CAR T-cell Therapy for Acute Lymphoblastic Leukemia: Past, Present, and Future Directions

Celebrating a Second Chance at Life Survivorship Symposium

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CAR T Cell therapy for B-Acute Lymphoblastic Leukemia

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Disclosures

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  - Kite/Gilead
  - Sanofi
  - Autolus

Learning Objectives

1. Discuss indications for CAR T cell therapy for B-cell acute lymphoblastic leukemia (B-ALL)
2. Review the patient's journey from initial consult to CAR T infusion
3. Explain short- and long-term toxicities following CAR T cell therapy for ALL
4. Review expected outcomes and future directions

B-cell Acute Lymphoblastic Leukemia (B-ALL) in Children

- Most common leukemia among children, accounting for 25% of all childhood cancers in the United States
- Average age at diagnosis is 17 years old
- Cure rates and survival have improved significantly over the past two decades, with 5-year overall survival ~90% among children!

B-cell Acute Lymphoblastic Leukemia (B-ALL) in Adults

- Not very common among adults
  - ~20% of all leukemias in patients >18 years old
- Although outcomes have improved among adults, the 5-year overall survival is not as good as observed in children
  - 55% in adults compared to 90% in children
- Adolescents and young adults (AYA) have suboptimal outcomes as compared to children due to differences in disease biology

Immunology 101

- T cells are a key part of the immune system that protects the body from threats such as infections or cancer
- They rely on the detection of antigens on the cell surface of abnormal cells to help identify a potential threat
- T cells may not be able to recognize cancer cells

What are CAR T cells?

- **C**himeric **A**ntigen **R**eceptor→ CAR T cells
- T cells are removed from the blood through a process called apheresis
- T cells cannot recognize the cancer cells, so cells are genetically modified with a CAR receptor that can recognize the “cancer cells”
- For B-ALL, the target is called CD19
- The CAR T cells are expanded in the lab
- CAR T cells are infused back into the patient

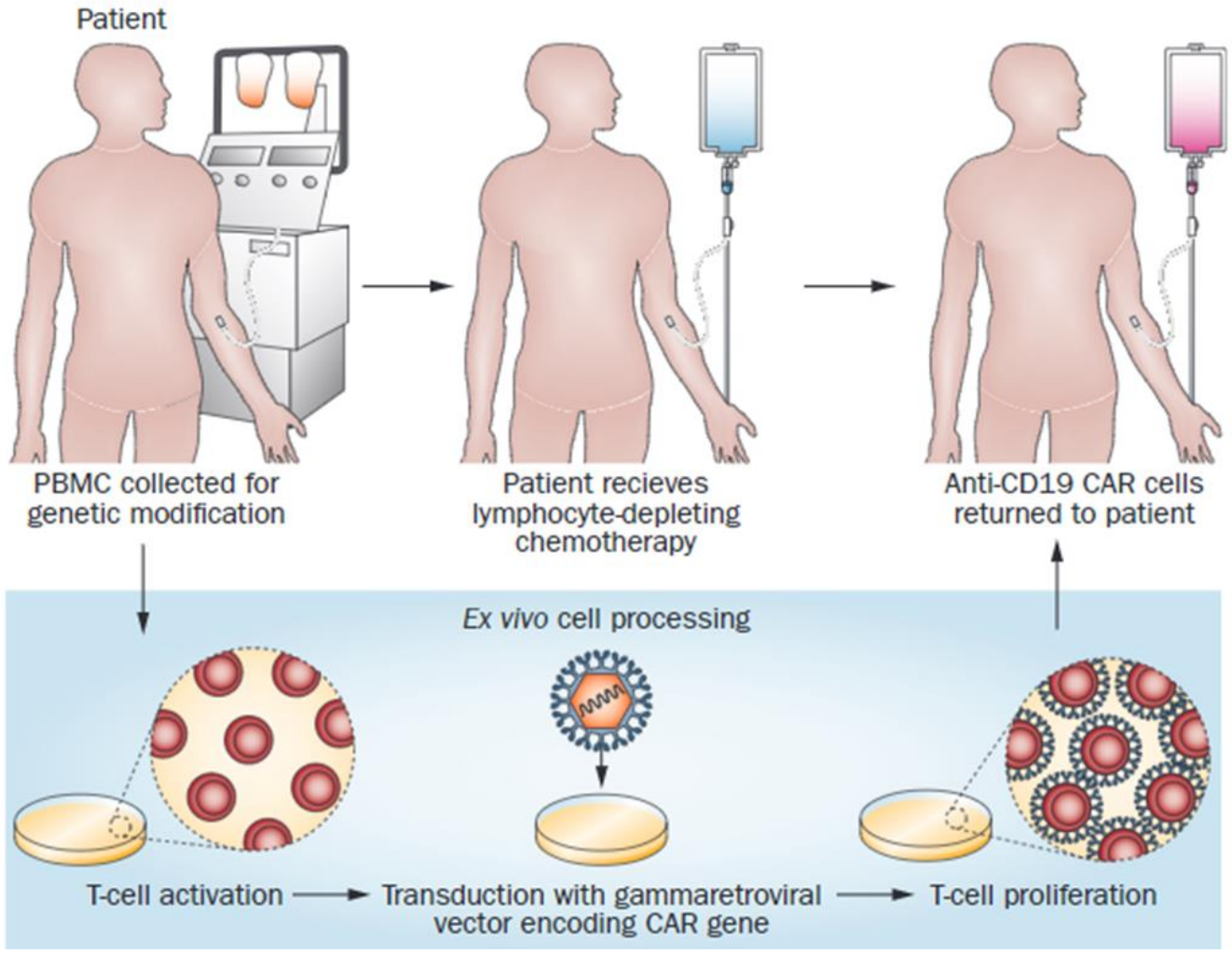
Kochenderfer, Nat Rev Clin Oncol 2013.

Products and Indications for CAR T cell Therapy for Patients with Relapsed/ Refractory B-ALL

Product	Indication	FDA approval	Pivotal Trial
Tisagenlecleucel KYMRIAH®	Patients up to 25 years of age with B-ALL that is refractory or in second or later relapse	2017	ELIANA
Brexucabtagene autoleucel TECARTUS®	Patients ≥18 years old with relapsed or refractory B-ALL	2021	ZUMA 3
Obecabtagene autoleucel AUCATZYL®	Patients ≥18 years old with relapsed or refractory B-ALL	2024	FELIX

1. Maude et al, N Eng J Med 2018
2. Shah et al, Lancet 2021
3. Roddie et al, NEJM 2024

Steps in CAR T cell therapy



Kochenderfer, Nat Rev Clin Oncol 2013.

Roadmap to CAR T treatment

1 Consultation

- Meet with CAR T clinical team
- Review indications for CAR T
- Submit insurance authorization for CAR T treatment
- Choose product based on patient and disease specific factors in addition to manufacturing time

2 Apheresis/Workup

- Apheresis scheduled
- ~2-3 weeks for cell manufacturing
- Undergo testing/ consult speciality services if indicated (neurology, cardiology etc)
- Additional therapy depending on disease burden

3 CAR T Treatment

- Lymphodepleting chemotherapy to help CAR T cells expand in the body
- CAR T cells are infused
- Patient monitored closely for 30 days
- Treatment may be given inpatient or outpatients

Initial CAR T consult

- Meet with the CAR T team to discuss if you meet indication for CAR T cell therapy
- FDA label is for patients with
  - ALL that recurs after initial therapy (relapsed disease)
  - ALL that doesn’t go into complete remission after initial therapy (refractory)
- The type of CAR T-cell therapy will be determined by your treating physician and will depend on age, manufacturing time, product availability
- After the clinical team determines you would benefit from CAR T cell therapy, insurance authorization is submitted

Workup/Apheresis

- Before CAR T treatment, tests are completed to ensure there are no active infections or other medical problems. These include imaging studies, bone marrow biopsy, and labs.
- The cells are then collected through a process called apheresis
- Apheresis is typically done in the outpatient setting and includes placement of a central venous catheter (IV) to collect the cells
- The T cells are then shipped to a facility and will take 2-3 weeks to manufacture

What is “bridging chemotherapy”?

- While CAR T cells are being manufactured, you may receive chemotherapy
- Several studies have shown that disease burden correlates with outcomes:
  - patients with less leukemia cells in the marrow have less toxicity and a better chance at achieving remission
- The type of bridging therapy will be determined by your treating physician and will depend on the subtype of your leukemia and prior therapy

The role of lymphodepletion chemotherapy

- After the T cells are manufactured, the patient receives 3-4 days of lymphodepletion chemotherapy, typically given outpatient. It is usually very well tolerated
- The goal of lymphodepletion chemotherapy is to:
  - help the CAR T cells expand in the body
  - prepare the body to receive the CAR T cells
- The most common lymphodepleting chemotherapy is a combination of fludarabine and cyclophosphamide

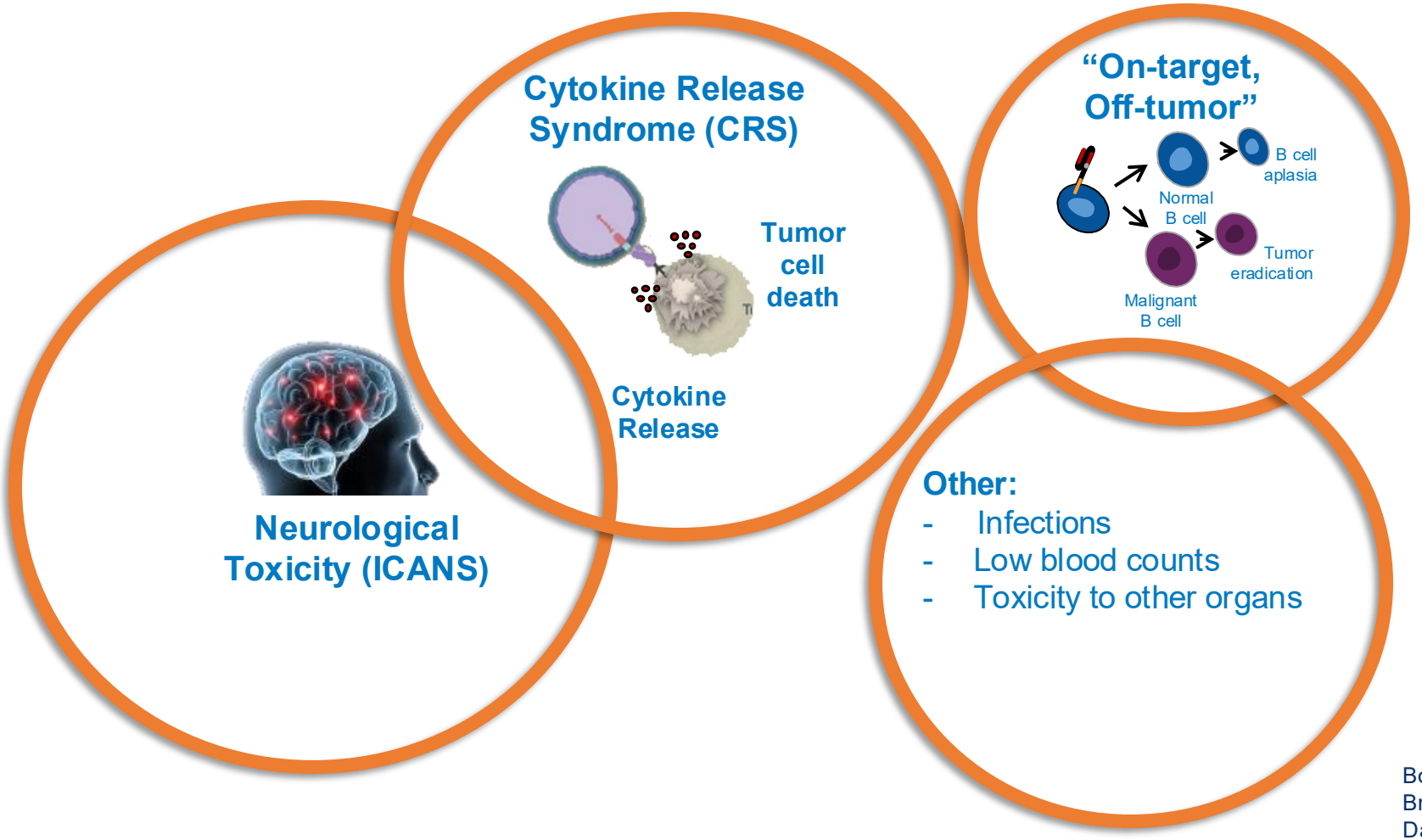
Kochenderfer, Nat Rev Clin Oncol 2013.

The CAR T infusion

- The CAR T cells are infused through an IV catheter
- CAR T infusion can occur either in the hospital or in the outpatient setting, depending on the center
- Patients are monitored closely for at least 30 days after infusion.
- Each program has specific guidelines about local lodging requirements

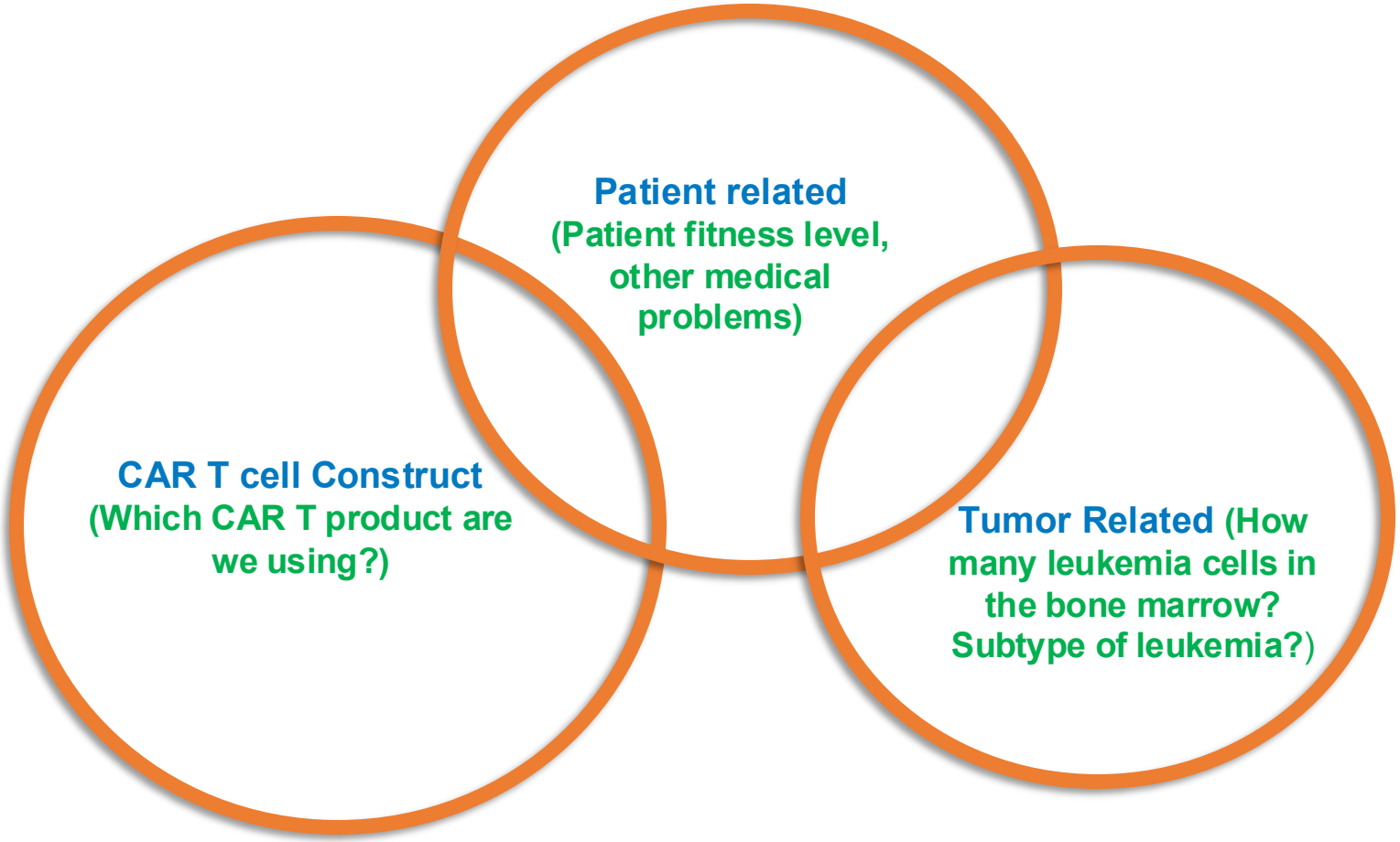
CAR T Toxicities

What are the Short-Term Toxicities of CAR T?

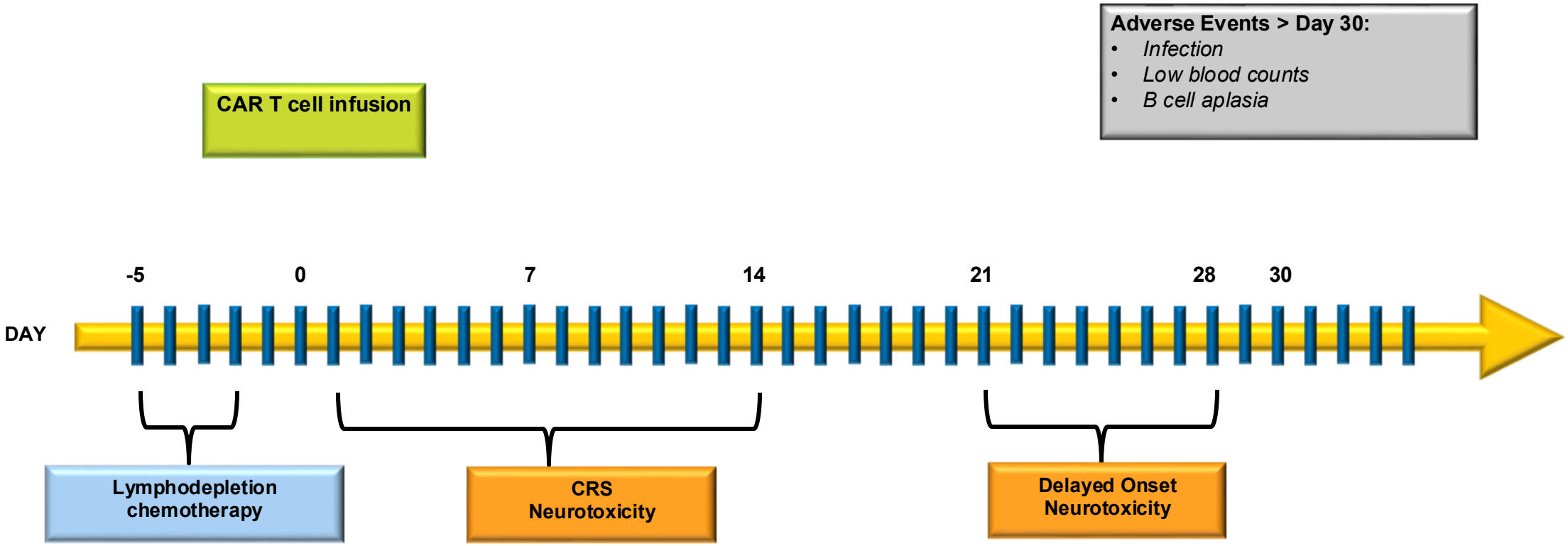


Bonifant CL, et al. *Oncolytics*. 2016.
Brudno JN, et al. *Blood*. 2016
Davila ML, et al. Science transl med. 2014
Adapted with permission from Bachmeier, C

Risk Factors for Immune Mediated Toxicities



Timeline of CAR T Related Toxicities



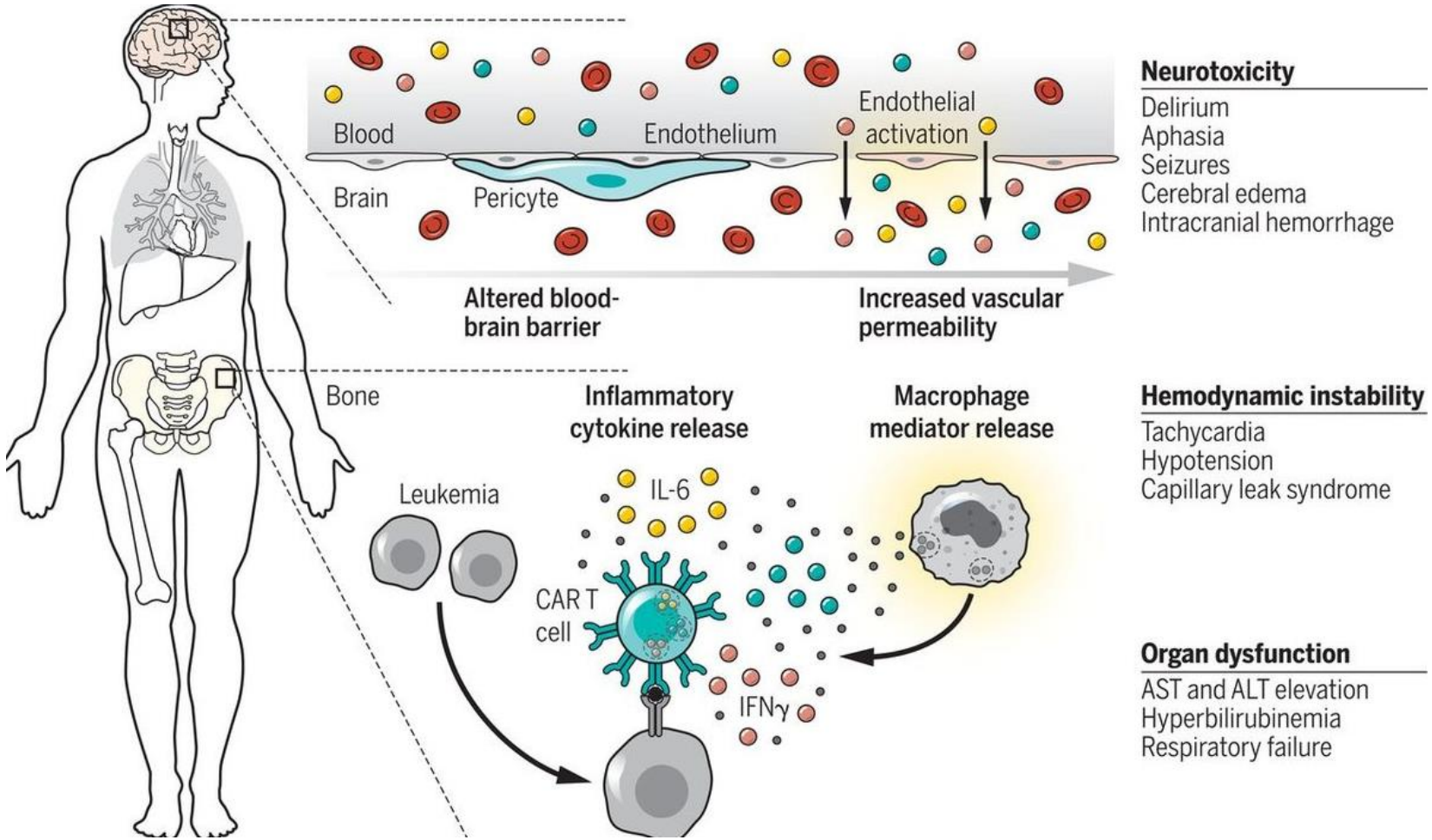
Brudno JN, et al. *Blood*. 2016;127:3321-30.
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15:47-62

Cytokine Release Syndrome (CRS)

- Most common toxicity of CAR T cell therapy
- It occurs in 70-90% of patients
- Potentially life-threatening
- Caused by immune activation of T-cells, resulting in inflammation
- Onset usually occurs within the first 7 days after CAR T-cell infusion
- Graded 1-4, depending on severity of symptoms
- Goal is to **prevent life-threatening complications while preserving the efficacy of CAR T cell therapy**

Lee DW, et al. *Blood 2014*
Brudno JN, et al. *Blood*. 2016
Neelapu SS, et al. *Nat Rev Clin Oncol*.
June at al, Science 2018

Effects of Cytokine Release Syndrome (CRS)



Lee DW, et al. *Blood 2014*
Brudno JN, et al. *Blood*. 2016
Neelapu SS, et al. *Nat Rev Clin Oncol*.
June at al, Science 2018

How Do We Manage CRS?

- Management of CRS depends on the severity
- For mild cases (fever only), they can be managed with symptom control such as Tylenol and hydration
- For more severe cases, treatment includes steroids, anti-cytokine therapy (for example Tocilizumab, Anakinra)
- For very severe CRS, patients may require care in the ICU

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019

Neurotoxicity after CAR T cell therapy

- Immune effector cell associated neurotoxicity syndrome (ICANS) is the second major side effect in patients treated with CAR T cells
- It occurs in 20-60% of patients
- Symptoms include:
  - Confusion
  - Difficulty speaking
  - Stroke-like symptoms
  - Weakness
  - Seizure
  - Rarely, swelling in the brain (cerebral edema)

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019

Onset of Neurotoxicity after CAR T cell therapy

- Onset varies and can occur in more than one phase:
- Early:
  - Symptoms occur concurrently with CRS symptoms (~within first 5 days)
- Late:
  - Symptoms begin after CRS symptoms have resolved
- Delayed:
  - 88-98% of neurotoxicity events occur within 8 weeks after cell infusion (seizures, episodes of confusion)

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019

How do we grade ICANS? The “ICE” score

- Orientation:
  - Orientation to year, month, city, hospital *(4 points)*
- Naming:
  - Ability to name three objects (e.g., point to clock, pen, button) *(3 points)*
- Follow commands:
  - Ability to follow simple commands (e.g., “show me two fingers” or “close your eyes and stick out your tongue”) *(1 point)*
- Writing:
  - Ability to write a standard sentence (e.g., “our national bird is the bald eagle”) *(1 point)*
- Attention:
  - Ability to count backwards from 100 by 10 *(1 point)*

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019

How Do We Grade ICANS?

Neurotoxity Domain[r]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[s]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[t]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[u]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;
Lee DW, et al. *Biol Blood Marrow Transplant*. 2019

How do we manage ICANS?

- Most patients (>90%) completely recover from neurologic toxicity
- We recommend medications to prevent seizures for the first month of CAR T treatment
- Mild neurologic toxicity can be managed with supportive care.
- Additional workup such as imaging and/or lumbar puncture may be needed to rule out other neurologic problems
- Majority of neurotoxicity cases can be managed with corticosteroids

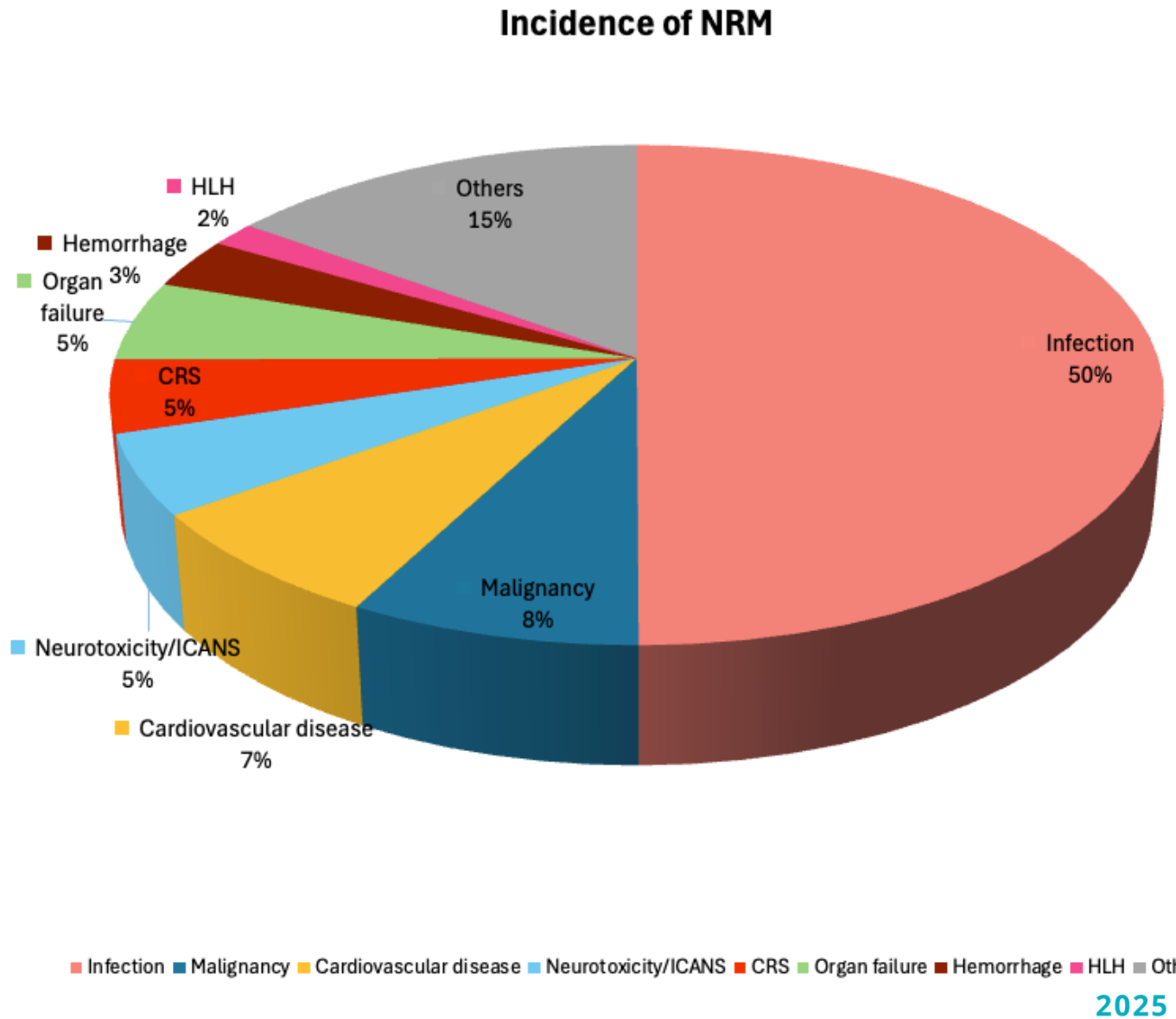
Lee DW, et al. *Biol Blood Marrow Transplant*. 2019

How Common are Toxicities for CAR T in ALL?

Product	CRS (%)	ICANS (%)
Tisagenlecleucel KYMRIAH®[1]	Any CRS: 77 Grade ≥ 3: 46	Any ICANS: 40 Grade ≥ 3: 13
Brexucabtagene autoleucel TECARTUS®[2]	Any CRS: 89 Grade ≥ 3: 24	Any ICANS: 60 Grade ≥ 3: 25
Obecabtagene autoleucel AUCATZYL®[3]	Any CRS: 69 Grade ≥ 3: 2	Any ICANS: 23 Grade ≥ 3: 7

1. Maude et al, N Eng J Med 2018
2. Shah et al, Lancet 2021
4. Roddie et al, NEJM 2024

What are the leading causes of death following CAR T?



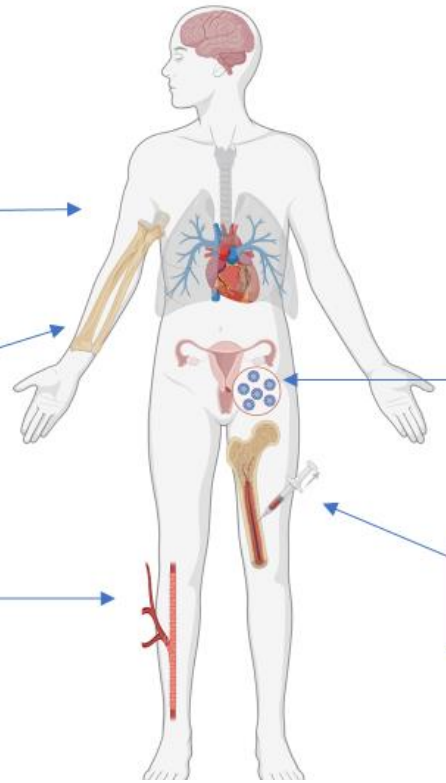
Infections Following CAR T

- Infections are very common following CAR T cell therapy, occurring in 20-60% of patients
- They are most common during the first 30 days; late infections can occur in 20-40% of patients.
- Antimicrobial therapy is recommended to prevent infections.
- Other approaches to prevent infections include using intravenous immune globulin to help boost immunity, because CAR T cell therapy lowers immunoglobulin levels
- Vaccines are also recommended to prevent infections
- Each program has recommendations to prevent infections post CAR T; most patients can return to work or school at 6 months post-CAR T treatment

Long-Term Toxicities

- Fatigue
- Mood changes
- Financial toxicity

- Hyperkinetic movement disorders
- Neurologic disability
- Cognitive changes



- Infections
- Hypogammaglobulinemia
- B cell aplasia
- Inferior response to vaccines

- Arrythmias
- Myocardial dysfunction

- Secondary malignancies

- Infertility
- Sexual dysfunction

- Anemia
- Thrombocytopenia
- Neutropenia

- Therapy related myeloid neoplasms

AYA Fertility and Sexual Health Post-CAR T

A study of 13 patients evaluated their:

- sexual health
- health-related quality of life (QOL)
- sexual health communication with healthcare providers (HCPs) among young adults (YAs) after CAR-T.

Three common themes:

- YA-perceived lack of HCP awareness of YA sexual health priorities
- Lack of sexual health communication and information post-CAR-T
- Parental caregiving is a barrier to YA-HCP sexual health communication

Buro et al, J Adolesc Young Adult Oncol 2024

AYA-Fertility and Sexual Health Post-CAR T: Other Findings

- Average interest in sex was low for females but not males
- Females reported worse fatigue, more impaired social function, and worse emotional experience
- Most did not, or did not recall, discussing sexual health with a healthcare provider before or after CAR T

Buro et al, J Adolesc Young Adult Oncol 2024

Outcomes after CAR T

Kymriah®(Tisa-cel): Pediatric Real-World Data

- First FDA-Approved CAR for Pediatric/Young Adult Patients up to Age 25
- CIBMTR analysis of tisa-cel across 73 US centers
- Cytokine release syndrome (CRS) = 55%; Grade CRS ≥3 = 16%
- ICANs (Neurotoxicity) = 27%; Grade ≥3 = 9%
- **12 months event-free survival (EFS) = 52%**
- **12 months and overall survival (OS) = 77%**
- 16% of patients received stem cell transplant

Pasquini M et al, Blood Advances 2020

Tecartus® (Brexucabtagene autoleucel): First FDA-Approved CAR T for Adults with B-ALL

- 73% achieved complete remission (CR) or complete remission with incomplete count recovery (CRi)
- Overall survival = 71%
- Recent updated analysis, median follow up of 54 months:
  - Median overall survival = 25.6 months in all patients
  - Median overall survival = 47 months in those who achieved CR/CRi

Shah B et al, Lancet 2021
Oluwole et al, ASCO 2024

Aucatzyl® (Obe-cel): The new kid on the block

- Obe-cel is given in **two infusions separated by at least week**
- **The starting dose of cells depends on how many leukemia cells are in the bone marrow prior to starting chemotherapy**
- Median age of 47, oldest patient 81 years old
- More than half of patients had prior stem cell transplant
- Median blast count 40%,
- 23% of patients had disease outside of the bone marrow (extramedullary disease)

Roddie C et al, NEJM 2024

Roloff G et al, JCO 2025

Aucatzyl® (Obe-cel): Outcomes of FELIX Trial

- With median follow up of 21.5 months, 78 % of patients achieved remission
- Median event-free survival (EFS) of 11.9 months; estimated 12 months EFS of 49.5%
- Median overall survival (OS) of 15.6 months, estimated 12 months OS of 61%

Roddie C et al, NEJM 2024

Efficacy Outcomes of CAR T for B-ALL

- Three commercially approved products for relapsed/refractory B-ALL
- Only one approved product for pediatrics
- Excellent initial response rates
- Work still needs to be done to decrease the risk of relapse

What happens after CAR T treatment?

- Some patients require stem cell transplantation after CAR T cells
- Ongoing clinical trials are helping guide who could benefit from stem cell transplant after CAR T (CAR CURE Study, CTN 2021)
- Continue close monitoring with your care team to check blood counts, monitor for infections, and to monitor for relapse

The Future is Bright

- Developing novel CAR T products
  - Using healthy donor T cells (allogeneic CAR T)
  - Targeting two antigens instead of one
  - Novel constructs to help the CAR T cells persist long
- Determining which patients can be treated with CAR T only without transplant
- Using CAR T cell therapy as an earlier line of treatment

Questions?

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Let Us Know How We Can Help You

Visit our website: bmtinfonet.org

Email us: help@bmtinfonet.org

Phone: 888-597-7674 or 847-433-3313

Questions?

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