CRS in ALL

<table>
<thead>
<tr>
<th>Institution</th>
<th>Pt Population</th>
<th>CRS incidence</th>
<th>CRS Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>Ped ALL (n=53)</td>
<td>Initial cohort: 25/25 (100%) Grade ≥ 1 = 48/53 (91%)</td>
<td>8/25 (32%) required vasopressors</td>
</tr>
<tr>
<td>NCI</td>
<td>Ped ALL (n=20)</td>
<td>Grade ≥ 1 = 15/20 (75%)</td>
<td>Grade 3 = 3 (15%) Grade 4 = 3 (15%) 1 pt with cardiac arrest</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Adult ALL (n=46)</td>
<td>11/46 (24%) with severe CRS (requiring vasopressors or mechanical ventilation)</td>
<td></td>
</tr>
<tr>
<td>FHCRC</td>
<td>Adult ALL (n=29)</td>
<td>7/27 (26%) with severe CRS requiring ICU care 2 (7.4%) fatal cases</td>
<td></td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult ALL (n=12)</td>
<td>11/12 (92%) ≥ Grade 3 3 (25%) fatal cases</td>
<td></td>
</tr>
</tbody>
</table>

Park JH. Blood. 2016; 127(26):3312-3320
## Incidence of CRS in B-NHL

<table>
<thead>
<tr>
<th>Institution</th>
<th>Pt Population</th>
<th>Incidence</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>Adult B-NHL (n=15)</td>
<td>Fever: 12/15 (80%) Hypotension: 4/15 (27%)</td>
<td></td>
</tr>
<tr>
<td>FHCRC</td>
<td>Adult B-NHL (n=28) CLL (n=6)</td>
<td>Severe CRS: Cy cohort 0/12 (0%) FluCy cohort 2/16 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult CLL (n=14)</td>
<td>Grade ≥1: 9/14 (64%)</td>
<td>Grade 3 and 4 n= 6 (43%)</td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult CLL (n=26)</td>
<td>Grade ≥1: 14/26 (54%)</td>
<td></td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult B-NHL (n=24)</td>
<td>Grade ≥1: 16/24 (67%)</td>
<td>Grade 2 n= 14 (58%) Grade 3 n= 1 (4%) Grade 4 n= 1 (4%)</td>
</tr>
</tbody>
</table>

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Cytokine Release Syndrome

• Possible correlation between development of CRS and response to therapy
  – Patients still achieve CR in the absence of CRS
• No strong correlation between the degree of CRS and response to therapy
• The severity of CRS may correlate with tumor burden at time of infusion

CRS Treatment

• Goals of Treatment
  – Supportive care for symptoms
  – Augmenting cytokine release with anti-cytokine therapy or lymphocytic corticosteroids
• Tocilizumab, an IL-6 antagonist (off-label) and corticosteroids used to abate CRS toxicity
• Early intervention with tociluzumab may decrease rates of severe CRS

## Supportive Care

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>• Acetaminophen, cooling blankets</td>
</tr>
<tr>
<td></td>
<td>• Avoid NSAIDs, meperidine</td>
</tr>
<tr>
<td>(Fevers, Rigors)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>• Stop or taper anti-HTN prior to CART therapy</td>
</tr>
<tr>
<td></td>
<td>• 1 L NS for SBP &lt;80% of BL and &lt;100 or if SBP &lt;85</td>
</tr>
<tr>
<td></td>
<td>• Transfer to ICU if not responsive to IFV</td>
</tr>
<tr>
<td></td>
<td>• Norepinephrine preferred vasopressors</td>
</tr>
<tr>
<td></td>
<td>• Tociluzimab 4 or 8mg/kg (max 800 mg) indicated per protocol</td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>• Antimicrobial ppx for HSV and PCP</td>
</tr>
<tr>
<td>Hematologic</td>
<td>• Allopurinol for TLS; PRBC and plt transfusions</td>
</tr>
<tr>
<td></td>
<td>• G-CSF for ANC &lt; 500</td>
</tr>
<tr>
<td></td>
<td>• Cyroprecipitate for Fibrinogen ≤100; FFP for &gt;PTT</td>
</tr>
<tr>
<td>Neurologic</td>
<td>• Standard anti-epileptic medications</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone 10 mg IV Q 6hr for grade 3 or 4</td>
</tr>
</tbody>
</table>

Brundo JN. Blood. 2016; 127(26): 3321-3330
Tocilizumab for CRS

- Tocilizumab is monoclonal antibody directed at IL-6, FDA indicated for severe to moderate rheumatoid arthritis
  - Dosing: 4 or 8 mg/kg IV over 1hr
- Improvement in CRS toxicity within hours
- Impacts the efficacy of CART remains unclear
  - Preliminary data suggests no difference in peak percentage engraftment, area under the curve, or functional persistence of CAR T cells
- Methylprednisolone 1-2 mg/kg IV q12hrs utilized if unresponsive to tocilizumab
Indication for Tocilizumab for CRS

- Clinical criteria for *early* treatment
  - Persistent fever $\geq$ 39°C despite antipyretics for 10h
  - Persistent/recurrent hypotension after IVF bolus
  - Initiation of oxygen supplementation

### Indications for Initiation of Tocilizumab in CRS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF $\leq$ 40% by ECHO</td>
<td>Creatinine $&gt;2.5 \times$ level prior to CAR T</td>
</tr>
<tr>
<td>Norepinephrine $&gt;2\mu g$/min required for $\geq$ 48 hrs (even if not continuous)</td>
<td>SBP 90 cannot be maintained with norepinephrine</td>
</tr>
<tr>
<td>O2 requirement of FiO2 $\geq$50% $\times$ 2 hrs</td>
<td>Creatinine kinase$&gt;5\times$ ULN</td>
</tr>
<tr>
<td>Clinically significant bleeding</td>
<td>Activated PTT $&gt;2\times$ ULN</td>
</tr>
</tbody>
</table>

CAR T-Cell Neurotoxicity

• Etiology is unclear
  – CAR T cells and IL-6 are seen in the spinal fluid of most patients

• Onset and duration
  – Can occur concurrently or following CRS
  – Median onset ~6 days (onset 2-17 days)
  – Generally resolves within 4 weeks

• Clinical presentation
  – Aphasia/dysphasia, confusion, somnolence, motor (tremor)
  – Global encephalopathy most common toxicity, but seizures have also been reported

## Incidence of Neurotoxicity

<table>
<thead>
<tr>
<th>Institution</th>
<th>Pt Population</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>Ped ALL (n=53)</td>
<td>13/25 <strong>(52%)</strong> initial cohort Delirium to global encephalopathy</td>
</tr>
<tr>
<td>NCI</td>
<td>Ped ALL (n=20)</td>
<td>6/20 <strong>(30%)</strong> Visual hallucinations n= 5 Transient dysphagia n=1</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Adult ALL (n=46)</td>
<td>Grade ≥ 3 = 13/46 <strong>(28%)</strong></td>
</tr>
<tr>
<td>FHCRC</td>
<td>Adult ALL (n=29)</td>
<td>Grade ≥ 3 = 17/27 <strong>(63%)</strong></td>
</tr>
<tr>
<td>NCI</td>
<td>Adult B-NHL (n=15)</td>
<td>6/15 <strong>(40%)</strong> - Confusion, obtundation, aphasia, encephalopathy</td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult CLL (n=14)</td>
<td>Grade ≥ 2 = 6/14 <strong>(43%)</strong></td>
</tr>
<tr>
<td>UPenn</td>
<td>Adult B-NHL (n=24)</td>
<td>Grade ≥ 2 = 3/24 <strong>(12.5%)</strong></td>
</tr>
</tbody>
</table>

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Treatment of Neurotoxicity

• Unclear if tocilizumab has benefit in neurotoxicity
  – Concern if it crosses the blood-brain barrier (BBB)
  – Tocilizumab did not ameliorate neurologic toxicity in a small number of patients

• Dexamethasone most utilized given excellent CNS penetration
  – Evaluation of IT Chemotherapy in some protocols

• Indication varies per protocol
  – Grade 3 or 4 neurologic toxicities (other than headaches > 24 hours) and if any seizures
  – Prophylactic anti-seizure medications may be used

Brundo JN. Blood. 2016; 127(26): 3321-3330
Treatment Summary

• IL-6 receptor blockade with tocilizumab mainstay pharmacologic therapy for CRS
  – Indications for administration vary among centers
• Corticosteroids indications include:
  – Neurologic toxicities
  – CRS not responsive to tocilizumab
• Risk of immunosuppressive therapy abrogating the antimalignancy activity of the CAR T cells
• No differences among the immunomodulatory groups
  – Regards to peak percentage engraftment
  – Area under the curve
  – Functional persistence of CAR T cells

Brundo JN. Blood. 2016; 127(26): 3321-3330
CT is a 52 yo M with relapsed, refractory B-cell ALL admitted to receive CAR T-cell therapy with Flu/Cy conditioning. Three days after his CAR T-cell infusion, he begins to experience fevers, malaise, and hypotension (SBP<90mm Hg). After not responding to IVF boluses, he is transferred to the ICU for vasopressor support with norepinephrine.
Question 3.

What would be the most appropriate plan of action?

A. Provide supportive care (vasopressors, O₂, etc.) only; patients can not achieve complete remission without experiencing CRS

B. Start tocilizumab to abate symptoms and decrease the risk of worsening of CRS

C. Start dexamethasone empirically for neurotoxicity which always occurs after CRS

D. Provide supportive care only; patients treated with tocilizumab +/- steroids will not achieve any response from the CAR T-cells

E. Start tocilizumab and dexamethasone because they should be used concomitantly to treat CRS
Ongoing Clinical Trials

• Over 150 clinical trials registered with NIH
• CAR T-cells directed at solid tumor malignancy
  – CEA in adenocarcinoma liver metastases
  – CD171 in neuroblastoma
  – GD2 in neuro-ectodermal origin
  – Glypican-3 for hepatocellular carcinoma
  – ERBB2 in metastatic colorectal
• CAR T-cells directed at BCMA in MM
• Targeting the tumor vasculature with CAR-T-cells, such as VEGFR-2-specific CAR-T-cells
Future Directions

• Combination therapy with check point inhibitors
• NK-cell-based recognition domains in CARs
• Infusion of two populations of CAR-T cells
• Engineered CAR-T-cells that secrete pro-inflammatory cytokines (armored CAR-T-cells)
• Allogenic CAR T-cells with suicide genes “off switches”

Conclusions

• Immunoncology focuses on cancer as a systemic disease directing therapy at overcoming tumor escape of immunosurveillance
• CAR T-cells are a promising treatment showing improved response rates in the setting of relapsed, refractory B-cell malignancies
• Aggressive supportive care of CRS and neurotoxicity is necessary to ensure patient safety throughout treatment
Chimeric Antigen Receptor (CAR) T-Cells for the Treatment of B-Cell Malignancies: Navigating the Road to Remission

Jilan Kubusek, PharmD, BCPS, BCOP
Clinical Pharmacist,
Hematology/Oncology/BMT
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