Chimeric Antigen Receptor (CAR) T Cell Therapy: What a Nurse Needs to Know

- **Theresa M Latchford, RN, MS**
- Clinical Nurse Specialist
- Cancer Cellular Therapy
- tlatchford@stanfordhealthcare.org
- Silicon Valley Chapter of Oncology Nursing Society

- 6/2023

Disclosures

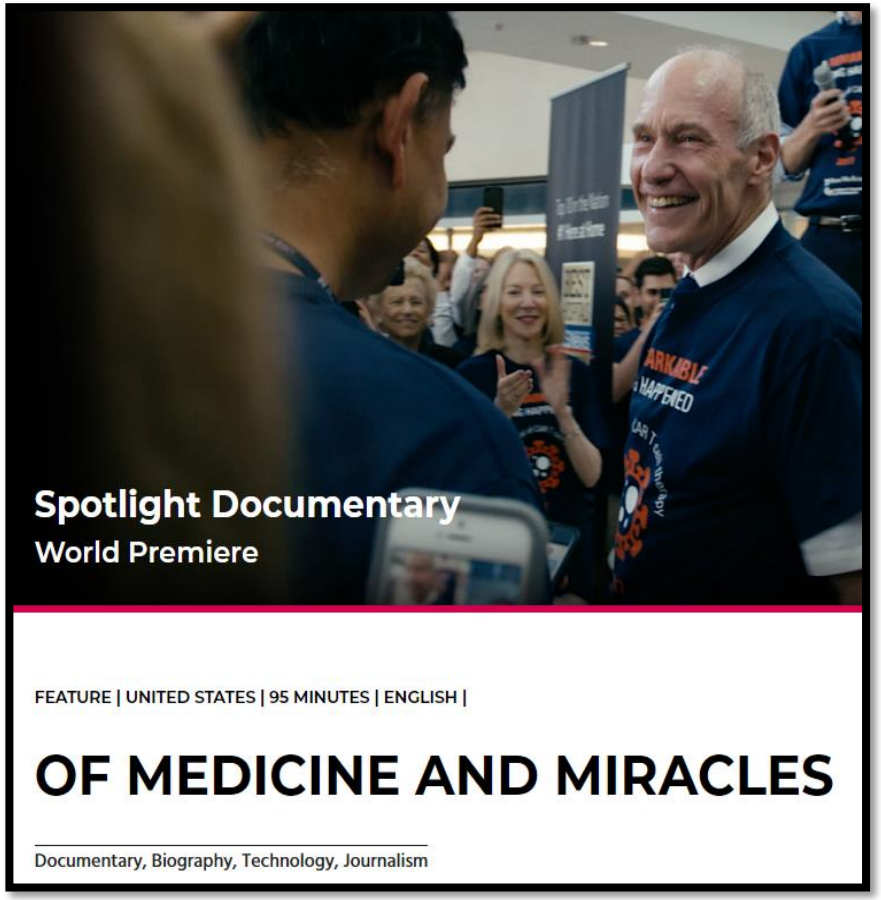
Kite- Gilead Sciences

Bristol Myers Squibb (BMS)

OBJECTIVES

- DESCRIBE THE FDA APPROVED CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY TYPES
- PROVIDE OVERVIEW OF TRIALS IN NON-HODGKIN'S LYMPHOMA, ACUTE LYMPHOCYTIC LEUKEMIA AND MYELOMA
- DISCUSS IMMEDIATE AND LONG-TERM TOXICITIES OF CAR T THERAPY
- STATE INTERVENTIONS TO IMPROVE THE MANAGEMENT FOR THE NURSE TO SUPPORT THE PATIENT UNDERGOING CAR T THERAPY

Emily Whitehead and Dr. Stephan Grupp celebrate Emily's 10-year anniversary of being cancer-free after CAR T-cell therapy. Credit: Children's Hospital of Philadelphia.



Starting the CAR

What is CAR T?

- CAR T therapy **chimeric antigen receptor (CAR) genetically modified T cells** that are designed to recognize **specific antigens** on tumor cells resulting in their activation and proliferation (supercharged) resulting in significant and durable destruction of malignant cells
- CAR T cells are considered **“a living drug”** since they tend to persist for long periods of time
- CAR T cells are generally created from the <u>patients own blood cells</u> although this technology is evolving to develop “off the shelf” CAR T cells

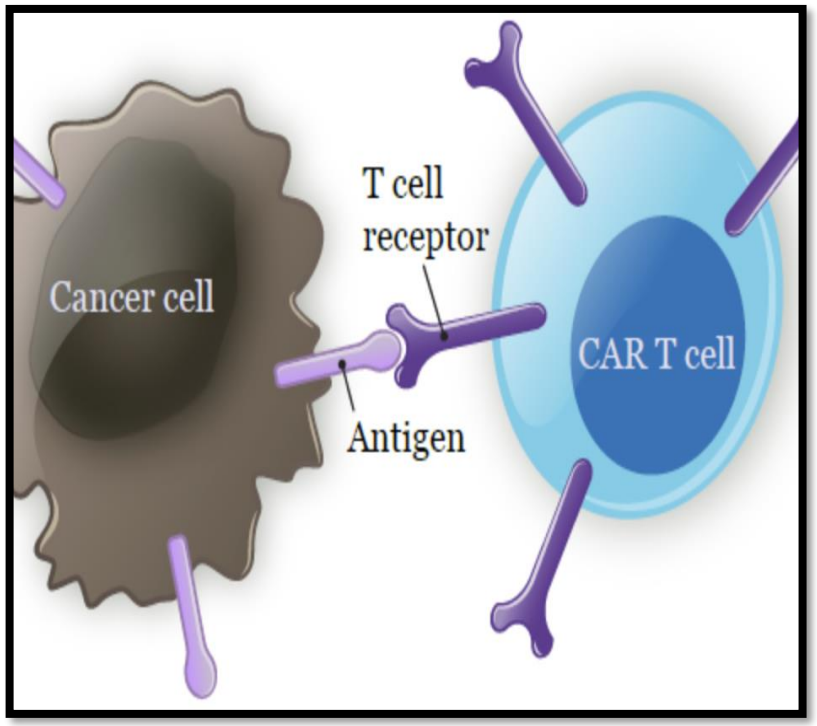
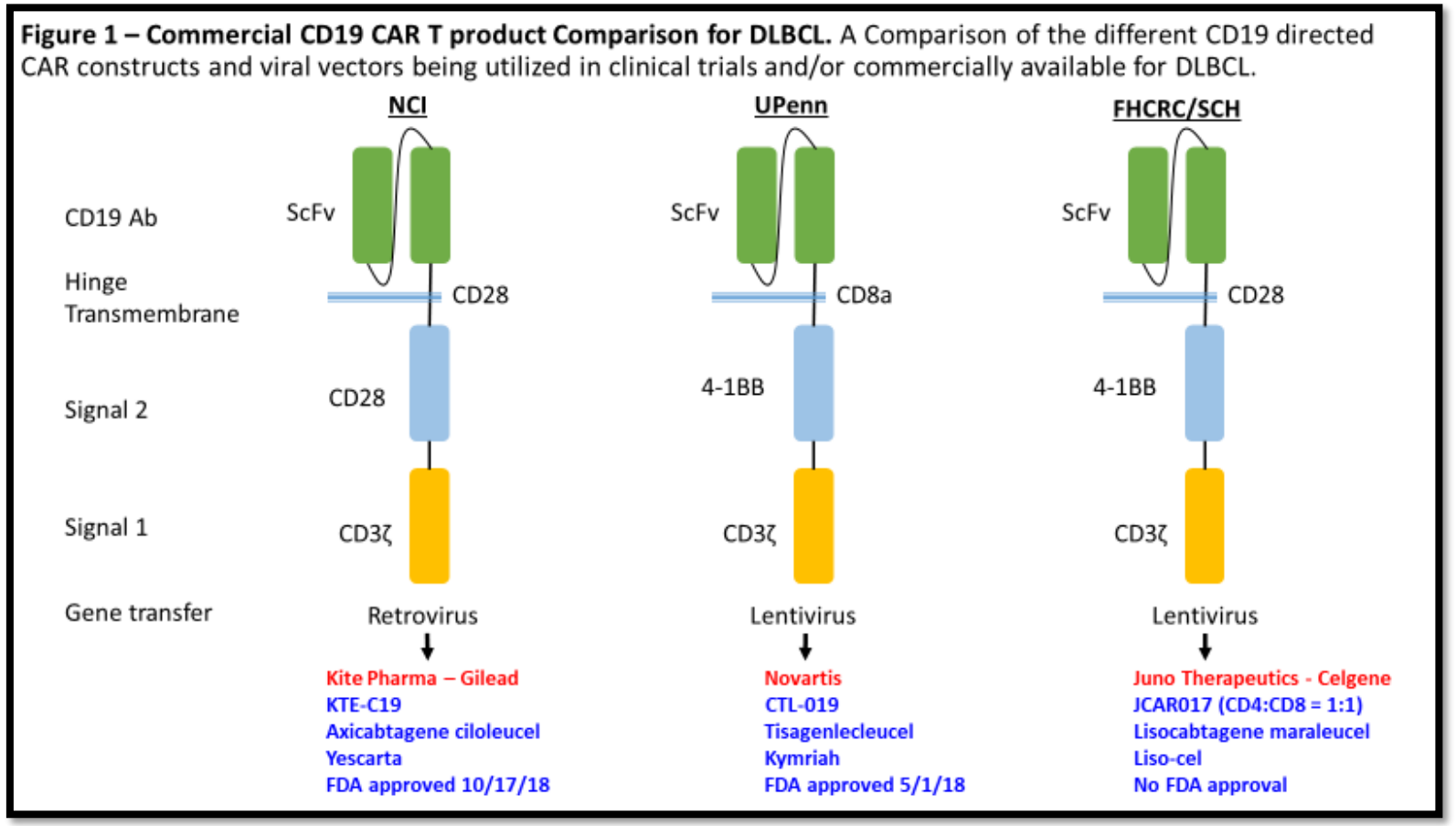


Image acquired from mskcc.org

How is the CAR Designed?

- Target-binding domain
  - Allows CAR-T cells to target specific molecules-binds to the antigen
- Costimulatory domain (CD28, or 41-BB)
  - Enhances growth and survival of CAR-T cell
- Activation domain (CD3z) -activation and proliferation



Latchford, T & Tierney, D (2019) Emerging Therapies, Chimeric Antigen Receptor T Cells in Hematopoietic Stem Cell Transplantation-A Manual for Nursing Practice

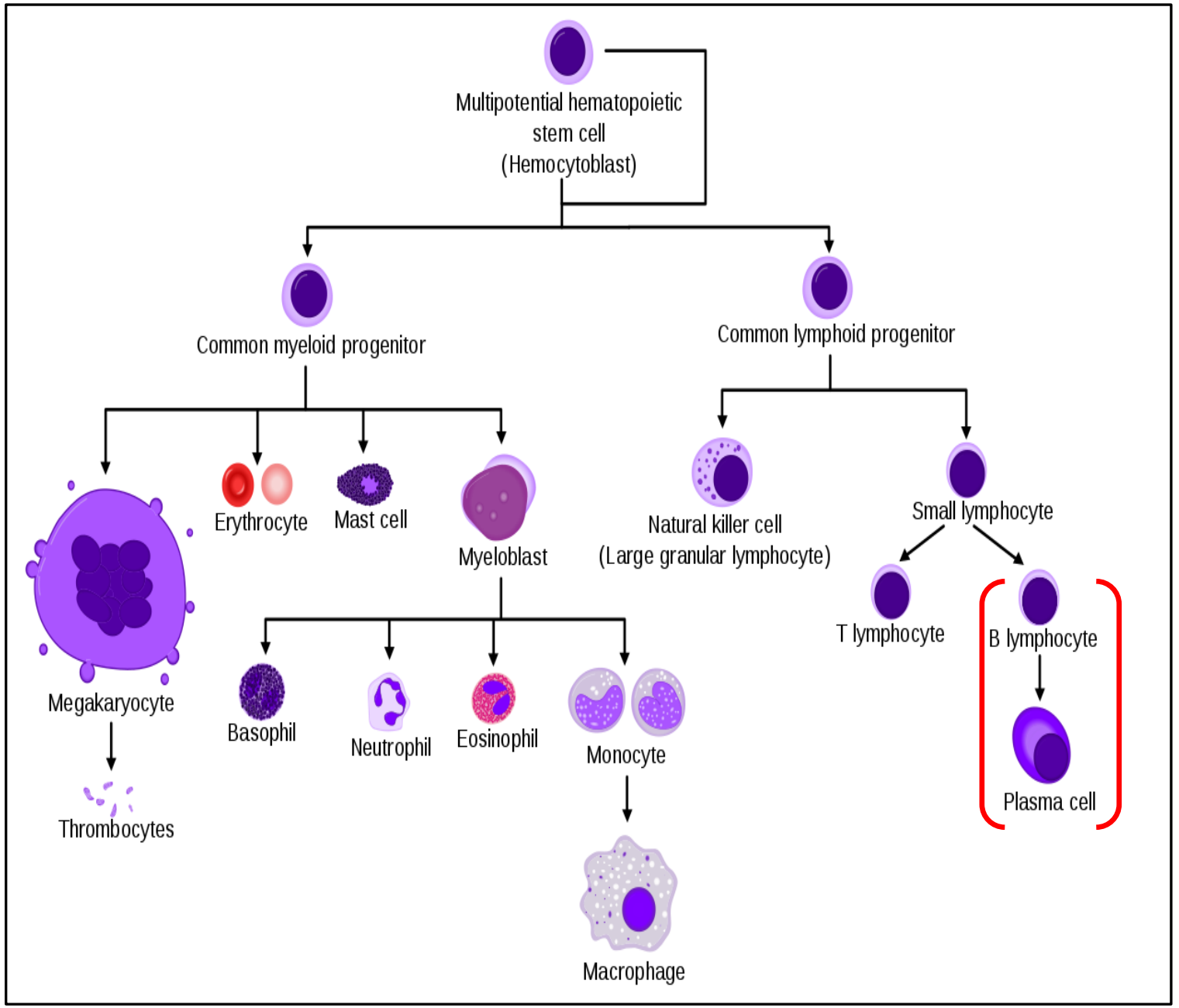
How much power is in the CARs Gas Pedal?

- Co-Stimulation Plays a major role in modulating T-Cell expansion and persistence
- Potential differences between CD28 and 4-1BB may help explain some of the clinical differences that have been observed, including differences in the clinical course.

CAR T WORKING GROUP

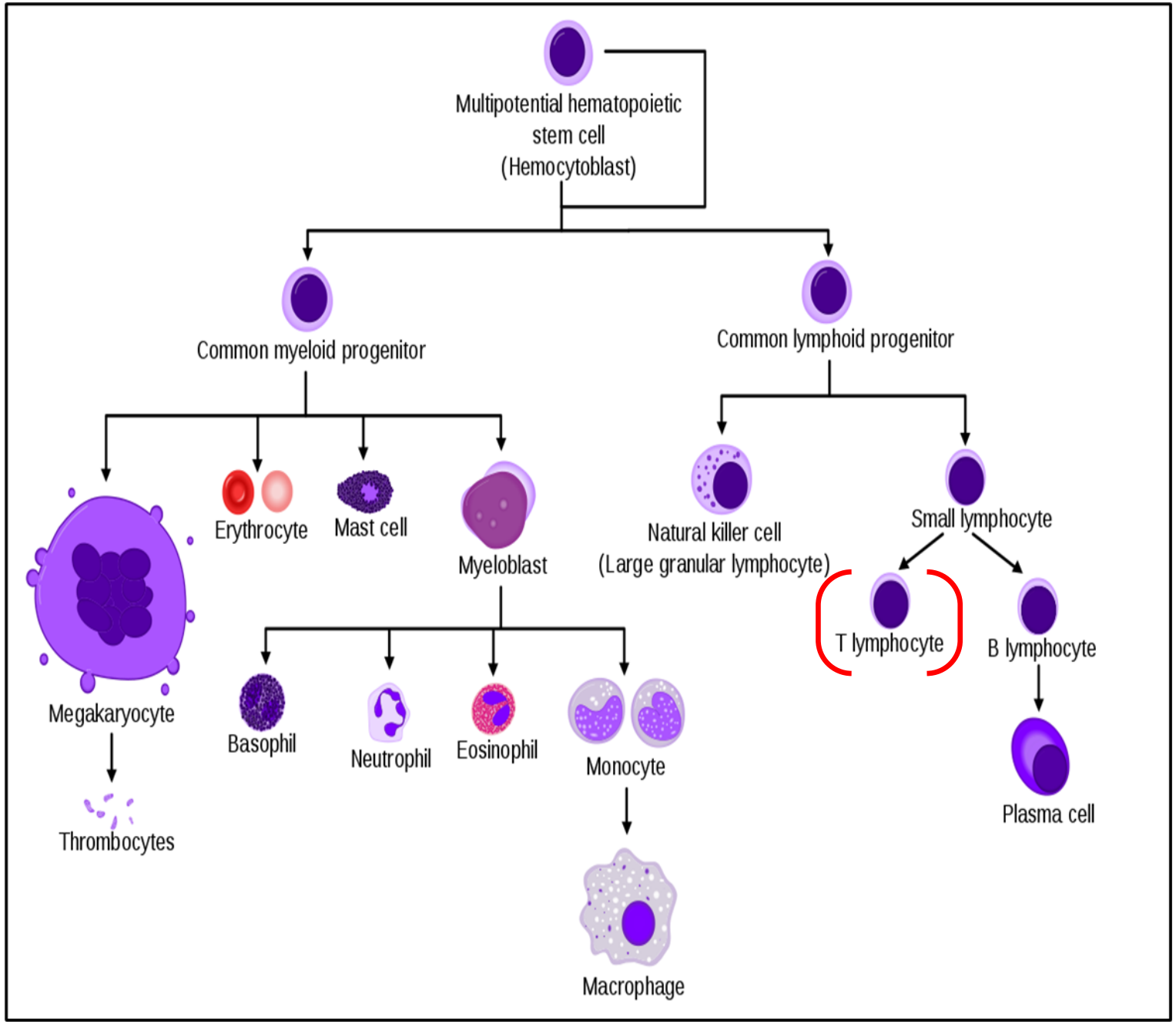
Immune System Refresher

- **B** cells are part of the **adaptive** immune system
- Generated in the **B**one marrow
- Activated by T helper cells causing them to multiply and transform into plasma cells
- Plasma cells produce antibodies which neutralize germs, and activate other immune system cells by attaching to their surface
- B cell mediated antibodies: IgA, IgD, IgE, **IgG** and IgM
- Some activated B cells transform into **memory cells**



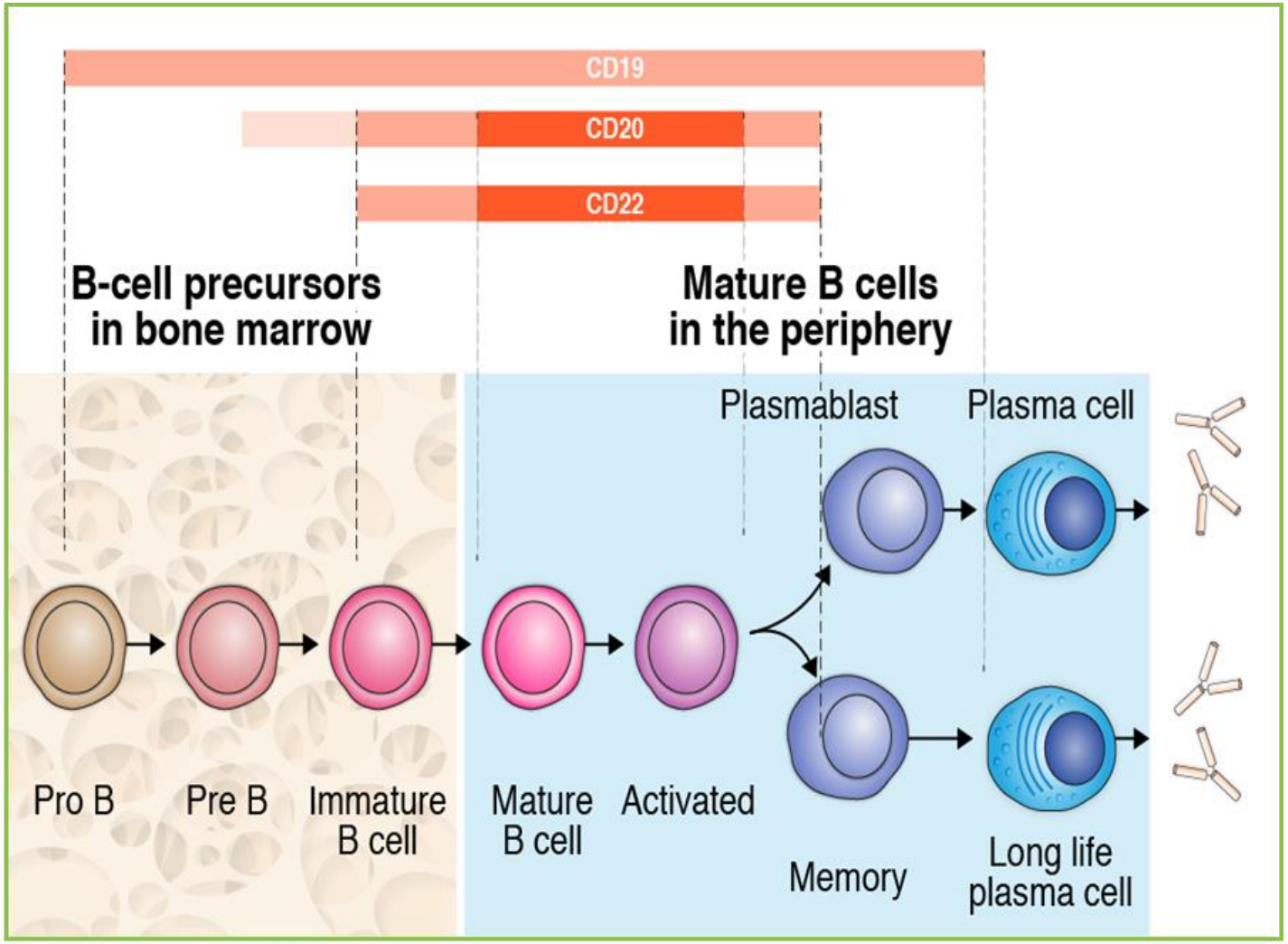
Immune System Refresher

- **T** cells are produced in the bone marrow and move to the **t**hymus
- T cells use chemical messengers to activate other cells to start the **adaptive immune system** (**T helper cells**)
- Detect cells infected by viruses or tumorous cells and destroy them (**cytotoxic T cells**)
- Some T helper cells become **memory T cells** after the infection is defeated.
- A matching T cell type for each infection (memory) i.e. lock and key



CAR Target (s)

- **CD19** is a protein expressed on the surface of almost all B-cell leukemias and lymphomas
- **BCMA (B Cell Maturation Antigen) Targets (BCMA)** is expressed on the cell membrane of malignant plasma cells
- **CD20 and CD22** are restricted primarily to mature B cells that have not been activated



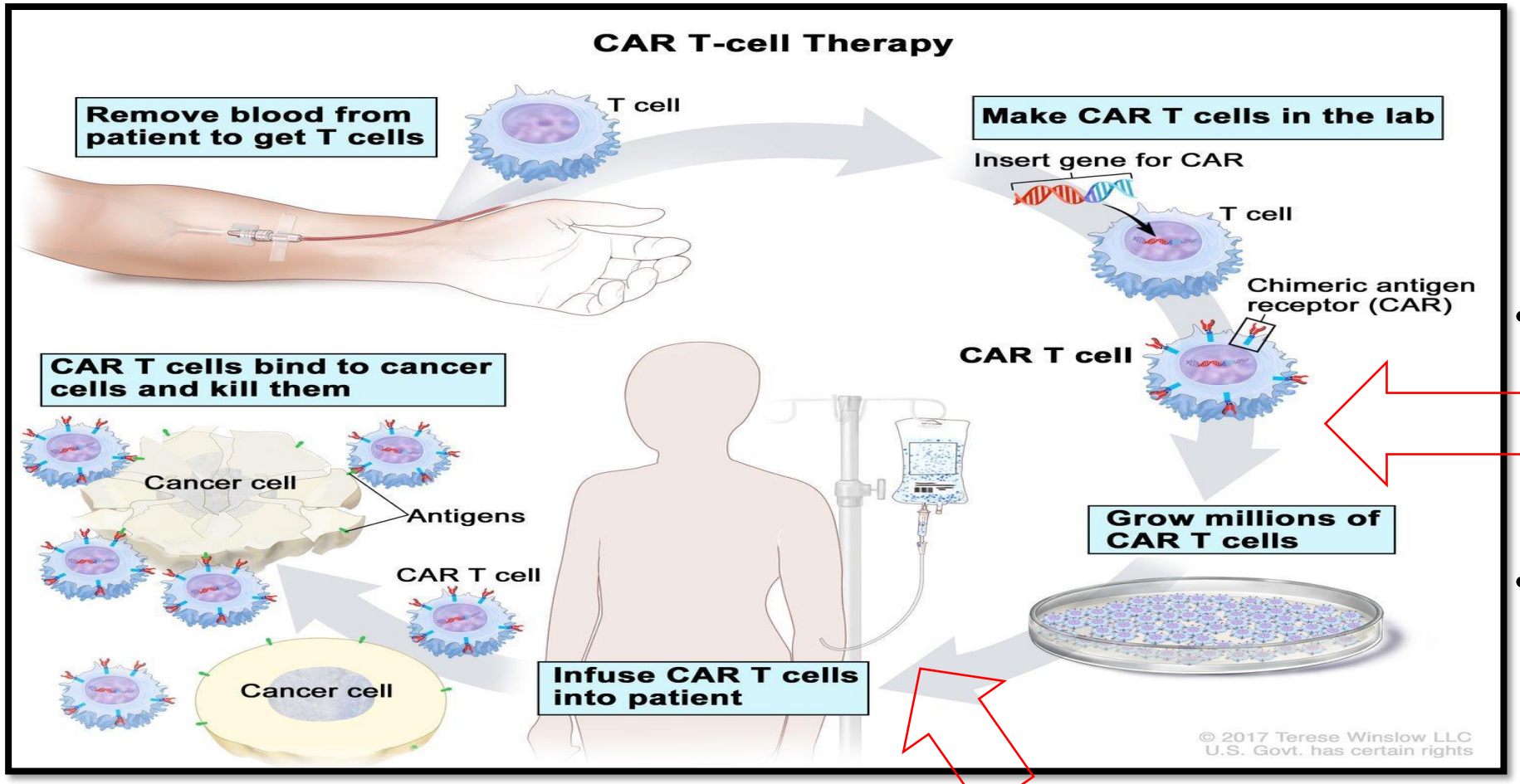
FDA APPROVED PRODCUCTS: Lymphoma

CAR T-Cell Therapy	Trial	FDA Approval	Target Dose
Lymphoma			
Axicabtagene ciloleucel YESCARTA	ZUMA-1 ZUMA-7	October 2017: Adult patients with relapsed or refractory large B-cell lymphoma **after ≥2** lines of systemic therapy including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from FL April 1, 2022: Adult patients with large B-cell lymphoma that is **refractory** to first-line chemoimmunotherapy or that **relapses** within 12 months of first-line chemoimmunotherapy	2 x 10^6 CAR-positive viable T cells/ kg, with a maximum of 2 × 10^8 CAR-positive viable T cells
	ZUMA-5	March 2021: Adult patients with relapsed or refractory FL after ≥2 lines of systemic therapy	
Brexucabtagene autoleucel TECARTUS	ZUMA-2	July 2020: Adult patients with relapsed or refractory MCL	2 x 10^6 CAR-positive viable T cells/ kg, with a max of 2 × 10^8 CAR-positive viable T cells
Tisagenlecleucel KYMRIAH	JULIET ELARA	May 2018: Adult patients with relapsed or refractory large B-cell lymphoma **after ≥2 lines** of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from FL Adult patients with relapsed or refractory follicular lymphoma **(FL) after two** or more lines of systemic therapy	0.6 to 6.0 x 10^8 CAR-positive viable T cells
Lisocabtagene maraleucel BREYANZI	TRANSCEND TRANSFORM	February 2021: Adult patients with relapsed or refractory large B- cell lymphoma **after ≥2** lines of systemic therapy, including DLBCL not otherwise specified (arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and FL grade 3B June 2022: **Refractory** disease to first-line chemoimmunotherapy or **relapse** within 12 months of first-line chemoimmunotherapy; or refractory disease to first-line chemoimmunotherapy **or** relapse after first line chemoimmunotherapy **AND** are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age	50 to 110 x 10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components)

FDA APPROVED PRODUCTS: Leukemia and Myeloma

CAR T-Cell Therapy	Trial	FDA Approval	Target Dose
Leukemia			
Tisagenlecleucel KYMRIAH	ELIANA	August 2017: Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse	Patients 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight Patients above 50 kg: 0.1 to 2.5 x 10^8 total CAR-positive viable T cells (non-weight based)
Brexucabtagene autoleucel TECARTUS	ZUMA-3	Oct 2021 Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).	1 x 10^6 CAR-positive viable T cells/ kg, with a maximum of 2 × 10^8 CAR-positive viable T cells
Multiple Myeloma			
Idecabtagene vicleucel ABECMA	KarMMA	March 2021: Adult patients with relapsed or refractory multiple myeloma after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody	300 to 460 x 10^6 CAR-positive T cells
ciltacabtagene autoleucel CARVYKTI	CARTITUDE-1	March 2022: adult patients with relapsed or refractory multiple myeloma after ≥four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody	dose range is 0.5-1.0×106 CAR-positive viable T cells/kg, max dose of 1×108 CAR-positive viable T cells per single-dose infusion

CAR T Cell Therapy Process



- Manufacturing-time line varies by product approx. 10-30 days
- Quality Testing and Release

Lymphodepleting Chemotherapy

[T-cell Transfer Therapy - Immunotherapy - NCI (cancer.gov)]

The process summary

CAR PRODUCTS

Treatment Schema – FDA Approved Products

Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day + 1 to + 14; +14-28
Outpatient				**Inpatient***		
Flu/Cy	Flu/Cy	Flu/Cy	Rest	Rest	CAR Cell Infusion	CAR Cell expansion
Nursing Care						
safe administration of LD chemotherapy symptom management: disease burden, pain patient/family support and education						bone marrow suppression, infection prevention, transfusion support, symptom management: cytokine release syndrome (CRS), neurologic changes (ICANS) patient/family support and education

- Axicabagtene ciloleucel – Yescarta
- Brexucabtagene autoleucel - Tecartus

Cyclophosphamide 500mg/m2,
Fludarabine 30mg/m2
ALL-Tecartus
Cyclophosphamide 900mg/m2 X1,
Fludarabine 25mg/m2 X3

Lisocabtagene maraleucel-Breyanzi
Cyclophosphamide 300mg/m2,
Fludarabine 30 mg/m2

Tisagenlecleucel – Kymriah
Cyclophosphamide 250/m2,
Fludarabine 25 mg/m2
ALL-Kymriah
Cyclophosphamide 500/m2 x2,
Fludarabine 30 mg/m2 x4

Ide-cel- Abecma
Cyclophosphamide 300mg/m2,
Fludarabine 30 mg/m2

Cilta-cel-Carvykti
Cyclophosphamide 300mg/m2,
Fludarabine 30 mg/m2

Common Side Effects

Cytokine Release Syndrome (CRS)

Neurotoxicity--

Immune Effector Cell Associated Neurotoxicity (ICANS)

Cytopenia

Hypogammaglobinemia

Cytokine Release Syndrome (CRS)

Definition: "A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."

Signs/Symptoms

- Fever
- Hypotension/Hemodynamic Instability
- Respiratory Changes requiring oxygenation
- Mild to moderate in severity and managed easily to severe, rapid onset and life-threatening

(Lee et al., 2018)

Symptom Complex of Cytokine Release Syndrome

Release of cytokines from cells targeted by the antibody

- C reactive protein (CRP), ferritin, interferon (IFN)-ϒ, interleukin (IL)-1,IL-2, soluble IL2Rα, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, granzyme B, granulocyte/macrophage colony stimulating factor (GM-CSF), soluble gp130 , macrophage inflammatory protein-1α (MIP-1α) and monocyte, chemoattractant protein-1 (MCP-1)

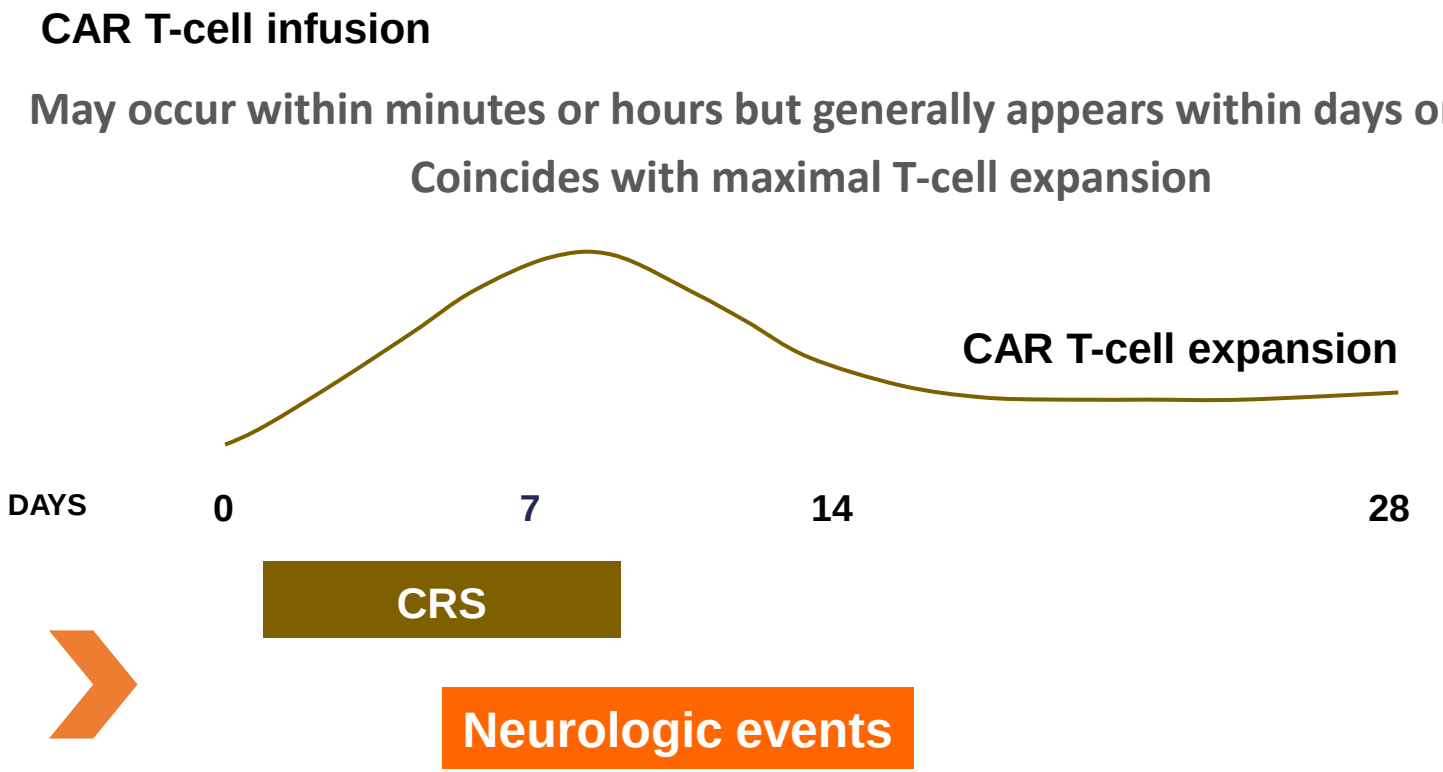
- Differential Infection/Sepsis, disease progression, heart failure, pulmonary embolism

<u>Systemic Symptoms of CRS</u>

- *Fever*
- *Hypotension/ Hemodynamic Instability*
- *Respiratory Changes requiring oxygenation*

Massive cytokine release is an oncologic emergency, and precautions must be taken to prevent life-threatening complications

Typical Onset and Resolution of CRS and Neurologic Events

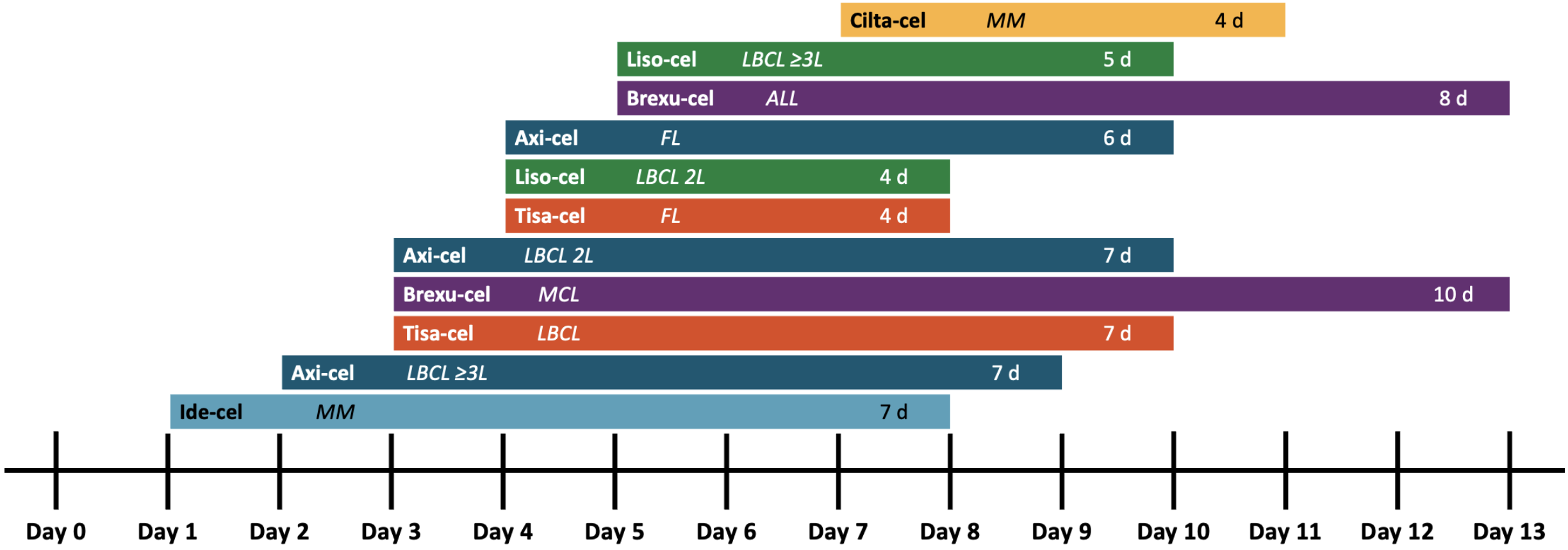


Patients MUST stay at authorized center for care 28 days

CAR T WORKING GROUP

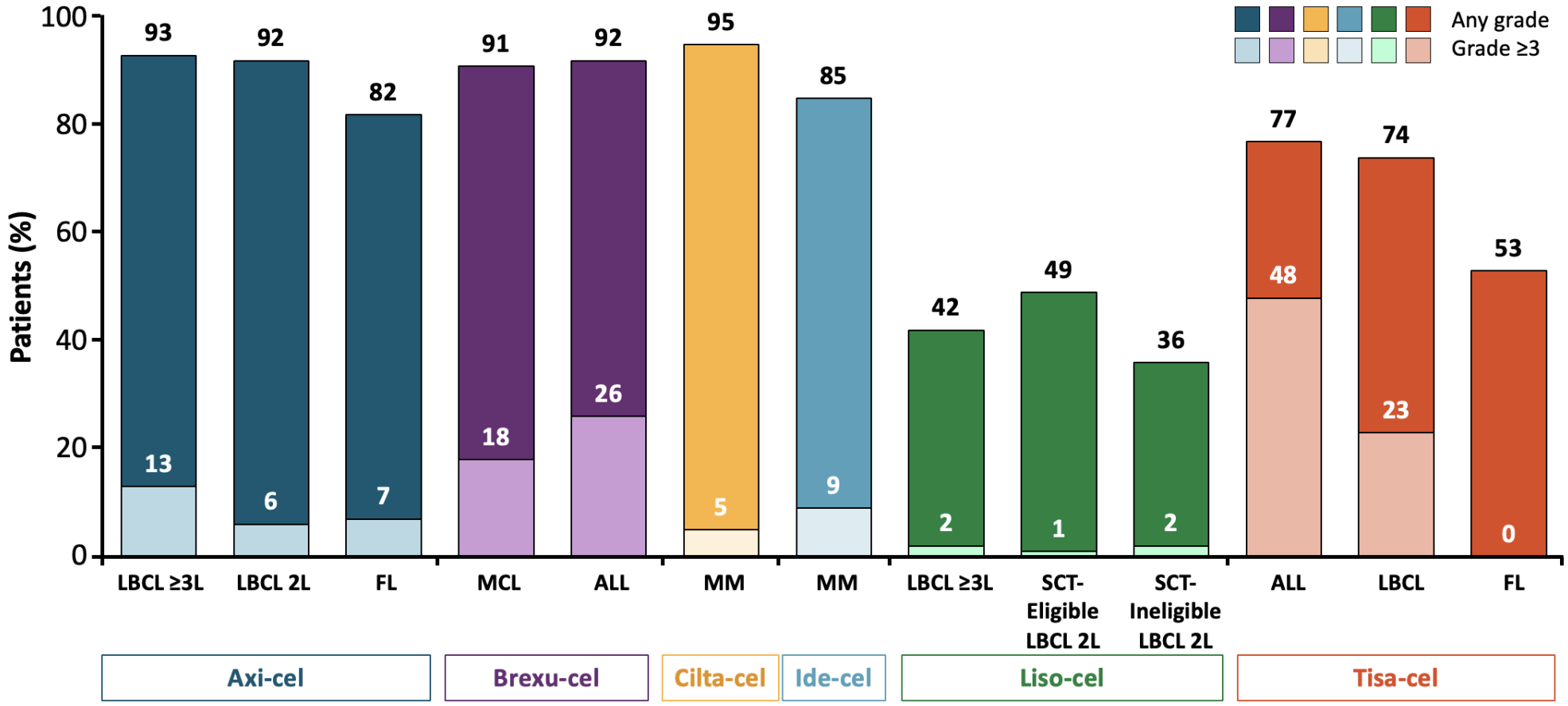
Lee DW, et al. *Blood*. 2014;124(2):188-195.

CRS: Median Time to Onset and Duration by CAR T-Cell Product



Slide Credit: Dr Dahiya

CRS Incidence by CAR T-Cell Product



Slide Credit: Dr Dahiya

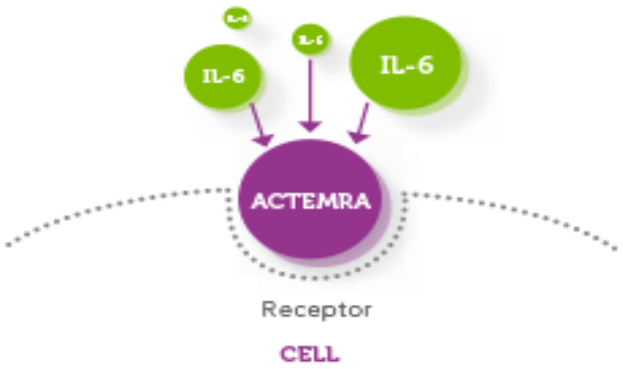
ASTCT Consensus CRS Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38 C	Temp ≥ 38 C	Temp ≥ 38 C	Temp ≥ 38 C
		WITH EITHER		
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		AND/OR		
Hypoxia	None	Requiring low flow nasal cannula or blow by	Requiring high flow nasal cannula, facemask, nonrebreather mask or Venturi mask	Requiring positive pressure (CPAP or BiPAP), intubation, and mechanical ventilation

(Lee et al., 2018)

Tocilizumab

- Dosing for CRS management is based on clinical parameters
  - Dosing of tocilizumab varies by protocol and / or institutional guidelines
    - Most common doses: 4 mg / kg or 8 mg / kg
    - Maximum dose: 800 mg
  - Timing of second dose of tocilizumab also varies by protocol and / or institutional guidelines
    - Range: every 2 to 12 hours



Siltuximab, interleukin-6 (IL-6) antagonist

ACTEMRA® [package insert] San Francisco, CA: Genentech, Inc.; May 2017.

Immune Effector Cell Associated Neurotoxicity (ICANS)

Definition: “Disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.

Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.”

Sign and Symptoms

Early Manifestations:

- Tremor, Myoclonus (muscle twitches), Dysgraphia, Expressive and receptive aphasia, presenting as impaired naming of objects, paraphasic errors (unintended speech), hesitant speech, verbal perseveration (repeating), impaired attention, apraxia (difficulty performing a task), lethargy, depressed level of consciousness

Later Manifestations:

- Global aphasia presenting as mute and unable to follow commands (akinetic), Obtundation, Stupor, Coma, Seizures, Cerebral edema

ICANS

- Neurotoxicity is reversible, potential to be life threatening
- Patients monitored daily for 7 (10 days for Carvykti) days following infusion
- REMS: Patients stay within 1-2 hour of treatment facility for 30 days post infusion, no driving for 8 weeks
- Treatment includes tocilizumab if concurrent CRS, steroids, and antiseizure agent
- *Astute Neuro Assessment a must!! Wake the sleeping baby during critical window*
  - ***Nights, nights, nights***

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells[1]

Acute

- Concurrent with CRS and high fevers
- Result of elevated cytokines
- Common; some degree of neurotoxicity occurs in nearly all CAR T patients
- Symptoms include decreased attention, confusion, disorientation, delirium, and ataxia
- **Effectively resolved with tocilizumab**

Delayed

- Occurs within days to weeks following CRS; often on resolution of CRS
- Range of symptoms: confusion, mental status changes, encephalopathy, seizures, hallucinations, aphasia, and coma
- **Generally reversible: typical duration ~3 days**

Cerebral Edema

- Rare
- Idiosyncratic
- Usually in the acute setting
- Rapid acute onset
- Requires immediate ICU transfer and intervention with mannitol with or without anti-seizure medications
- **May be fatal**

Each type of neurological toxicity is likely due to different manifestations of CAR T therapy (different underlying physiologies), responds to different mechanisms, and has a different likelihood of reversibility

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Immune Effector Cell Associated Neurotoxicity (ICE) Screening

- 10= No Impairment
- 7-9= Grade 1 ICANS
- 3-6= Grade 2 ICANS
- 0-2= Grade 3 ICANS
- Unarousable, unable to score is
- =Grade 4 ICANS

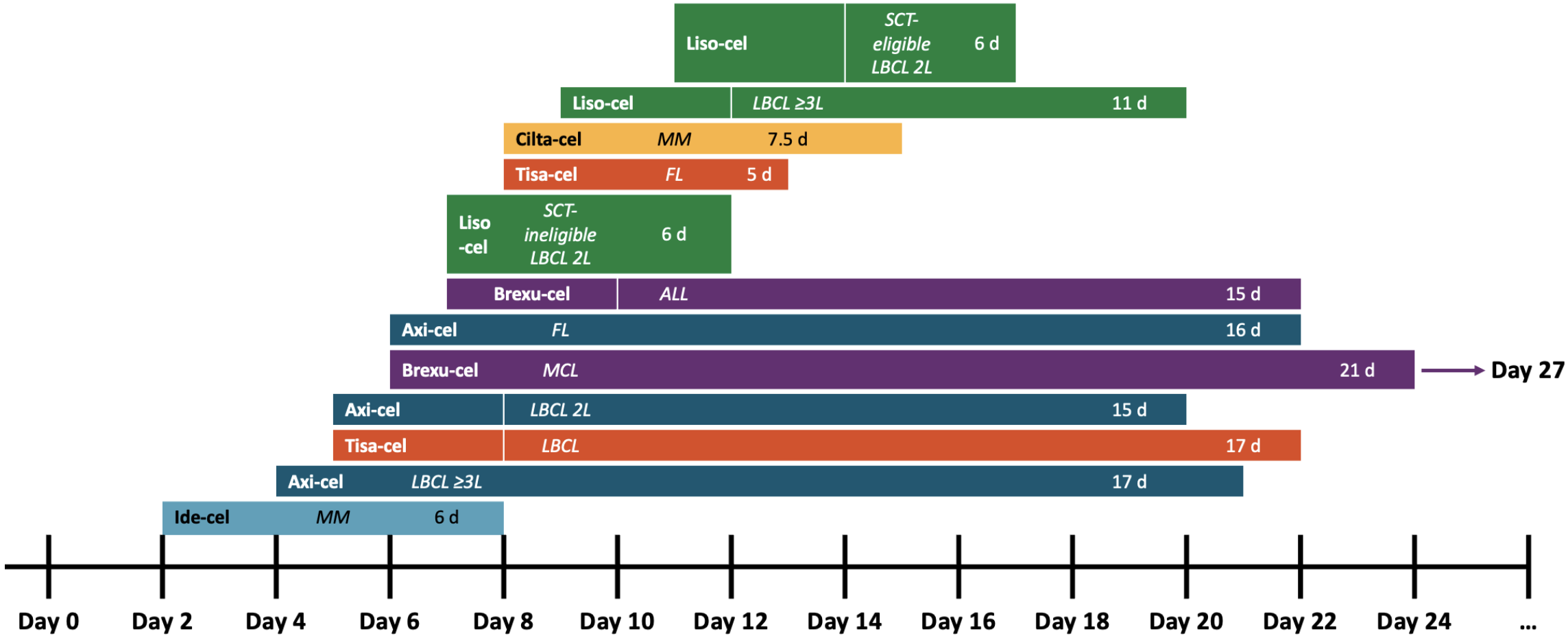
Immune Effector Cell Associated Neurotoxicity (ICE) Screening

Orientation (4)	Year, month, city, hospital	4 points
Naming Objects (3)	Clock, pen, button	3 points
Follow Simple Command (1)	Show me two fingers, close your eyes,	1 points
Attention	Count backwards by 10 starting from 100	1 point
Writing	New simple sentence	1 point

ASTCT Consensus Neurotoxicity Grading

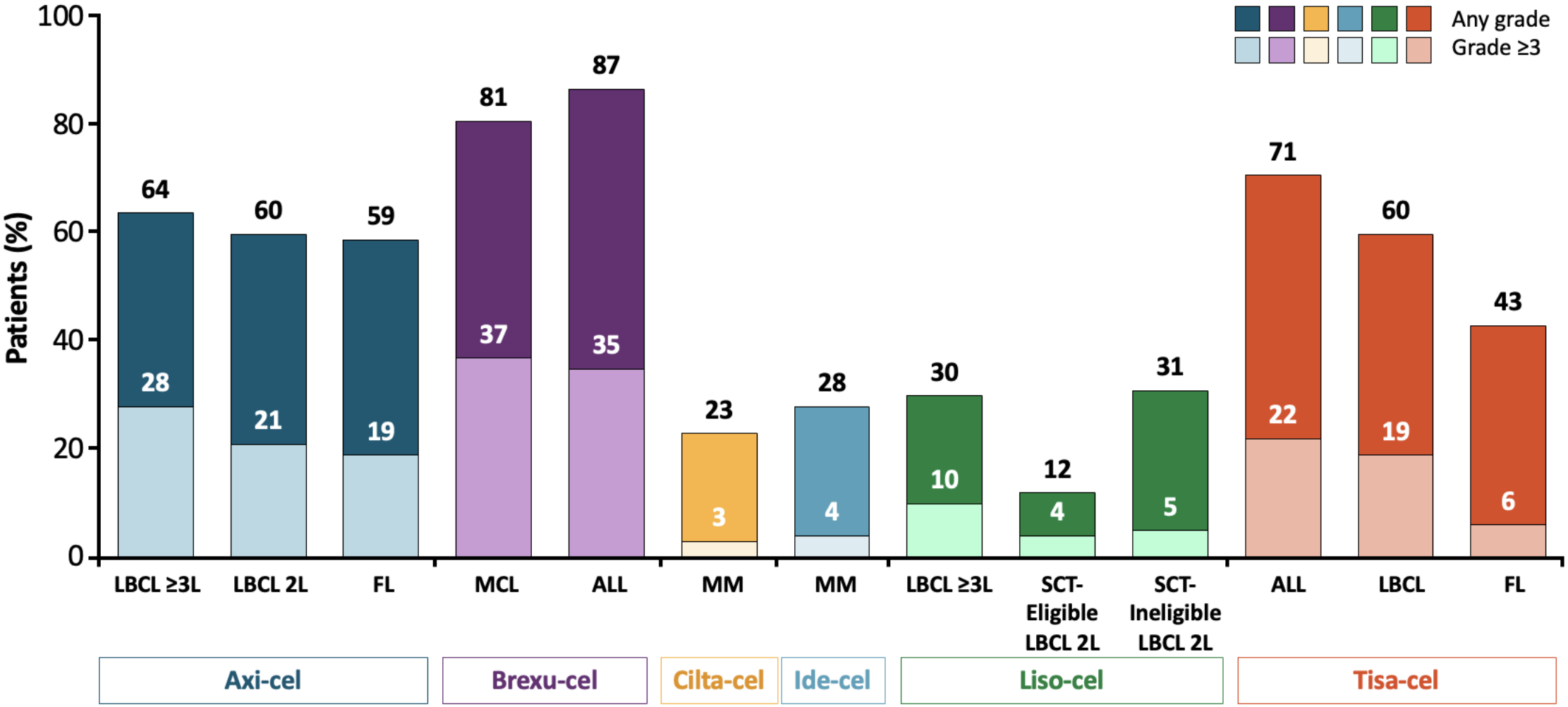
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score +	7-9	3-6	0-2	0 (unarousable, unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or non-convulsive seizure on EEG that resolves with intervention	Life threatening prolonged seizure (>5min); or repetitive clinical or electrical seizures without return to baseline
Motor findings*	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Increased ICP, Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on imaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS: Median Time to Onset and Duration by CAR T-Cell Product



Slide Credit: Dr Dahiya

ICANS Incidence by CAR T-Cell Product



Slide Credit: Dr Dahiya

Phases of Opportunistic Infections in CD19 CAR T Therapy Cell Recipients—INFECTION RISK IS HIGH-Cytopenias for up to 6 months++

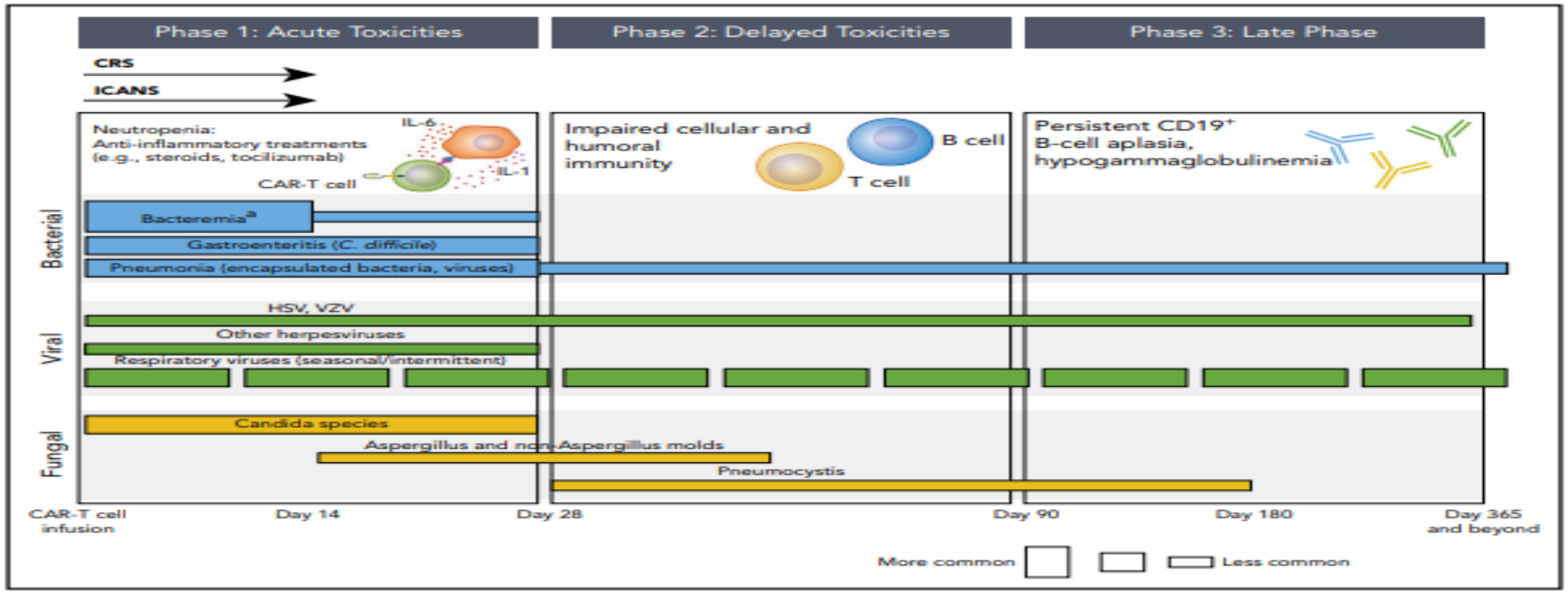
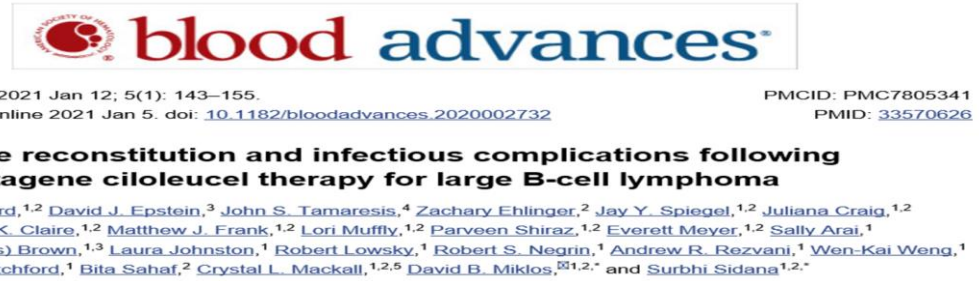


Figure 4. Phases of opportunistic infections in CD19-targeted CAR–T-cell therapy recipients. [a]Approximately 50% of bacteremia episodes are due to gram-positive organisms and 50% are due to gram-negative organisms. The conceptual model for this figure was adapted from Tomblyn et al.[35]

Hill JA, 2020. doi: 10.1182/blood.2019004000. PMID: 32582924; PMCID: PMC7441168.

Summary of Immune Reconstitution Following Axi-cel



blood advances

Blood Adv. 2021 Jan 12; 5(1): 143–155.
Published online 2021 Jan 5. doi: 10.1182/bloodadvances.2020002732
PMCID: PMC7805341
PMID: 33570626

Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma

John H. Baird,[1,2] David J. Epstein,[3] John S. Tamaresis,[4] Zachary Ehlinger,[2] Jay Y. Spiegel,[1,2] Juliana Craig,[1,2] Gursharan K. Claire,[1,2] Matthew J. Frank,[1,2] Lori Muffly,[1,2] Parveen Shiraz,[1,2] Everett Meyer,[1,2] Sally Arai,[1] Janice (Wes) Brown,[1,3] Laura Johnston,[1] Robert Lowsky,[1] Robert S. Negrin,[1] Andrew R. Rezvani,[1] Wen-Kai Weng,[1] Theresa Latchford,[1] Bita Sahaf,[2] Crystal L. Mackall,[1,2,5] David B. Miklos,[1,2,*] and Surbhi Sidana[1,2,*]

- Episodic, severe neutropenia occurs beyond D+28 in approximately half of patients
  - May continue beyond 1 year
- B-cell aplasia is prolonged in patients with durable response
- New hypogammaglobulinemia occurs in 25% of patients
  - Pre-existing hypogammaglobulinemia from prior therapy is prevalent
  - IgG titers against EBV, VZV appear preserved
- CD4 counts remain LESS than 200cells/mm for up to 1 year in most patients
  - Without prophylaxis, patients are high risk for opportunistic infections and risk of fungal pulmonary infections
- Respiratory infections and pneumonias are common
  - Peak around 3-6 months (when IgG nadirs)
- Herpes zoster is an ongoing risk for patients without acyclovir prophylaxis, even beyond 1 year

Other Side Effects-

- Parkinsonism (tremors, bradykinesia, masked face) (specific to Carvykti 5%)
- Guillain-Barré syndrome (GBS)
- Immune mediated myelitis
- Peripheral neuropathy
- Cranial Nerve Palsies

Long Term Management – Day 28 and Beyond

- **Prolonged Cytopenia- Up to 50% of pts may experience**
  - Can persist for up to 6++ months following infusion
  - Standard transfusion parameters: Transfuse!
  - GCSF 5mcg/kg to maintain ANC > 1000
  - Assess CBC/diff 1-2 times weekly as needed until cytopenia resolve
  - Last date requiring G-CSF: (date)
- **Infectious Disease Prophylaxis: GOAL: CD4 counts GREATER than 200cells/mm**
  - Acyclovir for 18+ months post
  - Sulfamethoxazole/ trimethoprim (TMP-SMX) 1 single strength tablet
  - Antifungal if high risk
  - Consider CMV PCR monitoring in CMV+ patients, if received steroids more than 5 days or previous HCT
  - Entecavir 0.5mg daily to continue at least 6 months for any chronic Hep B carrier

Long term management (continued)

Wallet Card (REMS)

- Local through day 28, **no driving for** 8 weeks

Seizure Prophylaxis

- Completed Levetiracetam 500mg BID on Day +28. Longer if neuro toxicity develops

Risk for Hypogammaglobinemia

- Recommend monitoring IgG levels at 3, 6, 9, and 12 months following infusion then give IVIG if IgG level <400 mg/dL

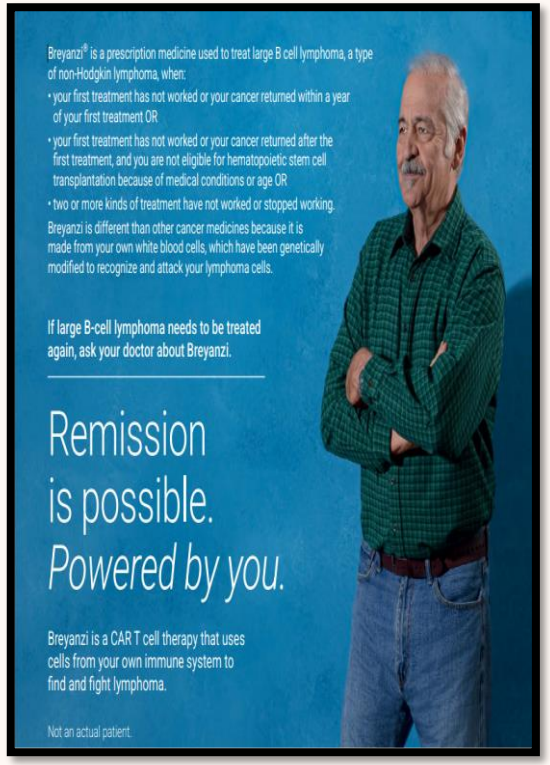
Disease Assessment

- 30 days , 3 months, 6 months and annually

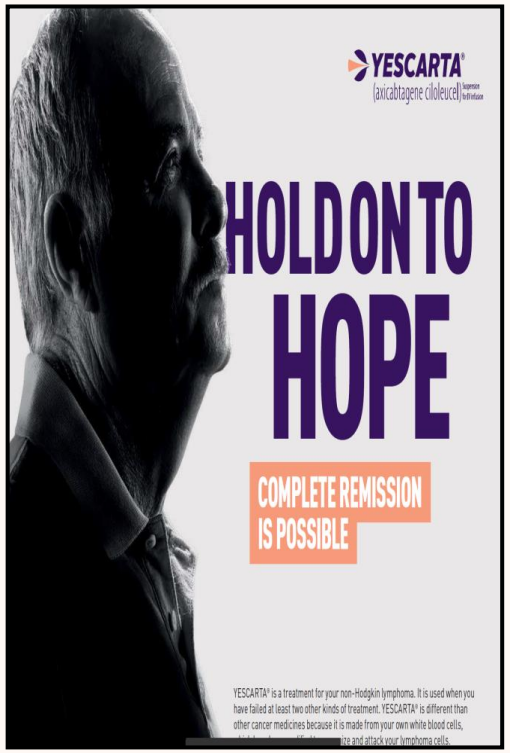
Cognitive follow up, increasing strength, survivorship

Education

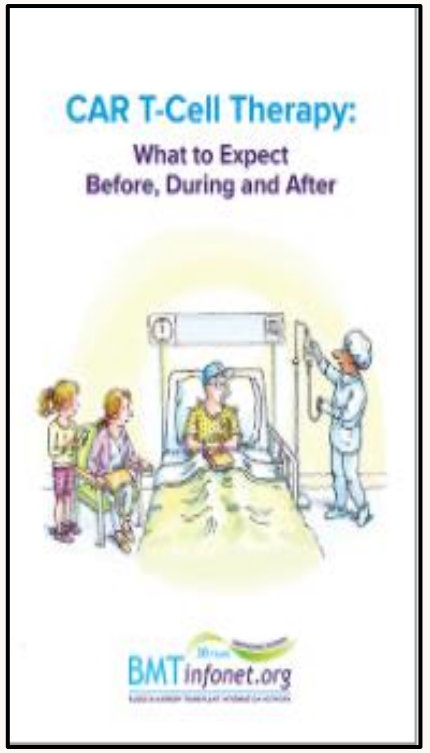
https://www.lls.org/resource-center/download-or-order-free-publications



https://www.breyanzi.com/assets/commercial/us/breyanzidtc/en/pdfs/Breyanzi_Patient_Brochure.pdf



https://getstartedwithyescarta.com/wp-content/uploads/PatientBrochure.pdf

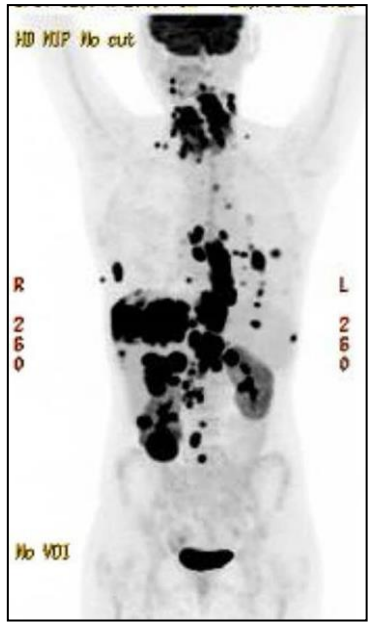


https://www.bmtinfonet.org/products

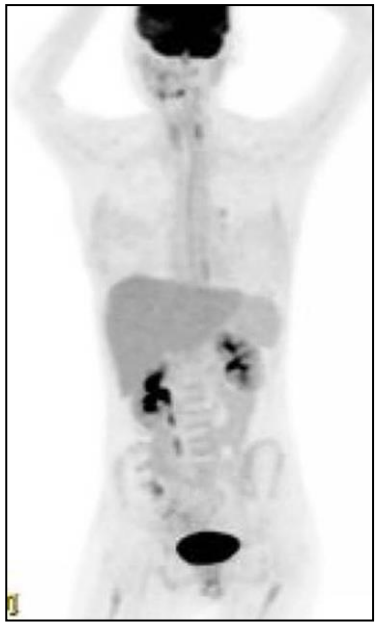
Does This CAR Work?

Overall Survival
Duration of Response
Progression Free Survival

Pre CAR T cell therapy



Day 30 post CAR T therapy

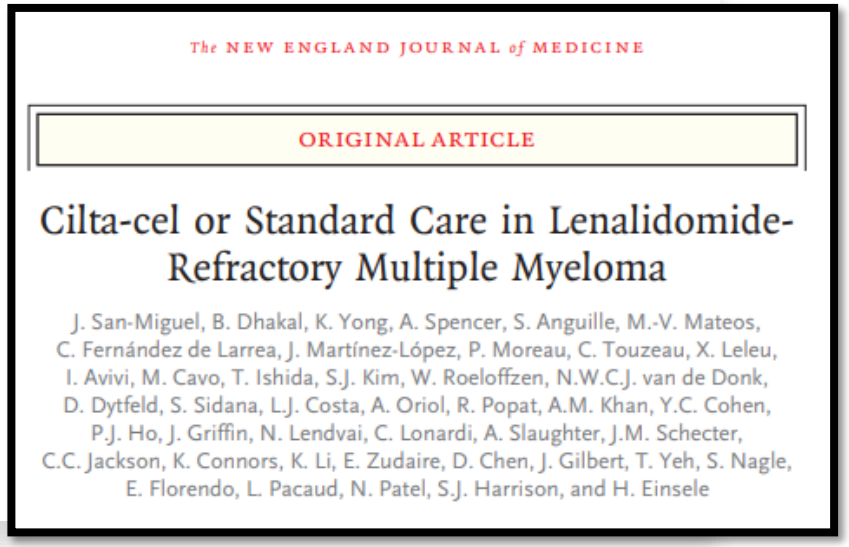


Response Rates: Myeloma

ABECMA: 72% of patients receiving ABECMA achieved a response with 28% achieving an sCR. Duration of response is about 8-11 months

CARVYKTI: Ninety-seven percent (97%) of patients who received CARVYKTI had a response with 78% achieving a sCR on the trial. The duration of response was measured at 21.8 months while progression free survival has not been reached (a large proportion of patients who were treated on trial continue to have a response). Median PFS 34.9 months in the phase 1-2 not reached in phase 3.

Progression-free survival at 12 months was 75.9% (95% CI, 69.4 to 81.1) in the cilta-cel group and 48.6% (95% CI, 41.5 to 55.3) in the standard care group



doi: 10.1016/S0140-6736(21)00933-8 (cilta-cel) & DOI https://doi. org/10.1200/JCO.22. 01365 (ide-cel)

Response Rates Lymphoma

Lymphoma					
Manufacture Approval and Protocol	**Product**	**Disease**	**Study**	**# of subjects in Phase 1/2 Trial**	**Response**
Gilead Oct 2017	**axicabtagene ciloleucel, Axi-cel, Yescarta**	DLBCL	Zuma 1 N=101	101	ORR 72%; 51% CR; 21% PR
Novartis May 2018	**Tisagenlecleucel, Kymriah**	DLBCL	Juliet	n=106	ORR 50%; 32% CR; 18% PR
Juno/Celgene Bristol-Myers Squibb (BMS) Feb 2021	**Liso-Cel, lisocabtagene maraleucel), Breyanzi**	DLBCL, follicular 3B	TRANSCEND	n=268	ORR 73%; 54% CR; 19% PR

Prior Paradigm: Chemotherapy Followed by HDT-ASCT

- For nearly 30 years, treatment for patients with refractory or relapsed Diffuse Large B-cell Lymphoma in the second-line curative setting was chemotherapy followed by HDT-ASCT
- Most patients could not receive HDT-ASCT, and their prognosis was poor

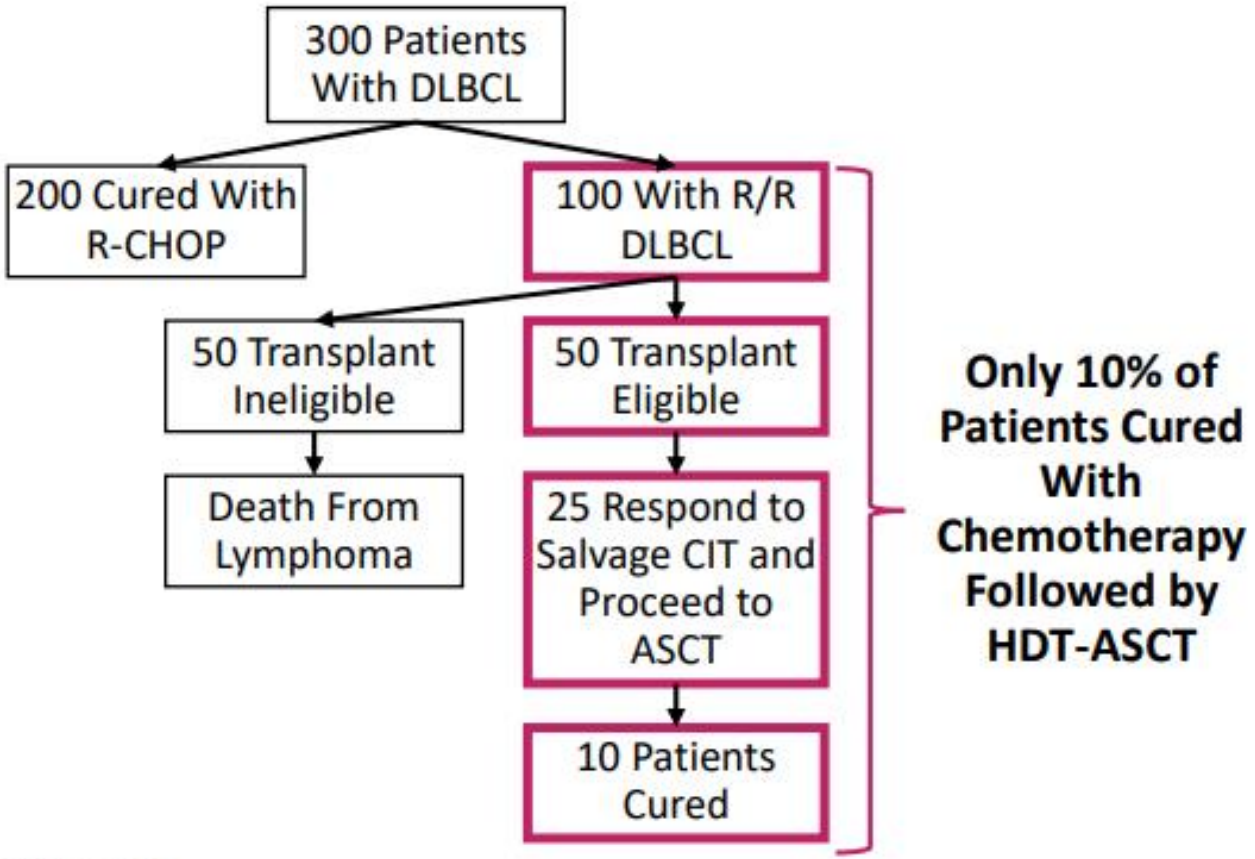
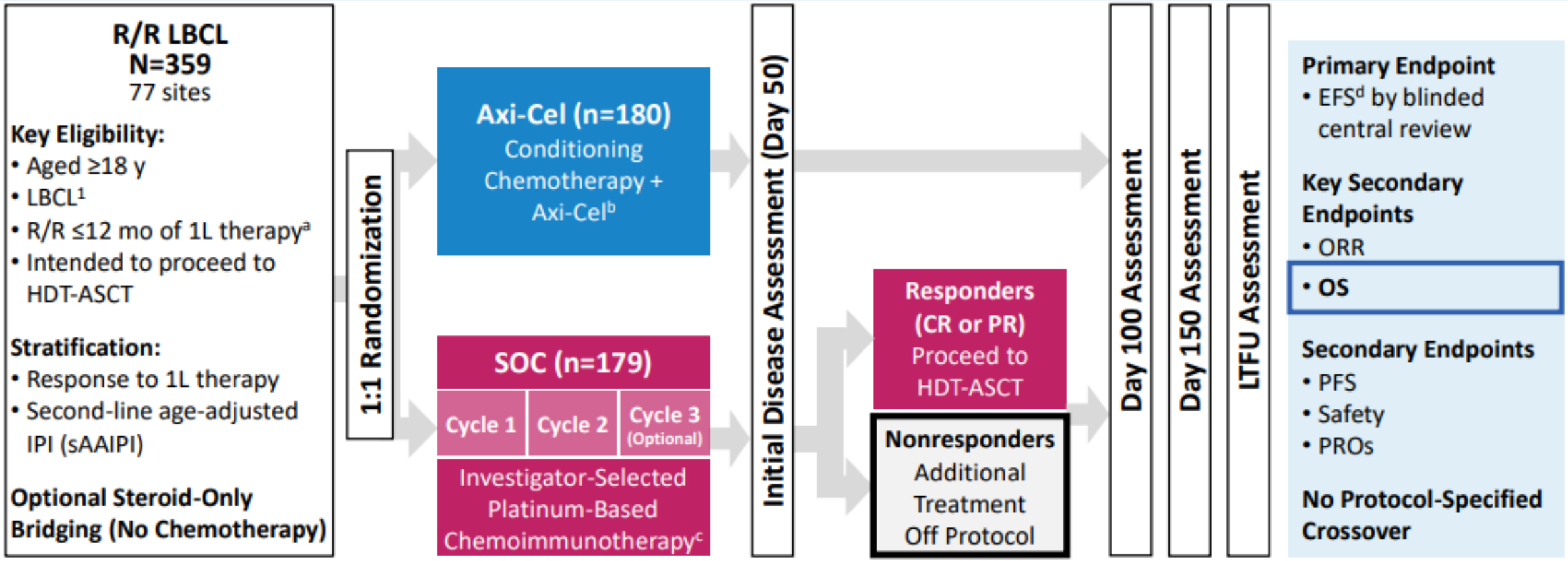


Figure adapted with permission from Friedberg JW. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505.
Zahid U, et al. *Curr Hematol Malig Rep*. 2017;12:217-226; Philip T, et al. *N Eng J Med*. 1995;333:1540-1555; Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190; Van Den Neste E, et al. *Bone Marrow Transplant*. 2016;51:51-57; van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551.
ASCT, autologous stem cell transplantation; CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; LBCL, large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.

ZUMA-7 Study Schema and Endpoints



[a] Refractory disease was defined as no complete response to 1L therapy; relapsed disease was defined as complete response followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

1L, first line; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LTFU, long-term follow-up; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; R/R, relapsed/refractory; SOC, standard of care.

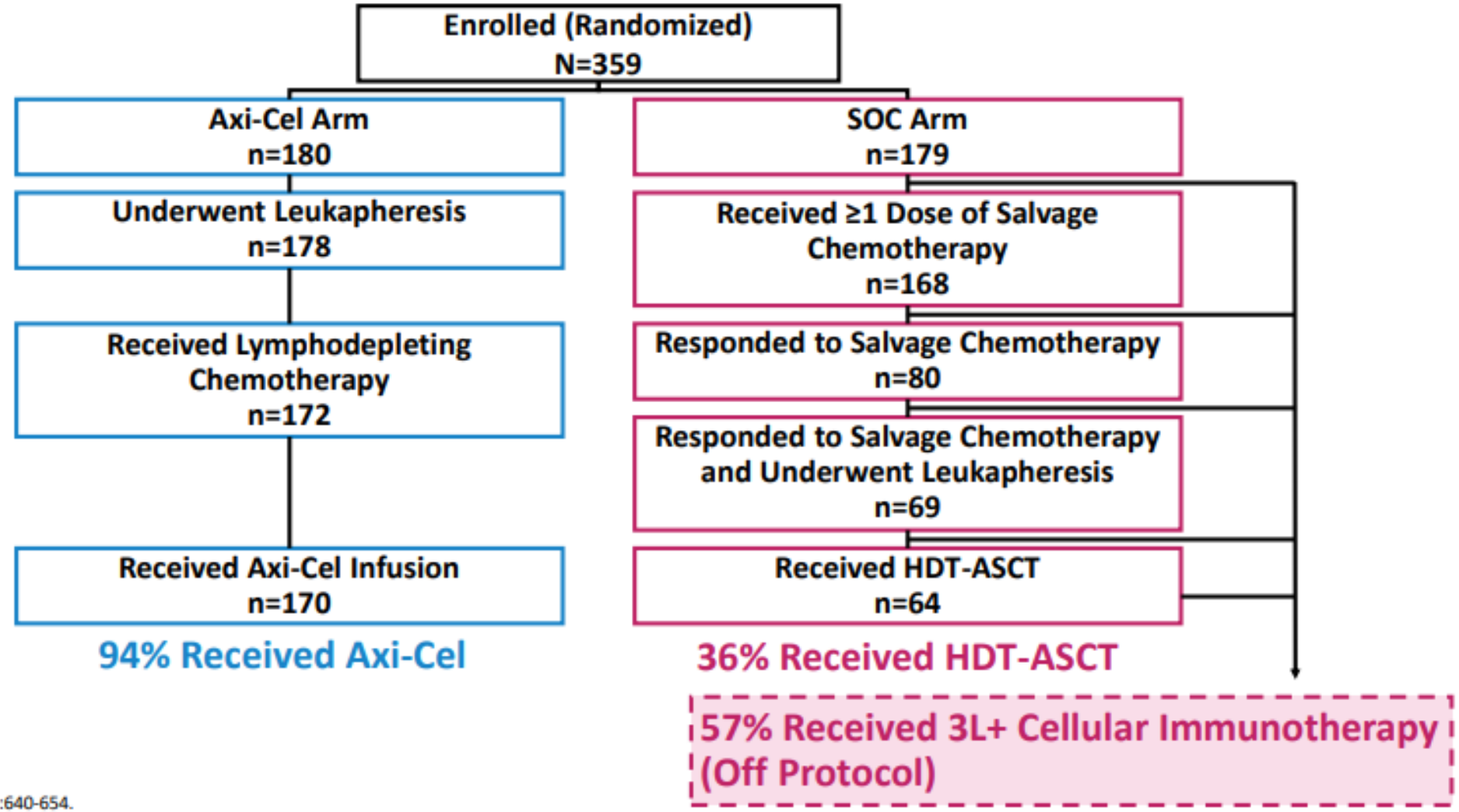
Baseline Characteristics Were Generally Balanced Between Axi-Cel and Standard of Care

Characteristic	Axi-Cel n=180	SOC n=179	Overall N=359
Median age (range), years	58 (21-80)	60 (26-81)	59 (21-81)
≥65 years, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
sAAIPI of 2-3[a], n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy[a], n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤12 mo of 1L therapy	47 (26)	48 (27)	95 (26)
Prognostic marker per central laboratory, n (%)			
HGBL (including double-hit lymphomas)	32 (18)[b]	25 (14)	57 (16)[b]
Double expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[c]	101 (56)	94 (53)	195 (54)

[a] As reported by investigator at the time of randomization. [b] Increase of n=1 from primary EFS analysis (Locke FL, et al. *N Engl J Med*. 2022;386:640-654) due to updated central laboratory results. [c] LDH level greater than upper limit of normal per local laboratory reference range.

1L, first line; axi-cel, axicabtagene ciloleucel; EFS, event-free survival; HGBL, high-grade B-cell lymphoma; LDH, lactate dehydrogenase; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care.

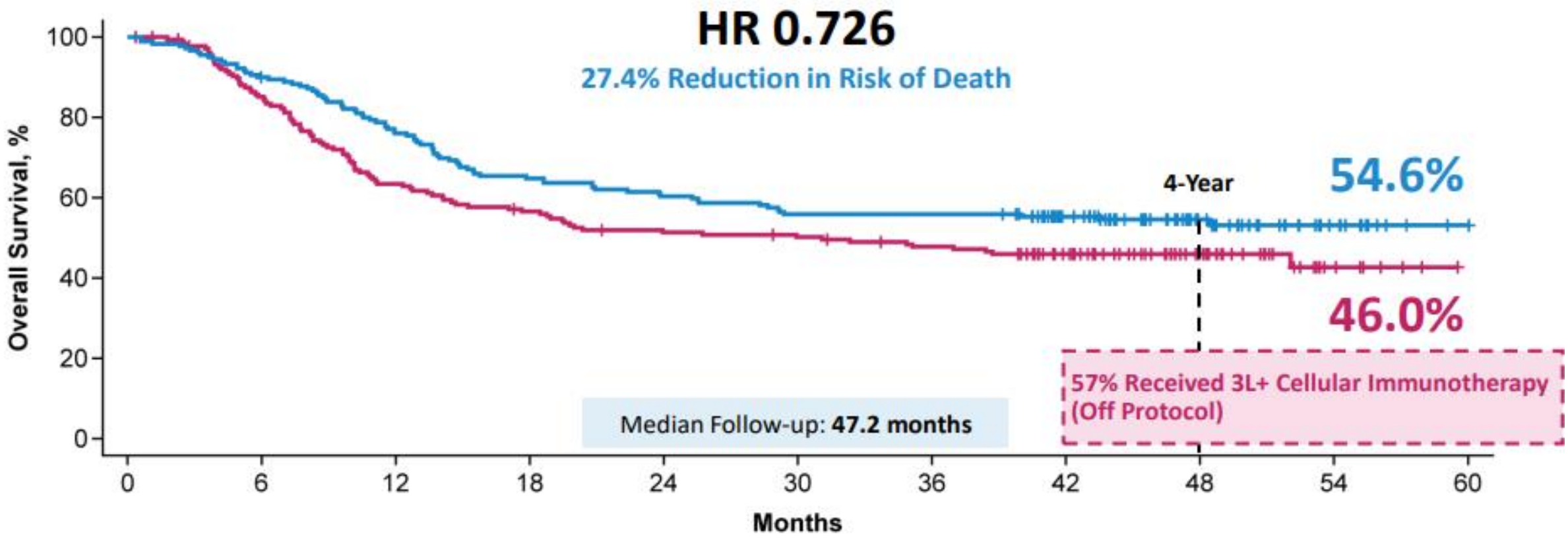
Nearly 3X Patients Received Axi-Cel Versus HDT-ASCT



Locke FL, et al. *N Engl J Med.* 2022;386:640-654.

AE, adverse event; axi-cel, axicabtagene ciloleucel; HDT, high-dose therapy; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; PD, progressive disease; SD, stable disease; SOC, standard of care.

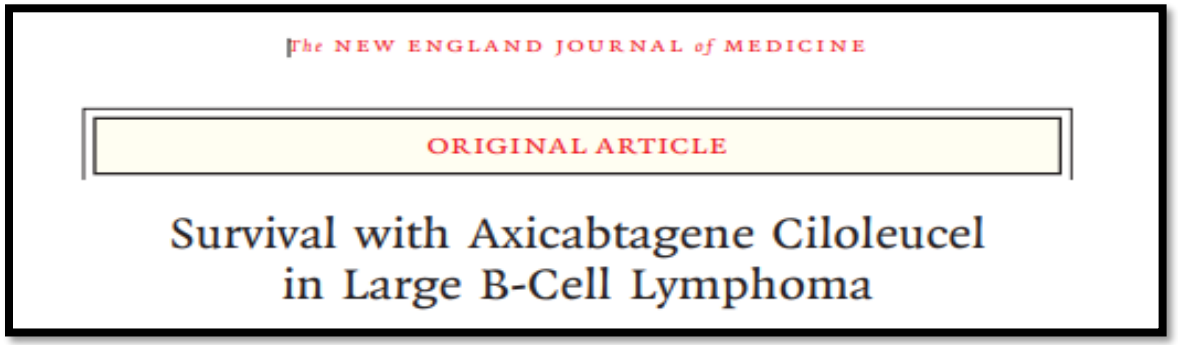
Axi-Cel Improved Overall Survival Versus Standard of Care



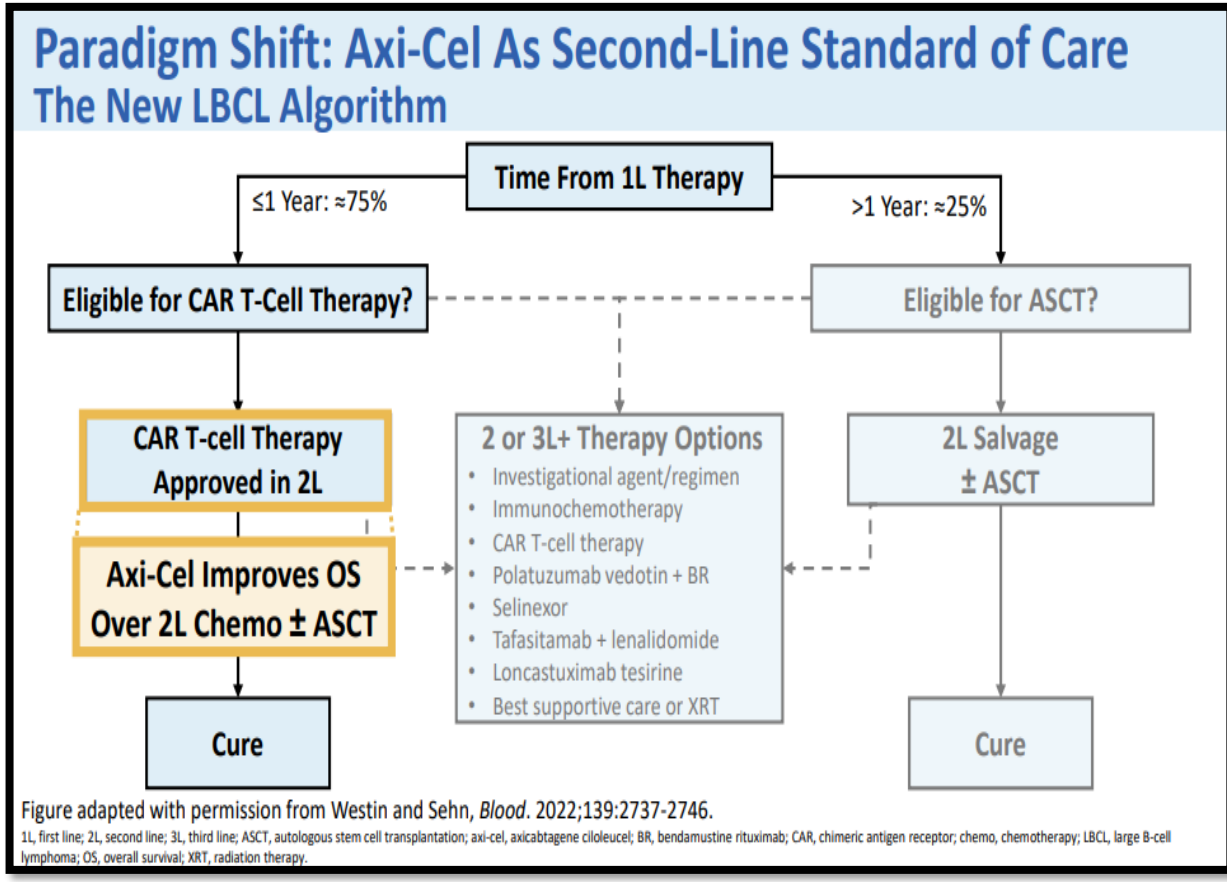
- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[a,b]

[a] Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551). [b] <40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190).
3L, third line; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

Hot of the press

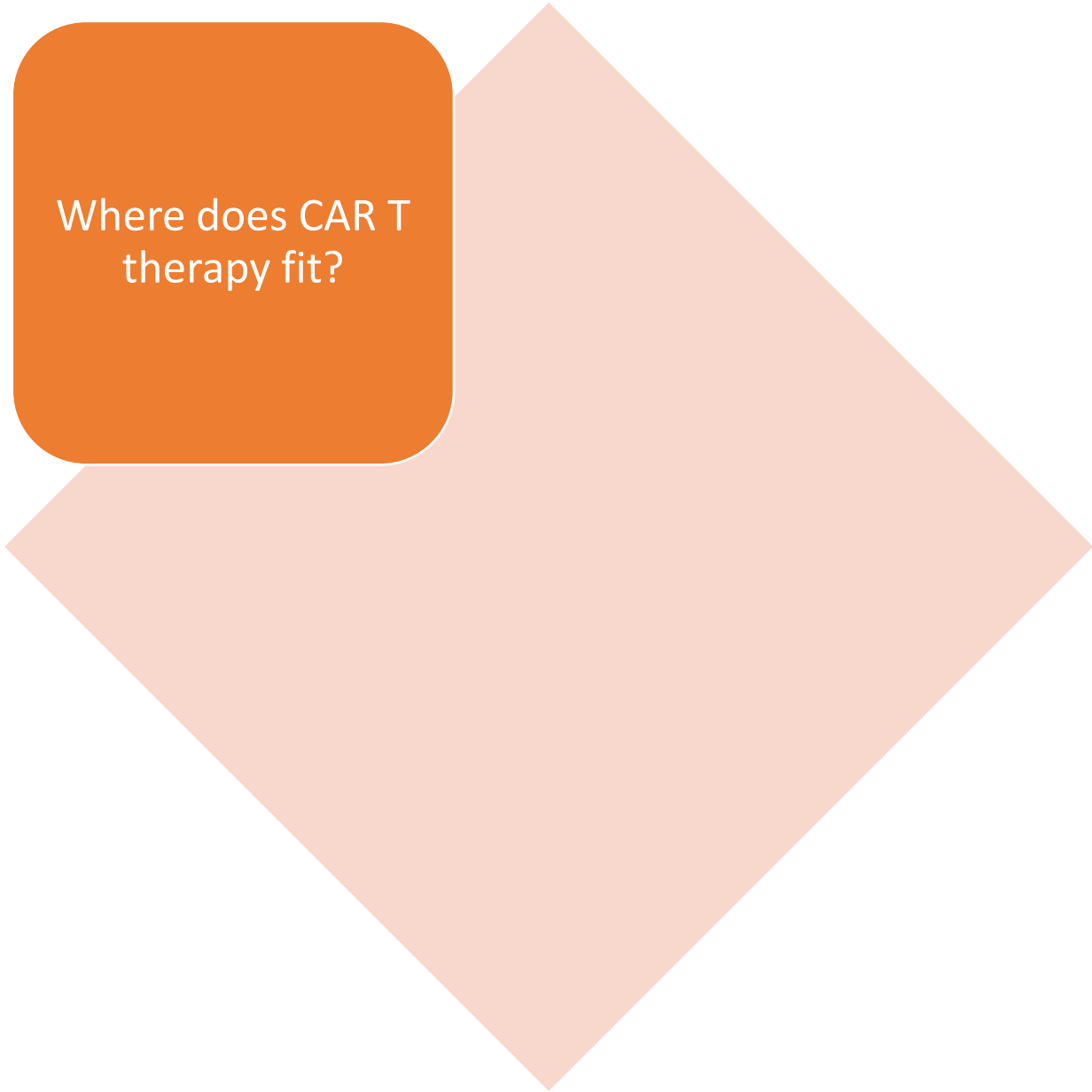


- First trial (ZUMA-7) in nearly 30 years in 2L to significantly improve overall survival
- Axi-cel improves overall survival in 2L for early R/R LBCL vs previous paradigm
- Risk of death reduced by 27.4% with axi-cel vs chemotherapy and HDT-ASCT, despite 57% subsequent cellular immunotherapy after standard of care
- Overall survival benefit similar across subgroups
- With median follow-up of 47.2 months, data are consistent with curative therapy



Westin et al ASCO 2023 Late-Breaking Abstract 107 & Westin JR,et al; Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med. 2023 Jun 5. doi: 10.1056/NEJMoa2301665. Epub ahead of print. PMID: 37272527.

How to Support Patients and our Referring Teams?



Conclusion

- CAR T provides unprecedented response rates for relapse refractory (r/r) DLBCL and ALL as well as with BCMA for myeloma
- More trials to move CAR T closer to upfront treatment (2nd line treatment)
- Challenges with toxicity: immediate and long term-
  - earlier management, improved guidelines for prophylaxis
- Early referrals to ensure patient is optimal for treatment (disease burden, fitness)
- Collaborative care with referring teams improves successful outcomes for patients

Thank You

References

- ABECMA U.S. Prescribing Information (bms.com)
- Bayer V, Amaya B, Baniewicz D, Callahan C, Marsh L, McCoy AS. Cancer Immunotherapy: An Evidence-Based Overview and Implications for Practice. Clin J Oncol Nurs. 2017 Apr 1;21(2 Suppl):13-21. doi: 10.1188/17.CJON.S2.13-21. PMID: 28315552.
- BREYANZI U.S. Prescribing Information (bms.com)
- Berdeja JG, et al . Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021 Jul 24;398(10297):314-324. doi: 10.1016/S0140-6736(21)00933-8. Epub 2021 Jun 24. Erratum in: Lancet. 2021 Oct 2;398(10307):1216. PMID: 34175021.
- Cancer and the immune system- the vital connection, Cancer Research Institute (2016) E book Cancer & the Immune System: The Vital Connection | CRI (cancerresearch.org)
- CARVYKTI-pi.pdf (janssenlabels.com)
- Hansen DK, Sidana S, Peres LC, Colin Leitzinger C, Shune L, Shrewsbury A, Gonzalez R, Sborov DW, Wagner C, Dima D, Hashmi H, Kocoglu MH, Atrash S, Simmons G, Kalariya N, Ferreri C, Afrough A, Kansagra A, Voorhees P, Baz R, Khouri J, Alsina M, McGuirk J, Locke FL, Patel KK. Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium. J Clin Oncol. 2023 Apr 10;41(11):2087-2097. doi: 10.1200/JCO.22.01365. Epub 2023 Jan 9. PMID: 36623248; PMCID: PMC10082273.
- Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood. 2020 Aug 20;136(8):925-935. doi: 10.1182/blood.2019004000. PMID: 32582924; PMCID: PMC7441168
- kymriah (novartis.com)
- Latchford, T & Tierney, D (2019) Emerging Therapies, Chimeric Antigen Receptor T Cells in Hematopoietic Stem Cell Transplantation-A Manual for Nursing Practice
- Liu C, Yang M, Zhang D, Chen M, Zhu D. Clinical cancer immunotherapy: Current progress and prospects. Front Immunol. 2022 Oct 11;13:961805. doi: 10.3389/fimmu.2022.961805. PMID: 36304470; PMCID: PMC9592930
- Iovance submits lifileucel BLA to US FDA - Pharmaceutical Technology (pharmaceutical-technology.com)
- tecartus-pi.pdf (gilead.com)
- Tumor-infiltrating Lymphocyte Therapy Explained | AACR Blog ; (2018) TIL therapy explained by Steven Rosenberg, MD, PhD
- yescarta-pi.pdf (gilead.com)
- Wilkes L, Jackson D, Miranda C, Watson R. The role of clinical trial nurses: an Australian perspective. Collegian. 2012;19(4):239-46. doi: 10.1016/j.colegn.2012.02.005. PMID: 23362610
- Westin JR, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med. 2023 Jun 5. doi: 10.1056/NEJMoa2301665. Epub ahead of print. PMID: 37272527.
- Westin et al, ASOCO 2023 Abstract 207