# Chimeric Antigen Receptor T Cell Therapy

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6/26/2021

Silicon Valley Chapter of Oncology Nursing Society

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# Objectives

- Describe the different types of Chimeric Antigen Receptor (CAR) T cell therapy
- Review pivotal trials in Non-Hodgkin's Lymphoma, Acute Lymphocytic Leukemia and Myeloma
- Describe patient management following CAR T therapy
- Describe the role of the nurse in supporting the patient undergoing CAR T therapy

Disclosures:

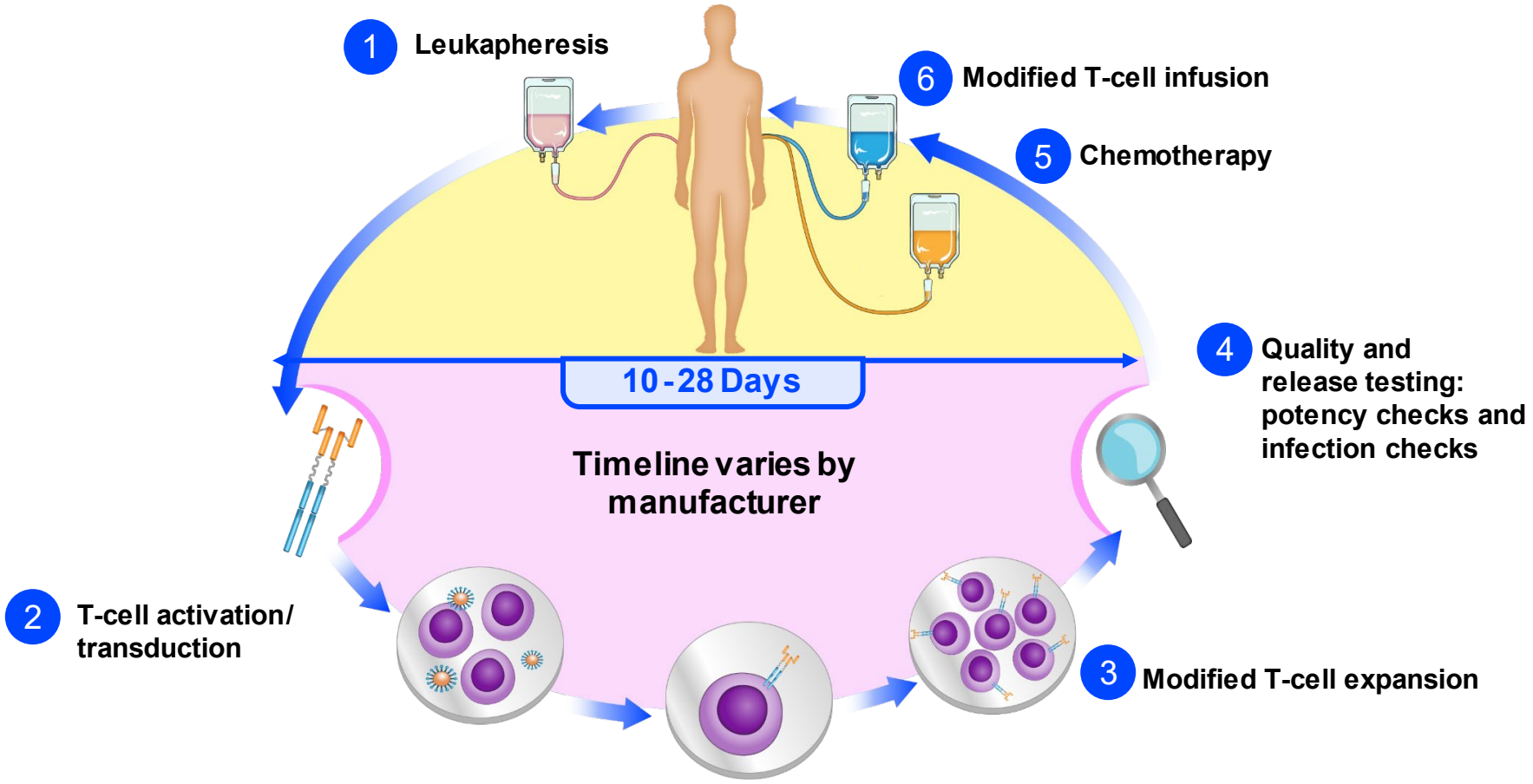
Kite Gilead Sciences

Bristol Myers Squibb (BMS)

# 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 eventually 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 patients own blood cells although this technology is evolving to develop “off the shelf” CAR T cells

# Overview of CAR T Therapy

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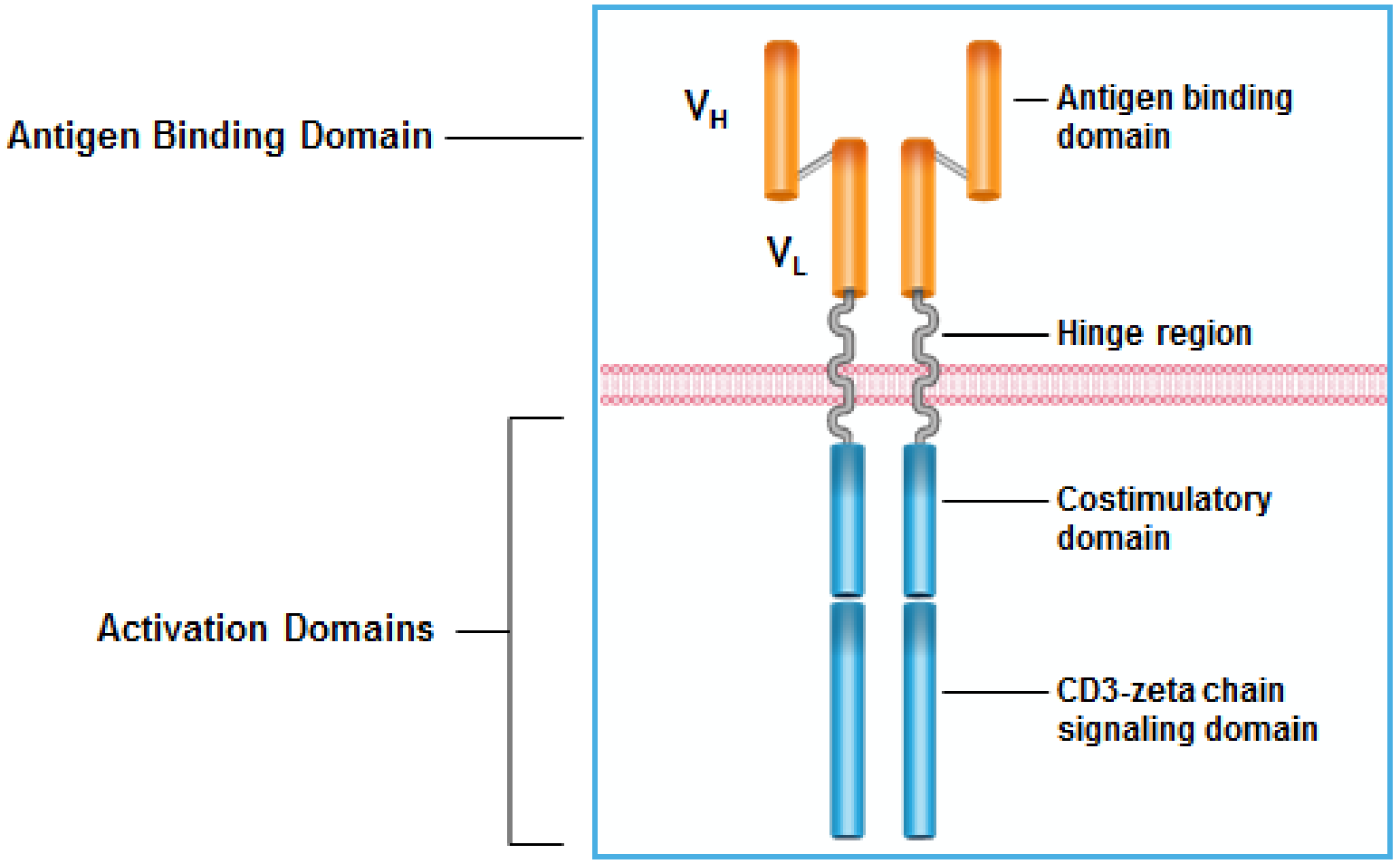
# Chimeric Antigen Receptors




**scFv**

*Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens*

**Hinge region**

*Essential for optimal antigen binding*

**Costimulatory Domain: CD28 or 4-1BB**

*Enhances proliferation, cytotoxicity and persistence of CAR T cells*

**Signaling Domain: CD3ζ chain**

*Proliferation and activation of CAR T cells*
*CAR T-cell-mediated killing of tumor cells*

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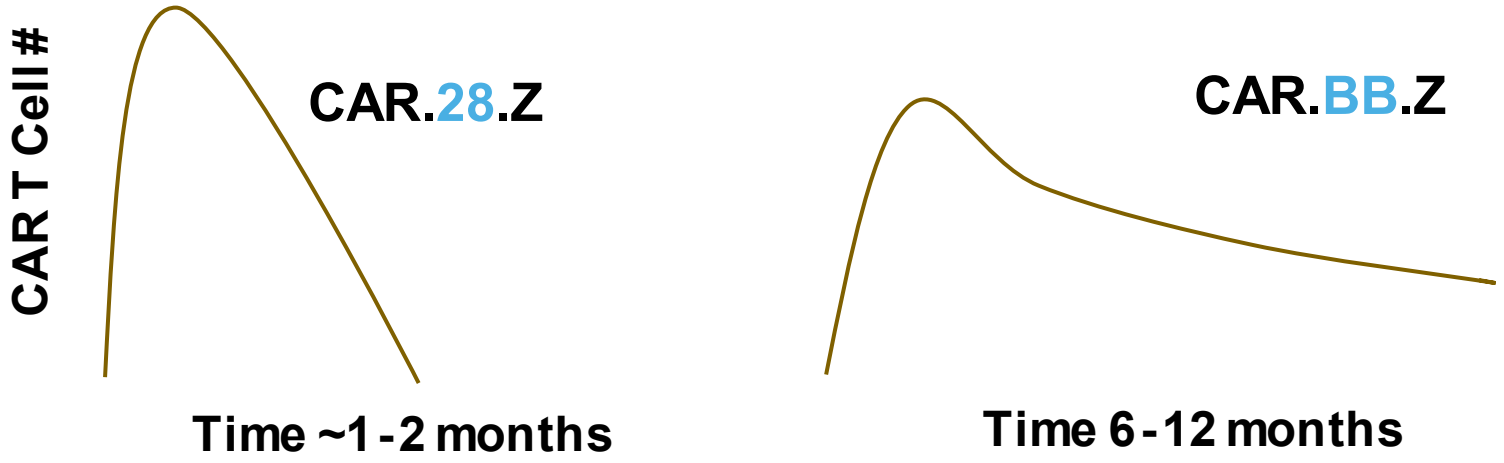
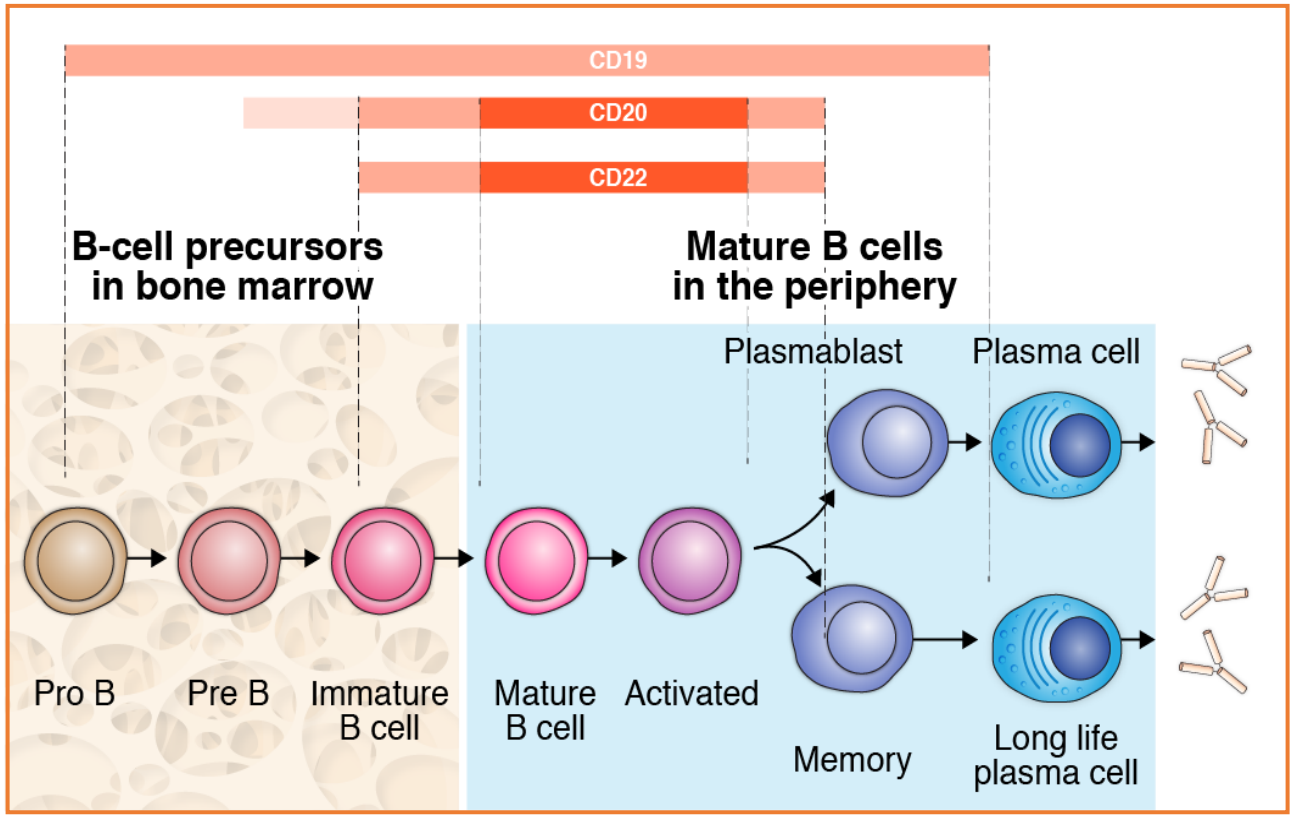
# Co-Stimulation Plays a Major Role in Modulating T-Cell Expansion and Persistence




**Both CD28-containing and 4-1BB–containing CAR T cells continue to be investigated. 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.**

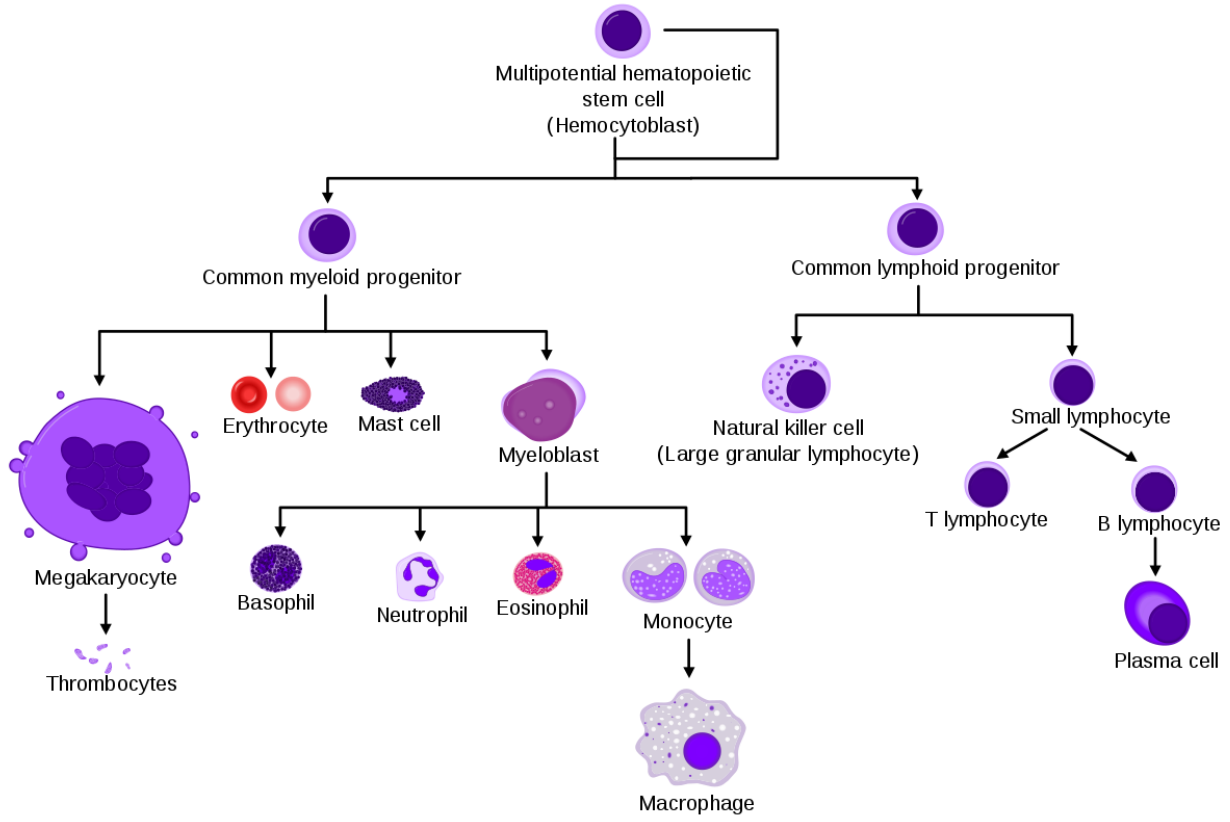
# B-Cell Development




Giraldo WAS. *Rheumatol Clin.* 2012;8(4):201-207.

# BCMA CAR T Cell for Myeloma

- B cell maturation antigen (BCMA) CAR T cell AKA a transmembrane glycoprotein in the tumor necrosis factor receptor superfamily member 17 (TNRFSF17) (gene) is not on other normal tissues except normal plasma cells
- Found on myeloma cells but limited in normal tissues



# Anti-CD19 CAR T Cells for Relapsed Refractory NHL

| | Commercially Approved for NHL | | |
|---|---|---|---|
| | **Axicabtagene Ciloleucel[1] (KTE-C19)** | **Tisagenlecleucel[2] (CTL019)** | **Lisocabtagene Maraleucel[3] (JCAR017)** |
| **Clinical Trial** | ZUMA-1<br>NCT02348216 | JULIET<br>NCT02445248 | TRANSCEND NHL 001<br>NCT02631044 |
| **Phase** | Phase 1/2 | Phase 2a | Phase 1 |
| **Dose Level** | 2 x $10^6$ cells | 3.1 × $10^8$ cells | Dose level 1: 5 × $10^7$ cells<br>Dose level 2: 1 × $10^8$ cells |
| **Conditioning Chemotherapy** | FLU 30 mg/$m^2$ and<br>CY 500 mg/$m^2$ × 3 days | FLU 25 mg/$m^2$ and<br>CY 250 mg/$m^2$ × 3 days (73%) *or*<br>Bendamustine 90 mg/$m^2$ × 2 days (20%) | FLU 30 mg/$m^2$ and<br>CY 300 mg/$m^2$ × 3 days |
| **Evaluable Patients (N)** | DLBCL/PMBCL/TFL (N = 101) | DLBCL (N = 93) | DLBCL (N = 68) |
| **Response Rates** | ORR = 82%<br>CR = 54% | ORR = 52%<br>CR = 40% | ORR = 75%<br>CR = 56% |
| **Toxicities (Grade ≥ 3)** | CRS = 13%<br>NT = 28% | CRS = 22%<br>NT = 12% | CRS = 1%<br>NT = 12% |

CRS, cytokine release syndrome; NT, neurotoxicity.
* Data presented do not reflect the final dataset for TRANSCEND NHL 001.


1. Neelapu SS, et al. *N Engl J Med*. 2017;377(26):2531-2544.
2. Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56.
3. Abramson JS, et al. ASCO 2018. Abstract 7505.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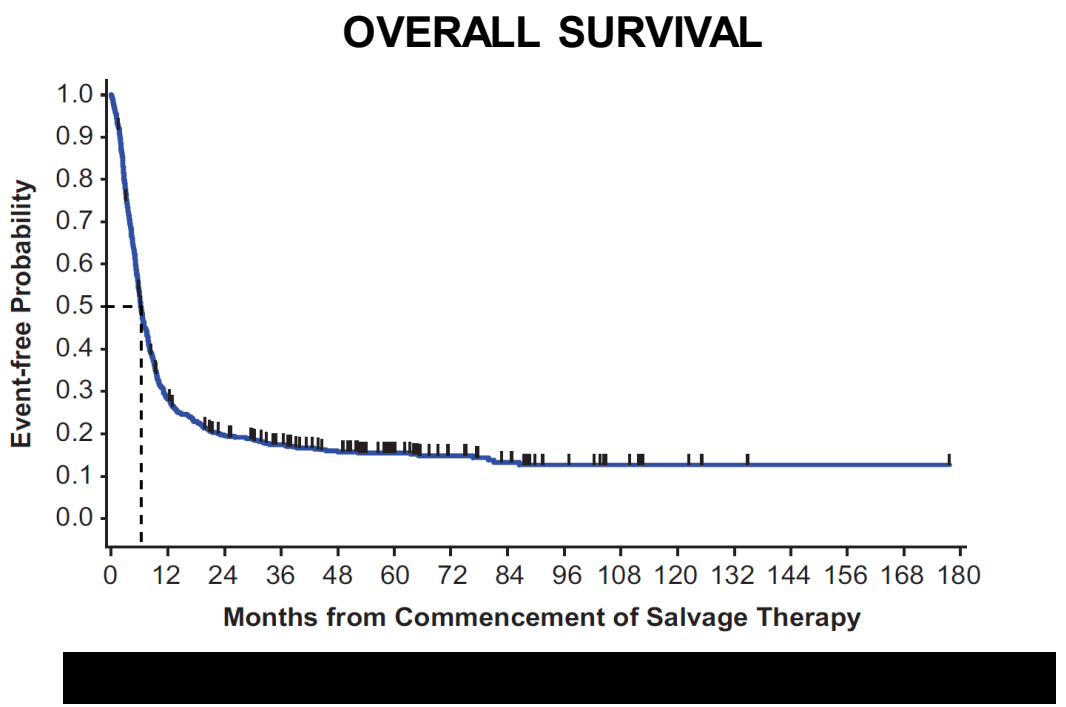
# SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research)

- SCHOLAR-1, a retrospective, international, patient-level, multi-institution study and the largest reported analysis of outcomes in patients with refractory large B-cell lymphoma, demonstrated that these patients have a very poor prognosis[1]
  - N = 636 (post-rituximab era, 2000 - 2017)
  - ORR = 26%
  - CR rate = 7%
  - Median OS = 6.3 months
- These results provided a benchmark for evaluation of new approaches




CR, complete response; ORR, objective response rate; OS, overall survival.


1. Crump M, et al. *Blood*. 2017;130:1800-1808.
2. Neelapu SS, et al. *Ann Oncol.* 2017;28(suppl 5):v403-v427. Abstract 1161P.
3. Neelapu SS, et al. ASH 2017. Abstract 579.

# FDA INDICATIONS AND USAGE: YESCARTA

YESCARTA (**Axicabtagene Ciloleucel)** is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Adult patients with relapsed or refractory large B-cell lymphoma **after two or more lines of systemic therapy, i**ncluding diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Oct 2017
  - Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.
- Adult patients with relapsed or refractory follicular lymphoma (FL) **after two or more lines of systemic therapy.** This indication is approved under accelerated approval based on response rate. (Zuma-5) Mar 2021

# FDA INDICATIONS AND USAGE: KYMRIAH

KYMRIAH (**Tisagenlecleucel)** is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:

- Adult patients with relapsed or refractory (r/r) large B-cell lymphoma **after two or more lines of systemic therapy inc**luding diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. MAY 2018
    - Limitation of Use: KYMRIAH is **not** indicated for treatment of patients with primary central nervous system lymphoma.

# FDA INDICATIONS AND USAGE: BREYANZI

- BREYANZI (**Lisocabtagene Maraleucel)** is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma **after two or more lines of systemic therapy, i**ncluding diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Mar 2021
- Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma

# Long Term Data/Outcomes?

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia. Jeff Swensen for The New York Times

December,2020

- Four-Year Data Show Long-Term Survival in Patients With Large B-Cell Lymphoma Treated With Yescarta® in ZUMA-1 Trial
  44% Estimated Four-Year Overall Survival Rate Among Refractory Large B-cell Lymphoma Patients

REAL WORLD DATA: 17 centers for DLCBL

Safety and efficacy

Pts meet the criteria for clinical trials?

Nastoupil, L. et al. (2020). Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, *38*(27), 3119–3128. https://doi-org.laneproxy.stanford.edu/10.1200/JCO.19.02104

# FDA INDICATIONS AND USAGE: TECARTUS

TECARTUS (brexucabtagene autoleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

July 2020

| | |
|---|---|
| Clinical Trial | ZUMA-2 NCT02601313 |
| Conditioning Chemotherapy | FLU 30 mg/m$^2$ and<br>CY 500 mg/m$^2$ × 3 days |
| Evaluable Patients | 60 |
| Response Rates | ORR = 87%<br>CR = 62% |
| Toxicities (Grade >3) | CRS 18%<br>NT 37% |

At 12 months, the estimated progression-free survival and overall survival were 61% and 83%,

Wang, M., Munoz, J., Goy, A., Locke, F. L., Jacobson, C. A., Hill, B. T., ... & Reagan, P. M. (2020). KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *New England Journal of Medicine*, *382*(14), 1331-1342.

# FDA INDICATIONS AND USAGE: KYMRIAH

Maude et al. *N Engl J Med* 2018

KYMRIAH (**Tisagenlecleucel)** is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:

- Patients **up to 25 years of age** with B-cell precursor acute lymphoblastic leukemia (ALL) that is **refractory or in second or later** relapse. AUG 2017

| | |
|---|---|
| Clinical Trial | ELIANA, NCT02228096 |
| Conditioning Chemotherapy | FLU 30 mg/m$^2$ x 4 days<br>CY 500mg/m$^2$ × 2 days |
| Evaluable Patients | 63 |
| Response Rates | ORR = 83% |
| Toxicities (Grade >3) | CRS 48%<br>NT 22% |

At a median follow-up of 12.3 months (range, 7.0 to 32.3), 57% of the 60 patients in the primary efficacy analysis were in remission.

# Future CARs??? B-cell ALL-Adults??

Kite's Tecartus® Demonstrates High Response Rate in **Adults** With Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia Earning Priority Review Designation

- *71% of Adult Patients in Phase 2 ZUMA-3 Study Achieved a Complete Response*
- *Supplemental Biologics License Application (sBLA) for Tecartus Accepted for Priority Review by the U.S. Food & Drug Administration (FDA)*
- Oct 2021

# BCMA-Directed CAR T Cells in Multiple Myeloma

| | bb2121<br>Bluebird | LCAR-B38M<br>Legend |
|---|---|---|
| **Population** | 36 (33*) | 57 |
| **Target** | BCMA | BCMA |
| **Ag-Binding Domain** | scFv (M) | 2-VHH (C) |
| **Vector** | Lentiviral | Lentiviral |
| **Costimulatory Domain** | CD3/41BB | CD3/41BB |
| **Lymphodepletion** | Flu (30 mg/m$^2$) /<br>Cy (300 mg/m$^2$) | Cy (300 mg/m$^2$) |
| **# Prior Tx** | 7 | 3 |
| **ORR** | 85% | 88% |
| **CR** | 45% | 74% |
| **CRS All Grades (Grade 3/4)** | 76% (6%) | 89% (7%) |
| **Med Onset of CRS** | 2 d | 9 d |
| **Neurotoxicity All Grades (Grade 3/4)** | 42% (2%) | 2% (0%) |

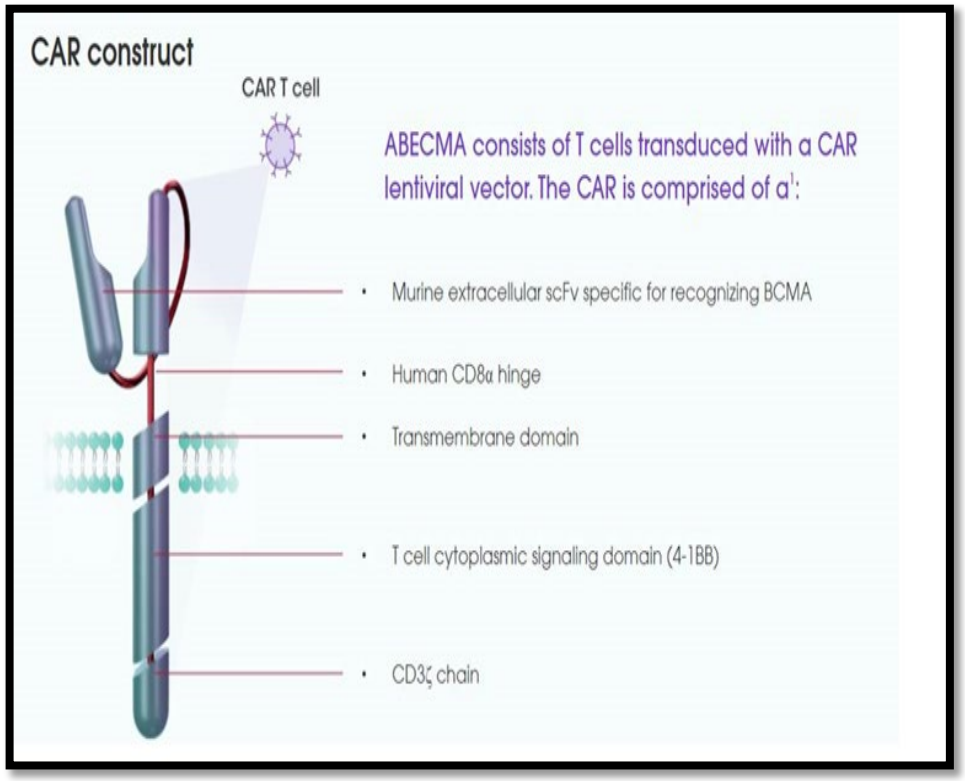
Raje N, et al. *N Engl J Med*. 2019;380(18):1726-1737. Zhao, et al. ASH 2018. Abstract 955. Mailankody, et al. ASH 2018. Abstract 957.

* Three patients underwent leukapheresis but discontinued the study owing to disease progression before bb2121 infusion. ** Based on early follow-up data

# FDA Grants First anti-BCMA CAR T Approval in Multiple Myeloma for Abecma

The FDA today approved the first anti-BCMA CAR T cell therapy for relapsed or refractory multiple myeloma, bringing a completely new and personalized immunotherapy drug class to the myeloma clinic. The approval opens an exciting door to a completely new era in myeloma care. The new one-time treatment, called Abecma, (also known as ide-cel) was approved based on data from the KarMMA trial, where 72% of patients achieved a deep and rapid response.

March 27, 2021




## Cilta-Cel Earns FDA Priority Review for Relapsed/Refractory Multiple Myeloma

May 27, 2021
Audrey Sternberg

*Based on data from the CARTITUDE-1, the BCMA-targeting CAR T-cell therapy ciltacabtagene autoleucel moves forward towards regulatory approval in multiple myeloma.*

The biologics license application for ciltacabtagene autoleucel (cilta-cel) for the treatment of patients with relapsed or refractory multiple myeloma has been accepted and granted priority review by the FDA, announced Legend Biotech Company, who is responsible for developing the chimeric antigen receptor (CAR) T-cell therapy.[1]

Data supporting the application are from the phase 1b/2 trial CARTITUDE-1 (NCT03548207), in which the B-cell maturation antigen (BCMA) therapy is being examined for safety and efficacy in the indicated patient population.

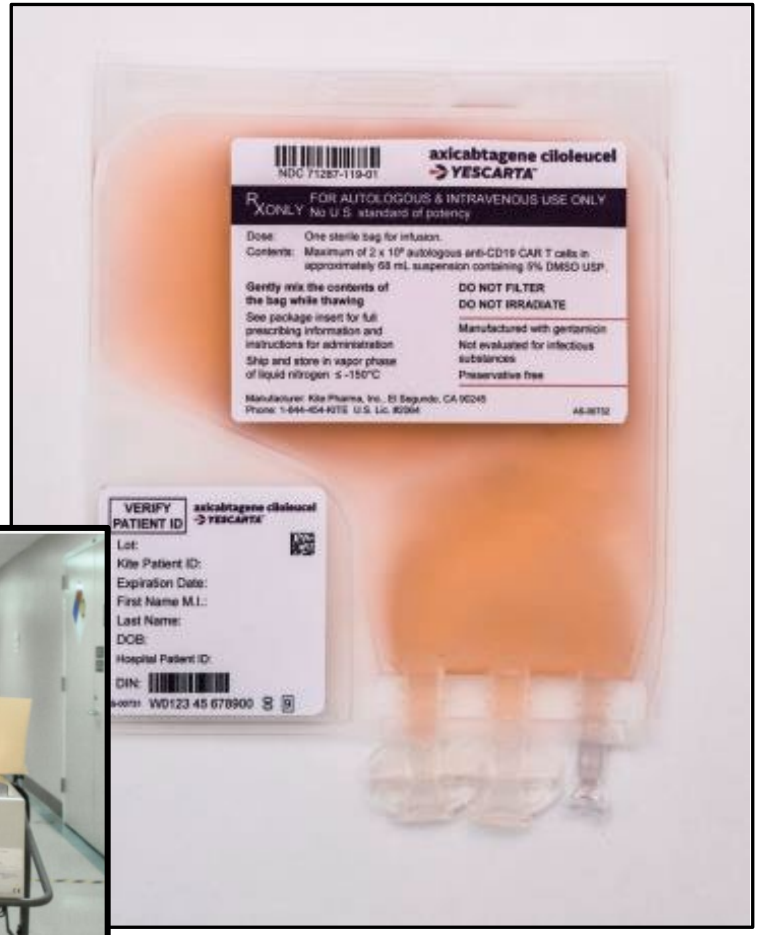
Prescription Drug User Fee Act (PDUFA) Date November 29, 2021

# FDA INDICATIONS AND USAGE: ABECMA

ABECMA is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma **after four or more prior lines of therapy,** including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Munshi, N. C., Anderson Jr, L. D., Shah, N., Madduri, D., Berdeja, J., Lonial, S., ... & San-Miguel, J. (2021). Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *New England Journal of Medicine*, *384*(8), 705-716.

# CAR T’s


NDC 71287-119-01
axicabtagene ciloleucel
YESCARTA
℞ ONLY
FOR AUTOLOGOUS & INTRAVENOUS USE ONLY
No U.S. standard of potency
Dose: One sterile bag for infusion.
Contents: Maximum of 2 x 10⁸ autologous anti-CD19 CAR T cells in approximately 68 mL suspension containing 5% DMSO USP.
Gently mix the contents of the bag while thawing
DO NOT FILTER
DO NOT IRRADIATE
See package insert for full prescribing information and instructions for administration
Manufactured with gentamicin
Not evaluated for infectious substances
Ship and store in vapor phase of liquid nitrogen ≤ -150°C
Preservative free
Manufactured: Kite Pharma, Inc., El Segundo, CA 90245
Phone: 1-844-454-KITE U.S. Lic. #0064
A6-38752
VERIFY PATIENT ID
axicabtagene ciloleucel
YESCARTA
Lot:
Kite Patient ID:
Expiration Date:
First Name M.I.:
Last Name:
DOB:
Hospital Patient ID:
DIN:
WD123 45 678900


YESCARTA


EXEMPT HUMAN SPECIMEN
THIS SIDE UP

# How to Support Your Patients

- >4 lines for MM
- >2 lines for DLBCL
  - CAR T for Second Line??? Transform trial phase 3 or Zuma 7

- First Line Treatment
  - Disease Assessment: Remission, Resistance or Relapse
- Second Line Treatment
  - Disease Assessment: Remission, Resistance or Relapse
- Third Line
  - Disease Assessment: Remission, Resistance or Relapse

- Where does CAR T therapy or BMT fit?
- Referrals to BMT/CT facility
  - Takes time!
- Education on treatment overview
  - Cell Collection
  - Cell Manufacturing
  - Treatment
  - Follow up care
- How to stay “healthy”
  - Bridging
  - Nutrition
  - Physical Mobility (ECOG)

# Treatment Schema – Lymphodepletion

| 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<br>symptom management: disease burden, pain<br>patient/family support and education | | | | | | bone marrow suppression, infection prevention, transfusion support, symptom management: cytokine release syndrome (CRS), neurologic changes patient/family support and education |

- Axicabagtene ciloleucel – Yescarta
- Brexucabtagene autoleucel - Tecartus

Cyclophosphamide 500mg/m2, Fludarabine 30mg/m2

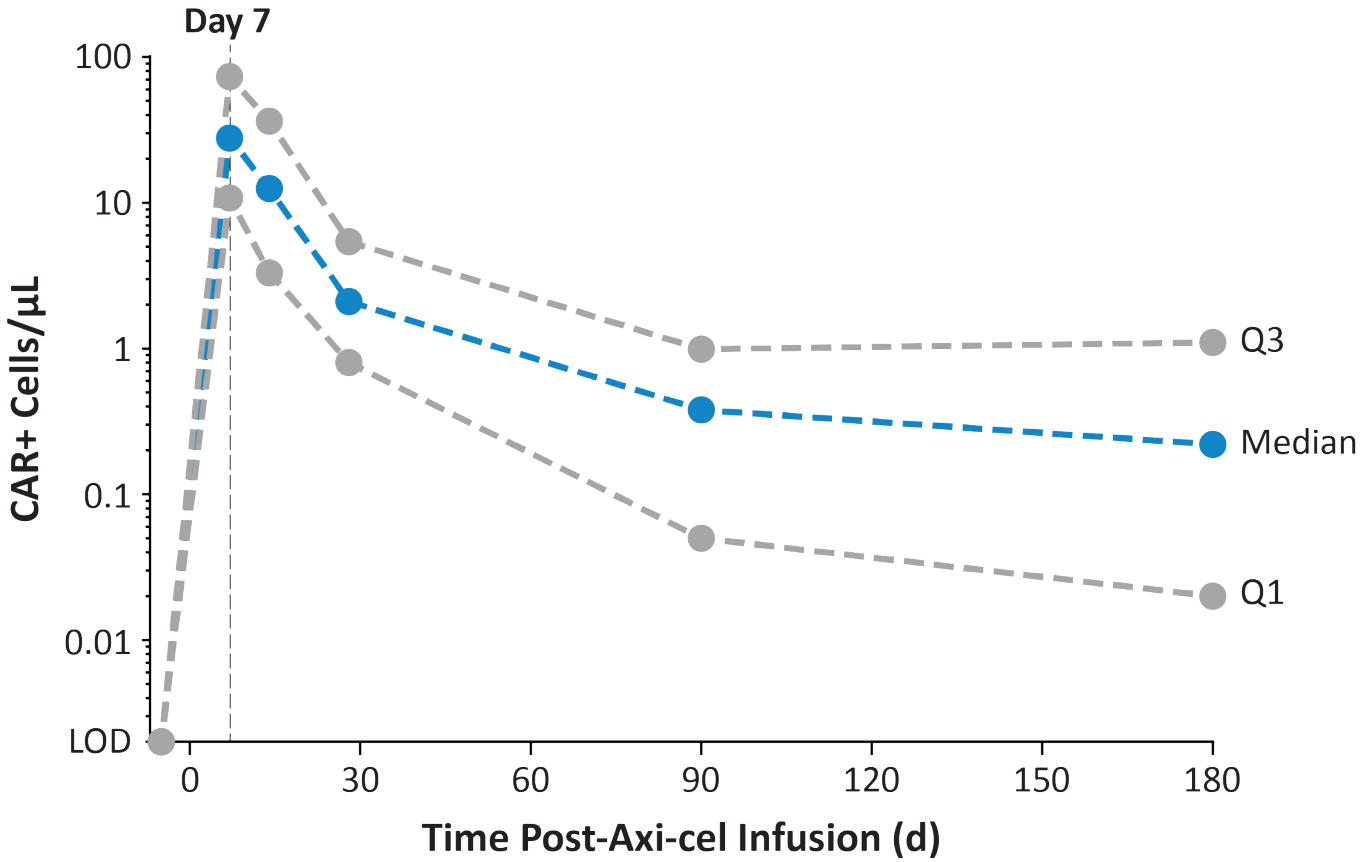
Lisocabtagene maraleucel- Breyanzi
Cyclophosphamide 300mg/m2, Fludarabine 30 mg/m2

Tisagenlecleucel - Kymriah
Cyclophosphamide 250/m2, Fludarabine 25 mg/m2

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

# Axi-Cel is a "living Therapy" that expands 4 logs in one week

Higher peak *in vivo* proliferation of CAR T cells has been associated with CRS grade and with development with severe neurologic toxicity



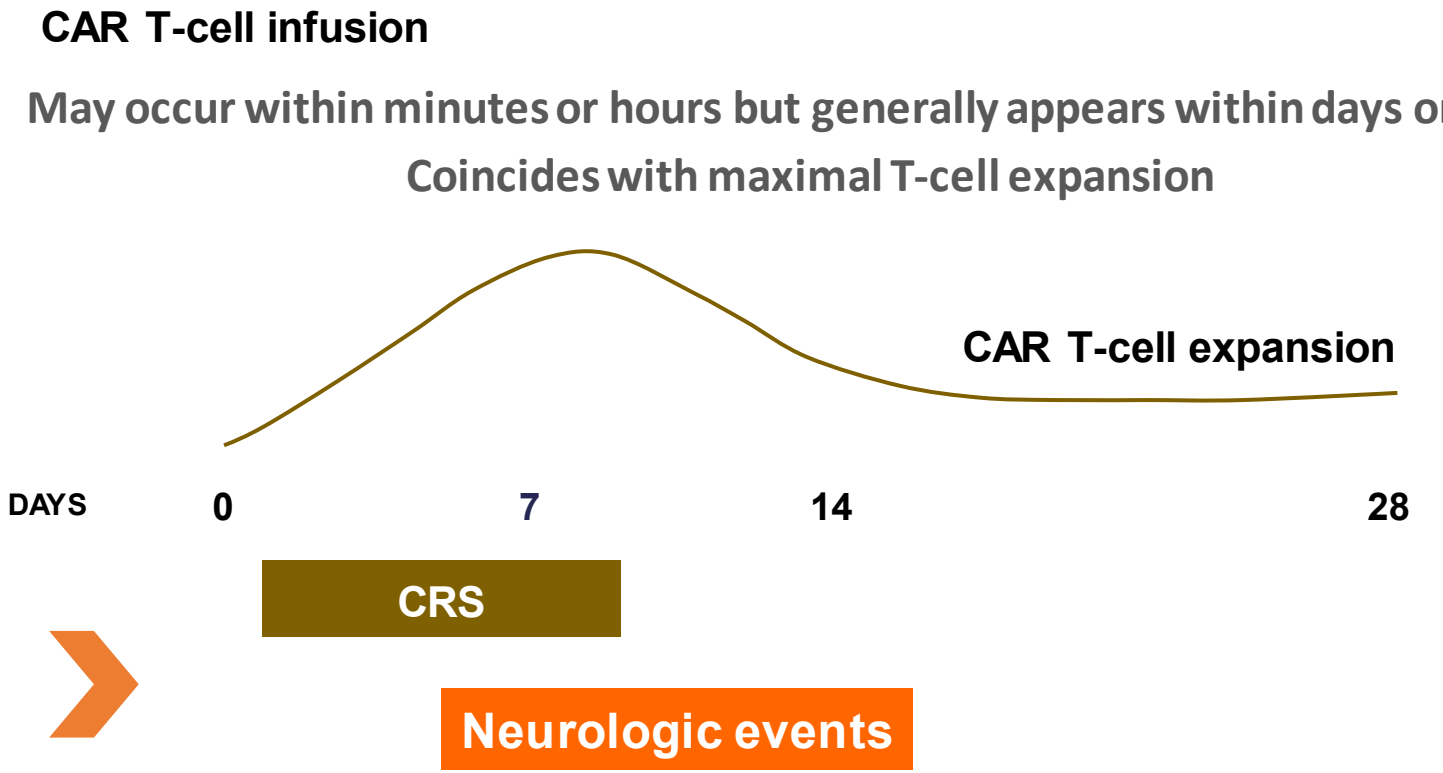

LOD = 0.002/1×$10^5$ peripheral blood mononuclear cells.

qPCR validated assay as per Locke et al. *Mol Ther*. 2015.

CAR T WORKING GROUP

Locke and Neelapu ET al. AACR 2017 #9986

# Typical Onset and Resolution of CRS and Neurologic Events




Patients MUST stay at authorized center for care 28 days

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

# 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

Cytokines: 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)

# CRS continues

- Median time to onset
  - 2-5 days with median duration 7+ days
- Management
  - supportive therapy:  blood cultures, antibiotics, fluids, Tylenol, lactate, NSIADS if indicated
  - Tocilizumab (anti interleukin 6, Il-6) , decadron, if severe vasopressors and  oxygen
  - Monitoring C reactive protein, ferritin

# 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, non rebreather mask or Venturi mask | Requiring positive pressure (CPAP or BiPAP), intubation, and mechanical ventilation |

(Lee et al., 2018)

# Neurologic Toxicity

- Neurotoxicity is reversible, potential to be life threatening
- Median onset 4 days with median duration up to 17 days
- Patients monitored daily for 7 days following infusion
- Patients stay within 1 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!!***

*Early Manifestations:*

- Tremor, Myoclonus (brief twitching), dysgraphia (inability to write), expressive and receptive aphasia, presenting as impaired naming of objects, paraphasic errors (unintended speech), hesitant speech, verbal perseveration, 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

| | 3/2/21 | | 3/3/21 | |
|---|---|---|---|---|
| | 0800 | 1939 | 0802 | 1933 |
| Answer whether each task was performed correctly using the options (Yes,No,Not Done). | | | | |
| What is the current year? | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| What is the current month? | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| What is the current city | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| What hospital are you in? | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| Perform Simple Command (Show two fingers) | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| Name this object (point to an object in the room) | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| Name this object (point to an object in the room) | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| Name this object (point to an object in the room) | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| Write a simple sentence (provide paper and pencil) | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| Count backwards from 100 in 10s | 1-Yes | 1-Yes | 1-Yes | 1-Yes |
| Total ICE Score | 10 | 10 | 10 | 10 |
| Comment | | | | |

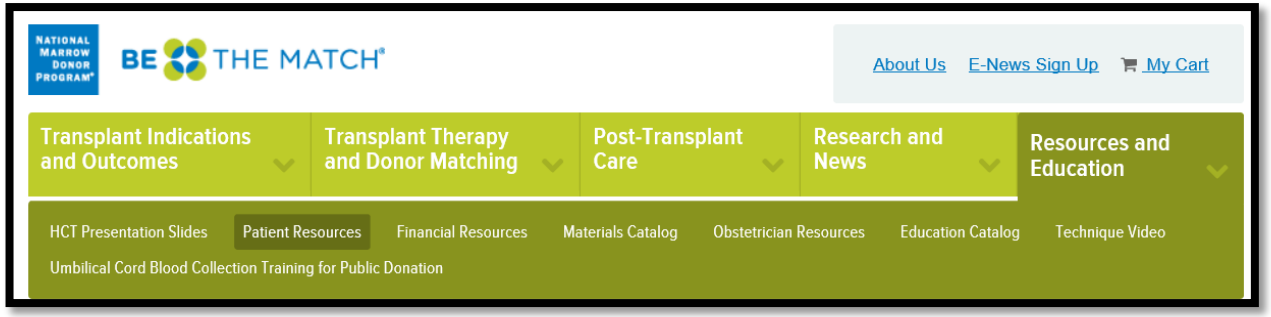
# ASBMT Consensus Neurotoxicity Grading

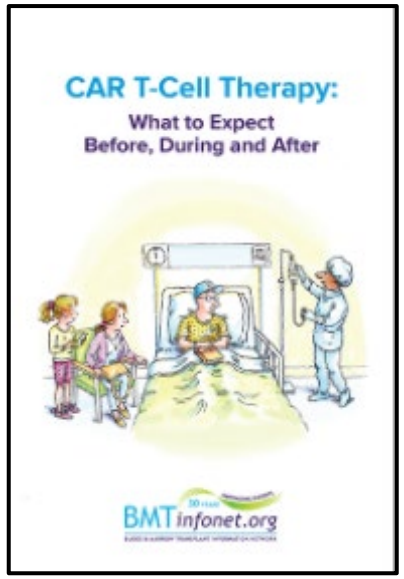
| Neurotoxicity Domain | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **ICE Score +** | 7-9 | 3-6 | 0-2 | 0 (unarousable, unable to perform ICE) |
| **Depressed level of consciousness** | Awakens spontaneously | Awakens to voice | Awakens only to tactile stimulus | Unarousable or requires 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 |

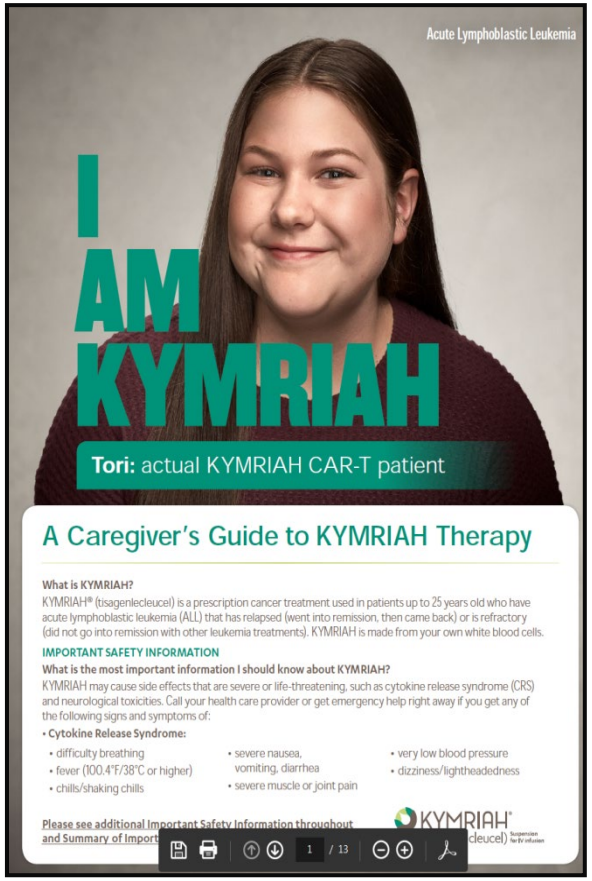
# Patient Education

https://bethematchclinical.org/resources-and-education/patient-resources/

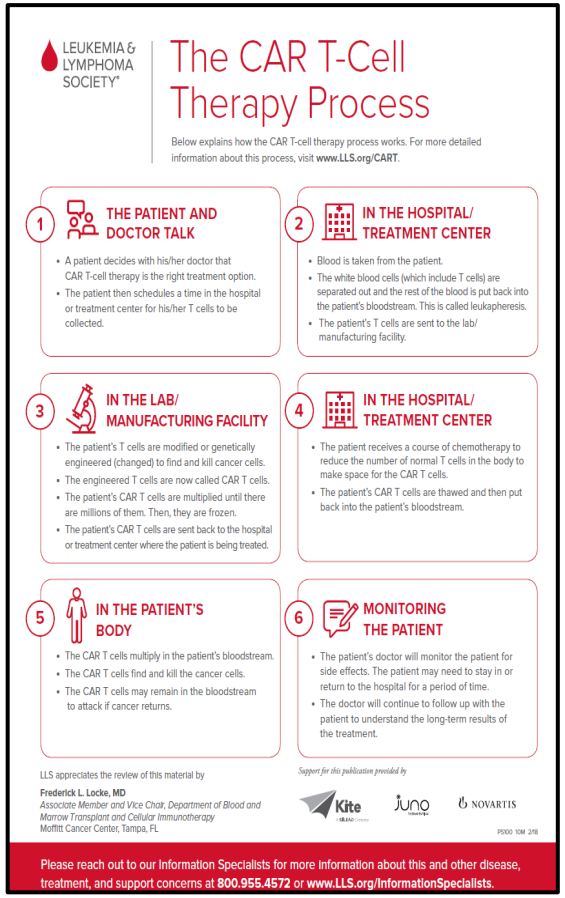
- Consents
- Guidebooks
- Commercial Patient Education tools
- Others



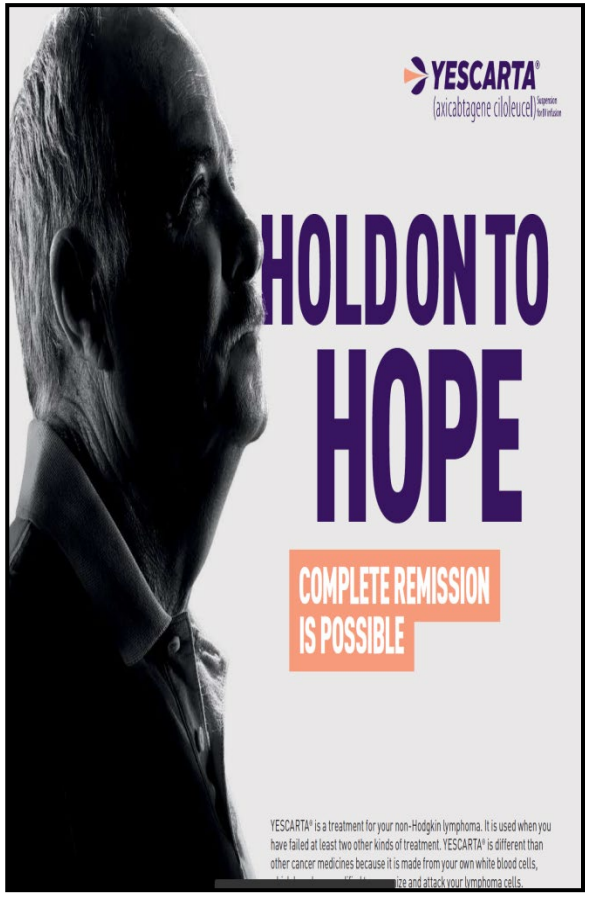




https://www.us.kymriah.com/acute-lymphoblastic-leukemia-children/patient-support/download-helpful-materials/



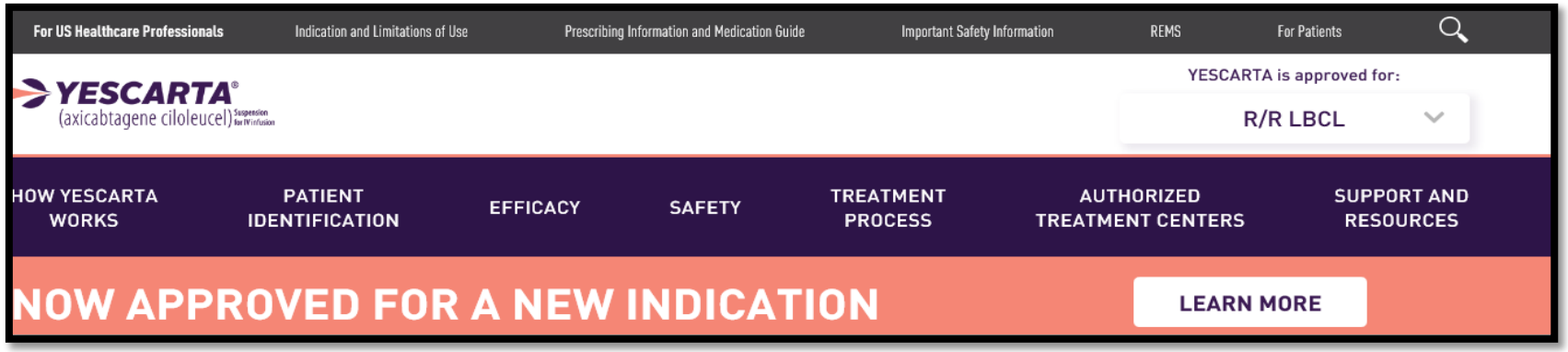

https://www.lls.org/resource-center/download-or-order-free-publications



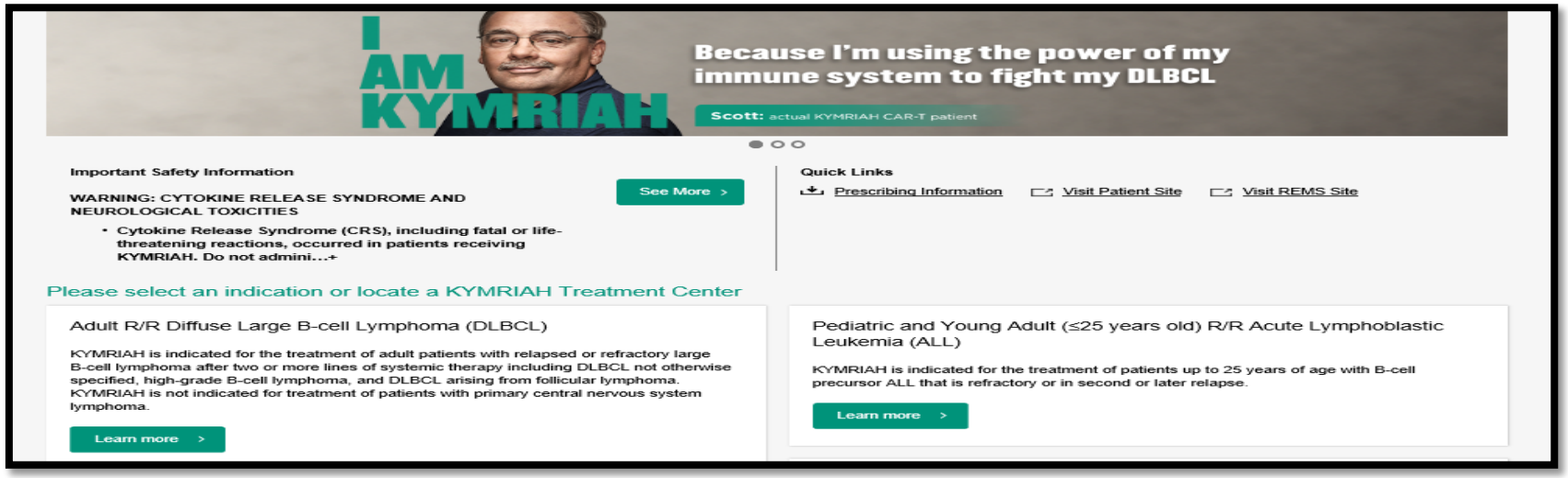

https://getstartedwithyescarta.com/wp-content/uploads/PatientBrochure.pdf

# DLBCL

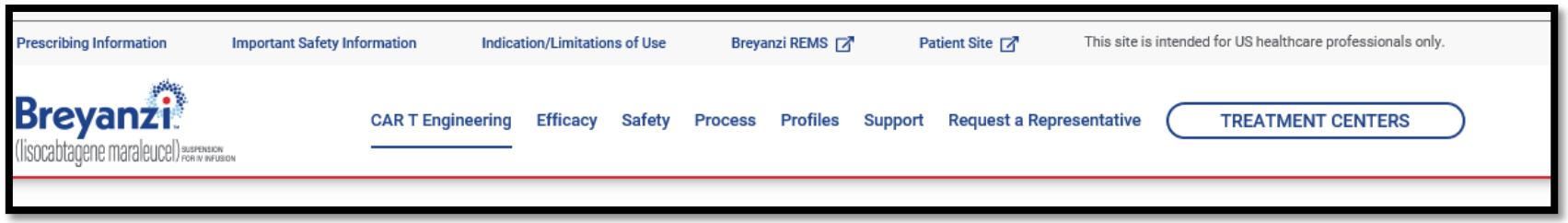
https://www.yescartahcp.com/large-b-cell-lymphoma




https://www.hcp.novartis.com/products/kymriah/

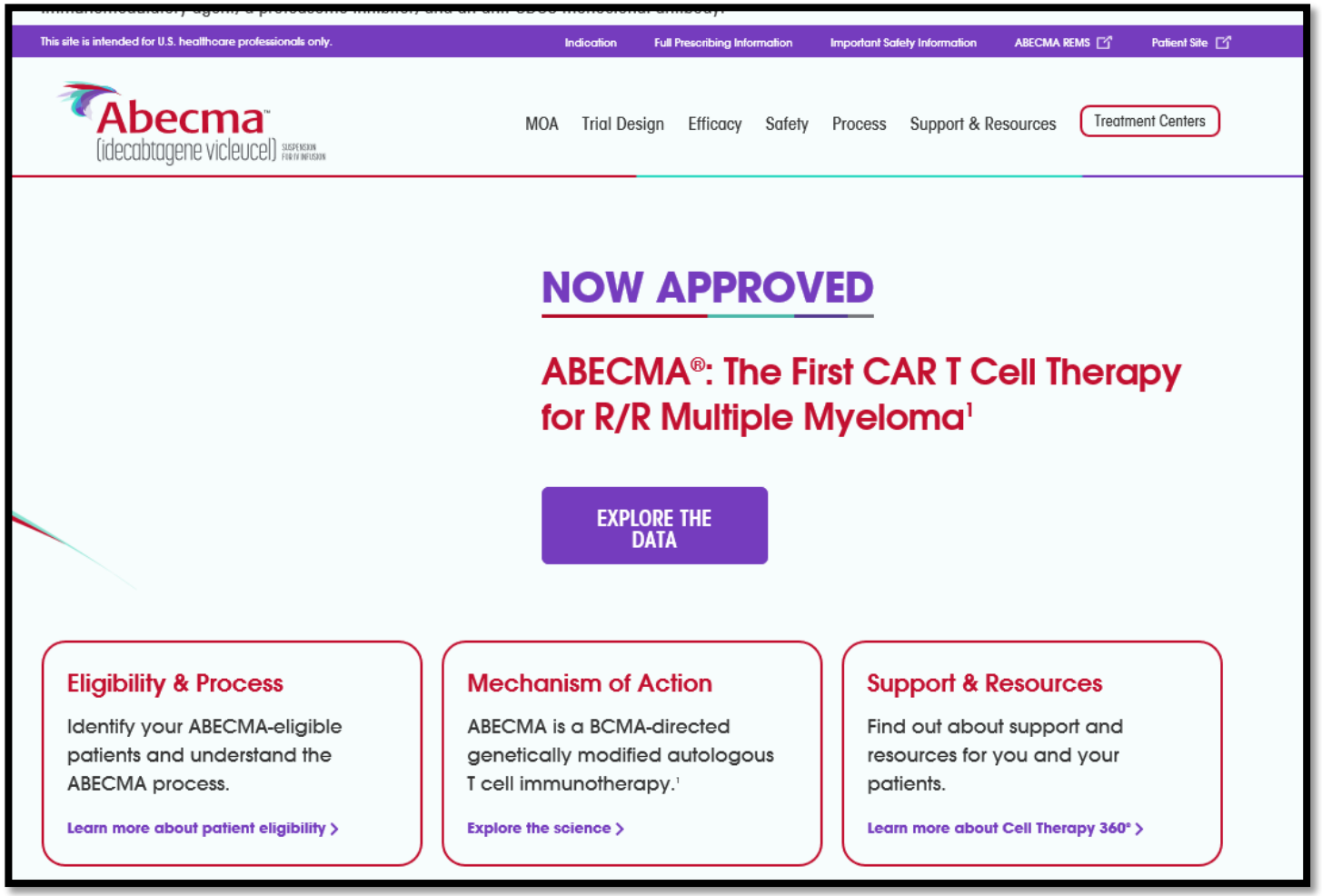



https://www.breyanzihcp.com/car-t-engineering/



# Multiple Myeloma

https://www.abecmahcp.com/



# Risk Evaluation Mitigation Strategy (REMS)Program

The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

## Información para el paciente

YESCARTA® y TECARTUS® pueden causar efectos secundarios que pueden provocar la muerte.

Llame o consulte a su oncólogo o busque ayuda de urgencia **DE INMEDIATO** si tiene alguno de **estos síntomas**:

- Fiebre (100.4 °F/38 °C o más)
- Dificultad para respirar
- Escalofríos o temblores
- Confusión
- Mareos o aturdimiento
- Náuseas, vómitos o diarrea intensos
- Latido cardíaco rápido o irregular
- Fatiga o debilidad intensa

YESCARTA, el logotipo de YESCARTA, TECARTUS, el logotipo de TECARTUS, KITE, y el logotipo de KITE son marcas comerciales de Kite Pharma, Inc. GILEAD es una marca comercial de Gilead Sciences, Inc.



DOBLAR

YESCARTA® (axicabtagene ciloleucel) | TECARTUS® (brexucabtagene autoleucel)

## Tarjeta de bolsillo del paciente

**Lleve esta tarjeta con usted en todo momento. MUESTRE ESTA TARJETA si va a un servicio de urgencias o si consulta a un médico.**

Informe al profesional sanitario que lo vea que está siendo tratado con YESCARTA® o TECARTUS®.

Permanezca muy cerca (a una distancia máxima de 2 horas) del lugar en el que recibió el tratamiento durante, al menos, 4 semanas después de recibir YESCARTA® o TECARTUS®.

## Information for Patient

BREYANZI may cause side effects that can lead to death.

**Call your oncologist or go to the emergency room right away if the following symptoms appear:**

- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heart rate
- Severe fatigue or weakness

BREYANZI® is a trademark of Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.



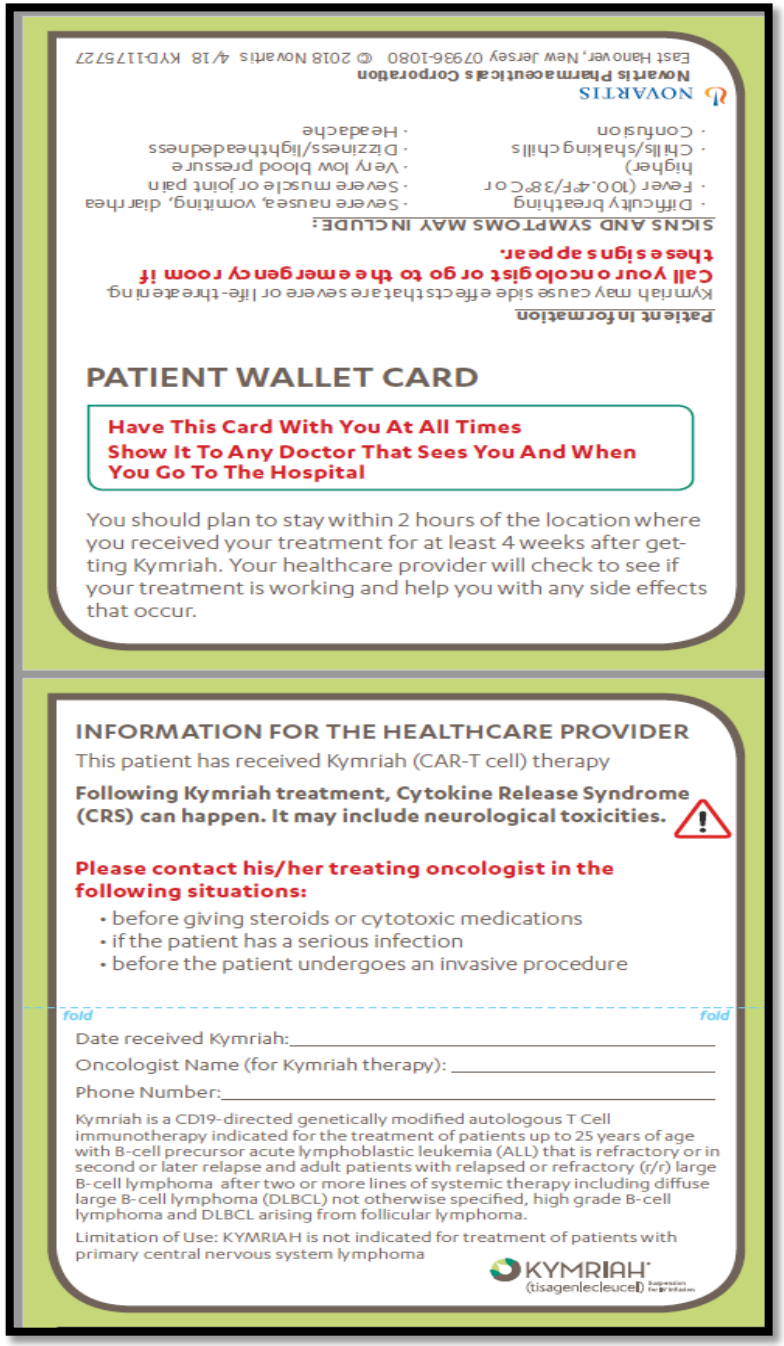
Bristol Myers Squibb™

Breyanzi® (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION

## Patient Wallet Card

**Have this card with you at all times. Show it to any doctor who sees you and when you go to the hospital.**

- Tell any healthcare provider who sees you that you are being treated with BREYANZI®.
- For at least 4 weeks after receiving BREYANZI, you should plan to stay within 2 hours of the location where you received treatment.
- Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after BREYANZI administration.



**Patient Information**

Kymriah may cause side effects that are severe or life-threatening. **Call your oncologist or go to the emergency room if these signs appear.**

SIGNS AND SYMPTOMS MAY INCLUDE:

- Difficulty breathing
- Fever (100.4°F/38°C or higher)
- Chills/shaking chills
- Confusion
- Severe nausea, vomiting, diarrhea
- Severe muscle or joint pain
- Very low blood pressure
- Dizziness/lightheadedness
- Headache

NOVARTIS

Novartis Pharmaceuticals Corporation
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## PATIENT WALLET CARD

**Have This Card With You At All Times**
**Show It To Any Doctor That Sees You And When You Go To The Hospital**

You should plan to stay within 2 hours of the location where you received your treatment for at least 4 weeks after getting Kymriah. Your healthcare provider will check to see if your treatment is working and help you with any side effects that occur.

## INFORMATION FOR THE HEALTHCARE PROVIDER

This patient has received Kymriah (CAR-T cell) therapy

**Following Kymriah treatment, Cytokine Release Syndrome (CRS) can happen. It may include neurological toxicities.**

**Please contact his/her treating oncologist in the following situations:**

- before giving steroids or cytotoxic medications
- if the patient has a serious infection
- before the patient undergoes an invasive procedure

fold fold

Date received Kymriah:_____

Oncologist Name (for Kymriah therapy): _____

Phone Number:_____

Kymriah is a CD19-directed genetically modified autologous T Cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse and adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma

KYMRIAH® (tisagenlecleucel)

# Hematologic Recovery & Immune Reconstitution

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,*]

Adult patients with r/r cd 19 LBCL treated with Axi-cel from Sept 2017 and March 2019
EMR reviewed to abstract patient and disease characteristics, laboratory data, infectious complications , CAR T associated toxicities, clinical events, B and T cell subsets IgG antibody titers

# Summary of Immune Reconstitution Following Axi-cel

- Episodic neutropenia occurs beyond D+28 in approximately half of patients.
  - May continue beyond 1 year and prophylaxis program is a must to prevent infections or hospitalizations
- New hypogammaglobulinemia occurs in 25% of patients.
  - Pre-existing hypogammaglobulinemia from prior therapy is prevalent
  - Antigen-specific IgG titers against EBV, VZV appeared mostly preserved
- B-cell aplasia is prolonged in patients with durable response to axi-cel.
- CD4 counts remain <200 for up to 1 year in most patients.
  - Without ppx, patients are high risk for opportunistic infections (e.g. PJP) and risk of fungal pulmonary infections (e.g. Aspergillus)
- Respiratory infections and pneumonias are the most common events post-axi-cel.
  - Peak around 3-6 months (when IgG nadirs)
- Herpes zoster is an ongoing risk for patients without acyclovir ppx, even beyond 1 year.

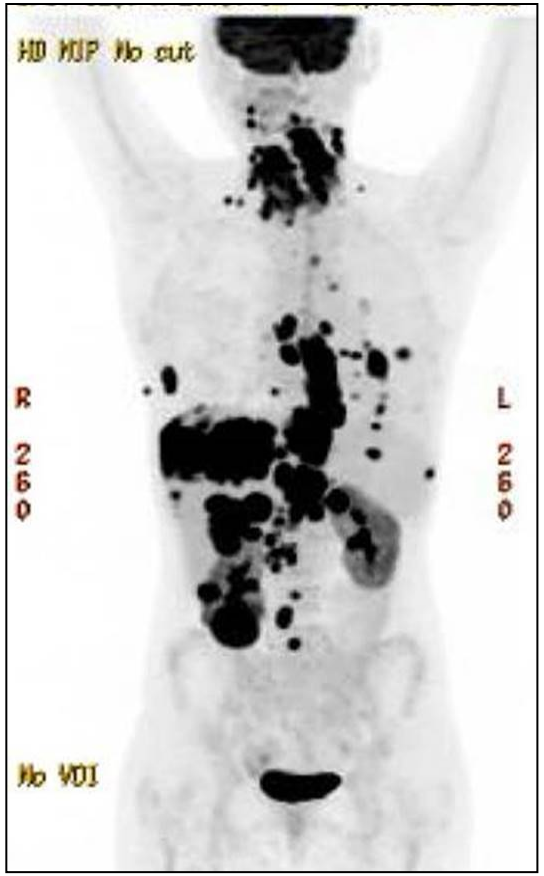
# Long Term – Day 28 and Beyond

- **Cytopenias**
  - Can persist for up to 6 months following infusion
  - Standard transfusion parameters: Transfuse!
  - GCSF 5mcg/kg to maintain ANC > 1500
  - Assess CBC/diff 1-2 times weekly as needed until cytopenias resolve
  - Last date requiring G-CSF: (date)
- **Infectious Disease Prophylaxis:**
  - Acyclovir for 18 months post
  - Mepron: Consider transition to bactrim if counts permit
  - 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
- **Wallet Card**
  - Local through day 28, **no driving for** 8 weeks
- **Use of corticosteroids**
  - for CRS/ICANS, previous HCT, and/or multiple lines of previous therapy, can significantly increase patient's risk for developing viral and **fungal** infections for up to 1 year following infusion
- **Seizure Prophylaxis**
  - Completed Levetiracetam 500mg BID on Day +28. Longer if neuro tox develops
- **Risk for Hypogammaglobinemia**
  - Recommend monitoring IgG levels at 3, 6, 9, and 12 months following infusion then give IVIG 0.5 g/kg to if IgG level <400 mg/dL
- **Disease Assessment**
- **Cognitive follow up and increasing strength**

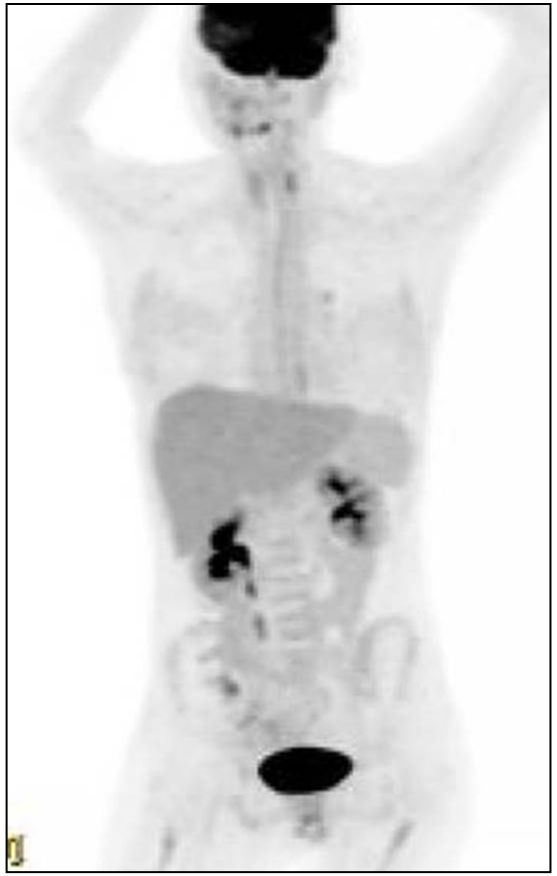
Treatment Summary Response

1. daEPOCH-R x6 PD PET/CT
2. R-DHAPx 2 PD PET/CT
3. XRT PD (outside Rt field)
4. High dose cytoxan with solumedrol for cytoreduction
5. 3 cycles Brentuximab and dexamethasone
6. CAR T infusion

Prior CAR T cell therapy




Day 30 post CAR T therapy



# Conclusions and QUESTIONS???

- CAR T cell therapy is new and emerging therapy for DLBCL, ALL and MM
- New generation of CAR T's, and new indications are the future
- Improved toxicity management and long-term management has contributed to the success
- Improved knowledge base of management strategies, relapse, and persistence is the future

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