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Chimeric Antigen Receptor (CAR) T-Cell Therapy

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Objectives

- Define CAR T-cell therapy and discuss the physiology
- Understand the CAR T-cell treatment phases
- Identify and discuss major toxicities associated with the therapy
- Discuss the two FDA approved treatments and summarize key clinical studies
- Present the Institute for Clinical and Economic Review (ICER) evaluation
- Discuss CAR T-cell role in therapy and future considerations

CAR T-Cell Technology

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- Chimeric Antigen Receptor T-cell therapy is a type of adoptive immunotherapy that uses tumor-specific antigen recognition
- CAR: engineered receptor that specifically binds to certain proteins on cancer cells
- It uses a patient's own modified white blood cells (T-cells) to target and eliminate cancerous cells
- Most advanced in B-cell cancers with known antigen targets such as CD19 (such as DLBCL, B cell ALL)

Role of CAR T-cell therapy

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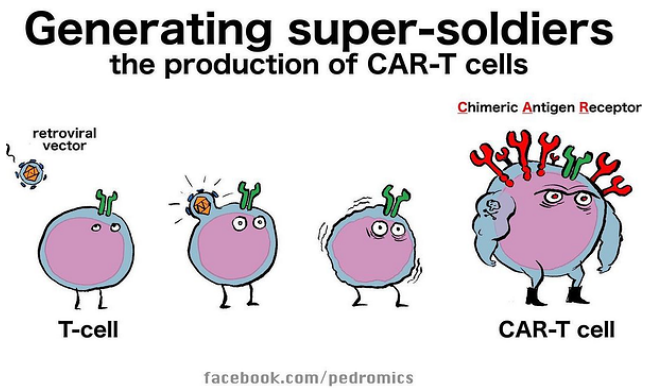
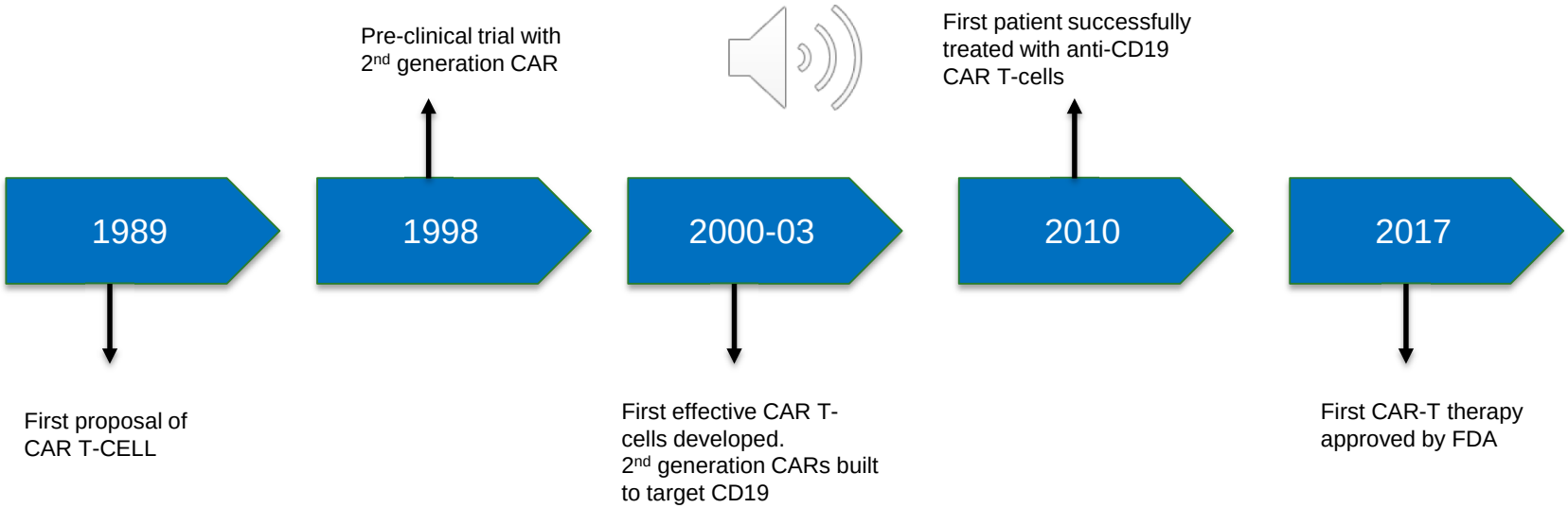
- **DLBCL** patients who:
  - ✓ Failed first line chemotherapy
  - ✓ Failed second or greater lines of chemotherapy
  - ✓ Relapsed within 12 months of an autologous stem cell transplant
  - ✓ Previous therapies must have included an anti-CD20 antibody and an anthracycline

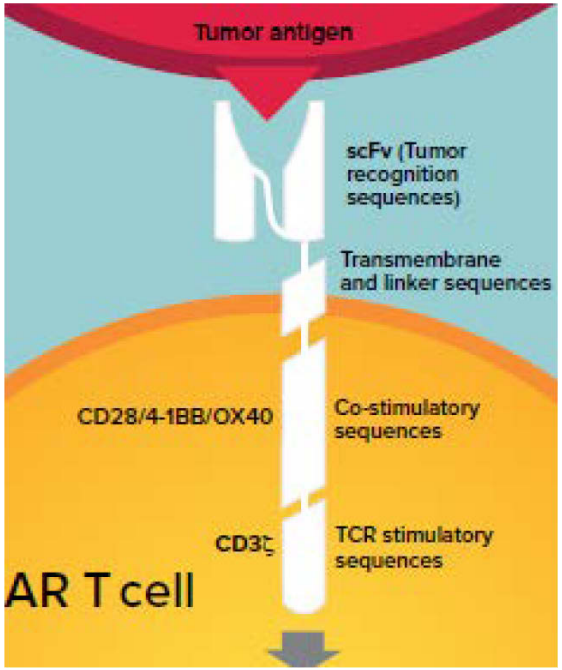
- **ALL** patients that is
  - ✓ Refractory
  - ✓ Second or later relapse

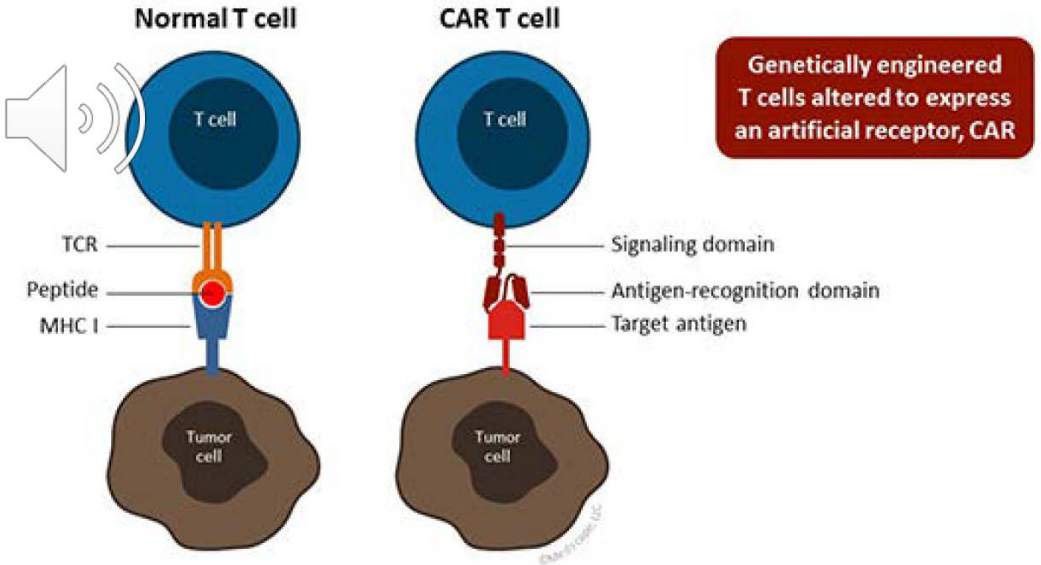


Development of CAR T-cells



CAR T-cell Design



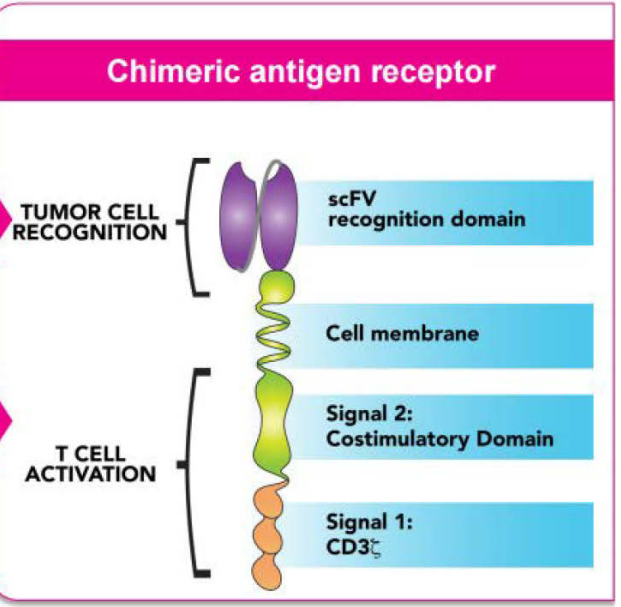


CAR Design: Critical Elements

CARs are fusion proteins designed to do two things[1]:

1. **Target** cancer cells by engineering a recognition domain (commonly a antibody fragment [scFV]) on the T cell surface

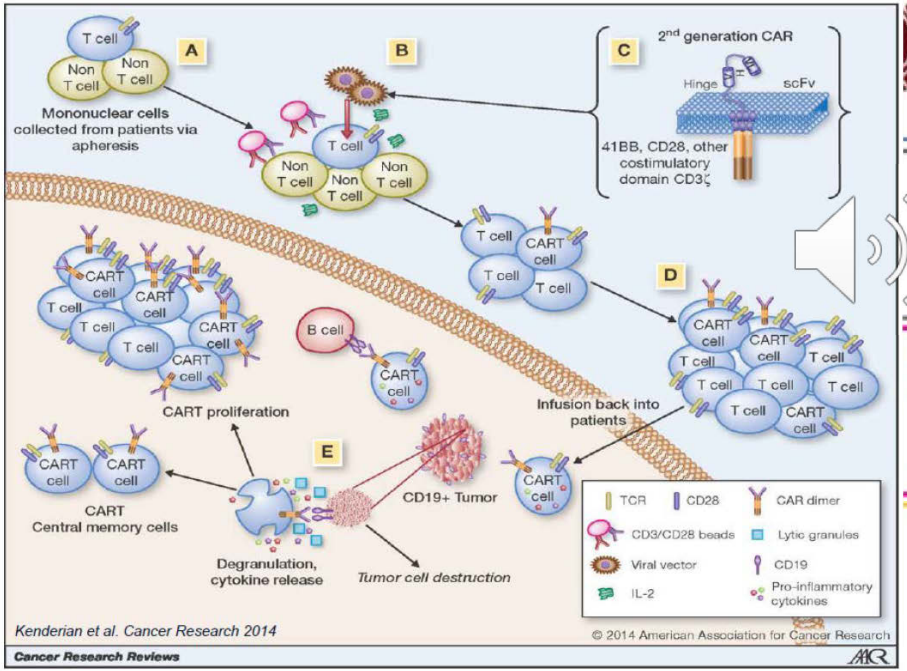
2. **Activate** the CAR T cell by signaling through the CAR's intracellular signaling domain resulting in
   - Proliferation & activation of the T cell
   - CAR T cell-mediated killing of tumor cells



CAR=chimeric antigen receptor; scFV= single chain variable fragment.

1. Camicia R, et al. *Molecular Cancer*. 2015;14:207.

CAR T-Cell Mechanism of Action



CD19 and B Cell Malignancies

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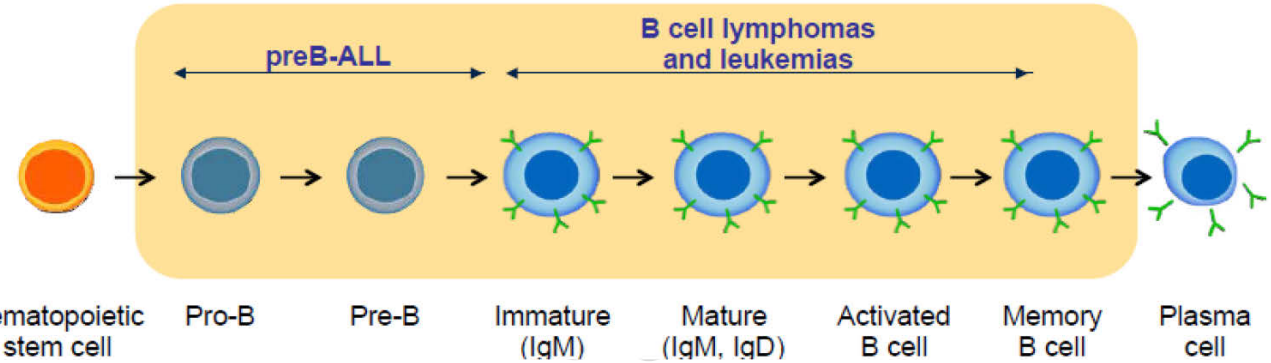
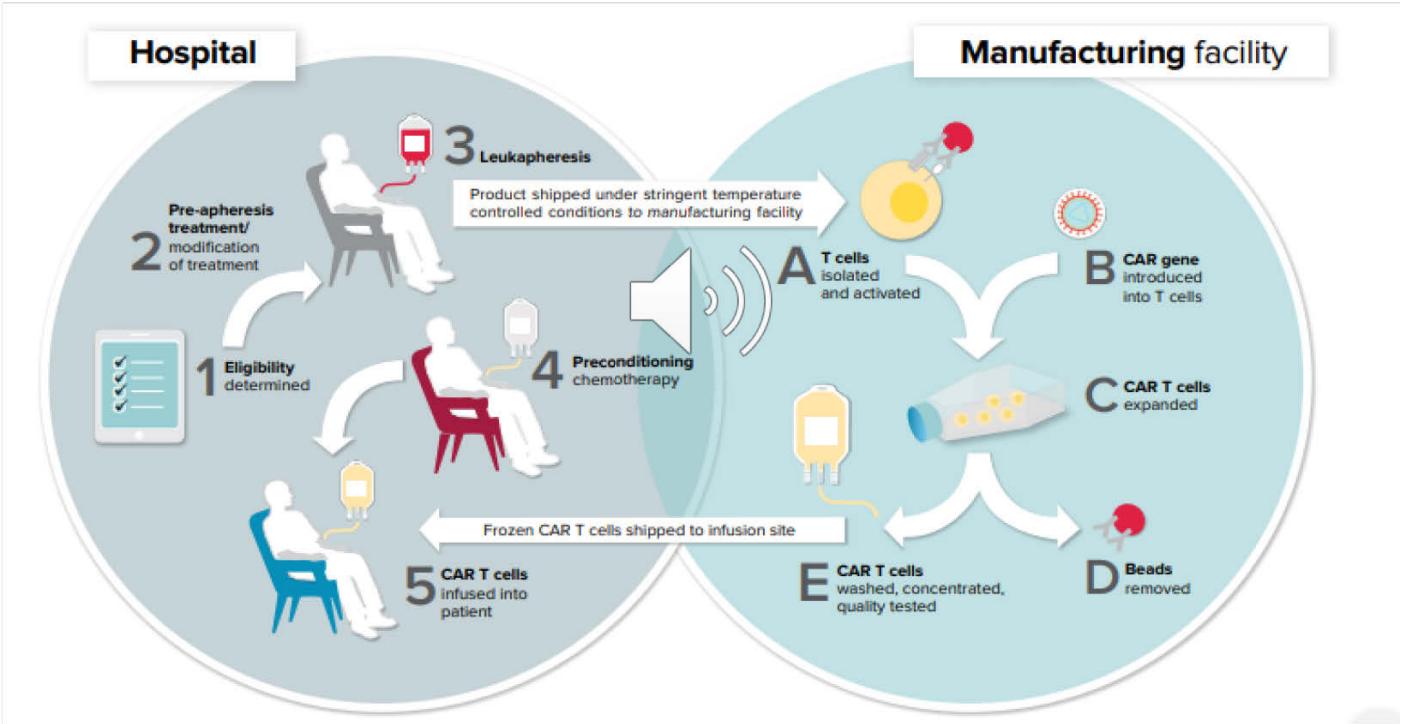
- CAR T-cells recognize and bind to a target antigen CD19
- CD19 is on the surface of B-cells and B-cell malignancies
  - Ideal target for T-cell mediated killing due to its specificity
  - It is present almost throughout the entire B cell maturation process
  - This minimizes off-target toxicity and enhances anti-tumor efficacy
- Various types of lymphomas and acute lymphoblastic leukemia (ALL) can express CD19
- Clinical trials targeting CD19 have shown remarkable success in B cell malignancies



Treatment Phases



Leukemia & Lymphoma Society

Treatment Phases Cont.

1. Screening: patients are evaluated for safety and efficacy of the treatment
   - ✓ Must have tumors that are CD19 positive
   - ✓ Have an adequate number of T-cells
   - ✓ No active uncontrolled infection
   - ✓ Have adequate performance status and organ function

2. Leukapheresis: T-cells are harvested from the patient by leukapheresis
   - ✓ Corticosteroids should be avoided within a certain time prior to the procedure
   - ✓ Salvage/rescue chemotherapy within a certain time prior to the procedure

The collected cells may be frozen and shipped to manufacturing facilities for processing

3. T-cells are activated: isolated T-cells are placed in culture and are exposed to antibody-coated beads to activate them

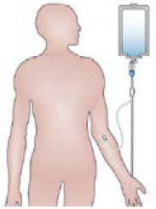
4. The CAR gene is introduced into activated T cells in vitro: use of several viral vectors, which results in permanent genome modification

5. The CAR T-cells are expanded in vitro: following expansion, the cells are washed, concentrated, and samples are removed for quality testing

The CAR T-cells may be frozen for shipment to the infusion sites

Treatment Phases Cont.

6. Patient undergoes “preconditioning” chemotherapy



- ✓ patient receives lymphocyte-depleting chemotherapy days prior to the CAR T-cells infusion
  - ➢ Fludarabine, cyclophosphamide or alternatives
- ✓ It allows the engraftment and expansion of CAR T-cells
- ✓ CAR T-cell infusion 2-14 days after completion of lymphodepleting chemotherapy
- ✓ Regimens vary by protocol and individual patient

7. CAR T-cells infusion
   - ✓ Generally reach peak level between 1-2 weeks after infusion
   - ✓ The degree of expansion and persistence of CAR T-cells is one indicator of efficacy

On average, the production of CAR T-cells takes approximately 10-14 days. The time from cell collection to infusion varies but typically ranges from 1-4 weeks

Recommended Timing to Stop Therapies Before Leukapheresis

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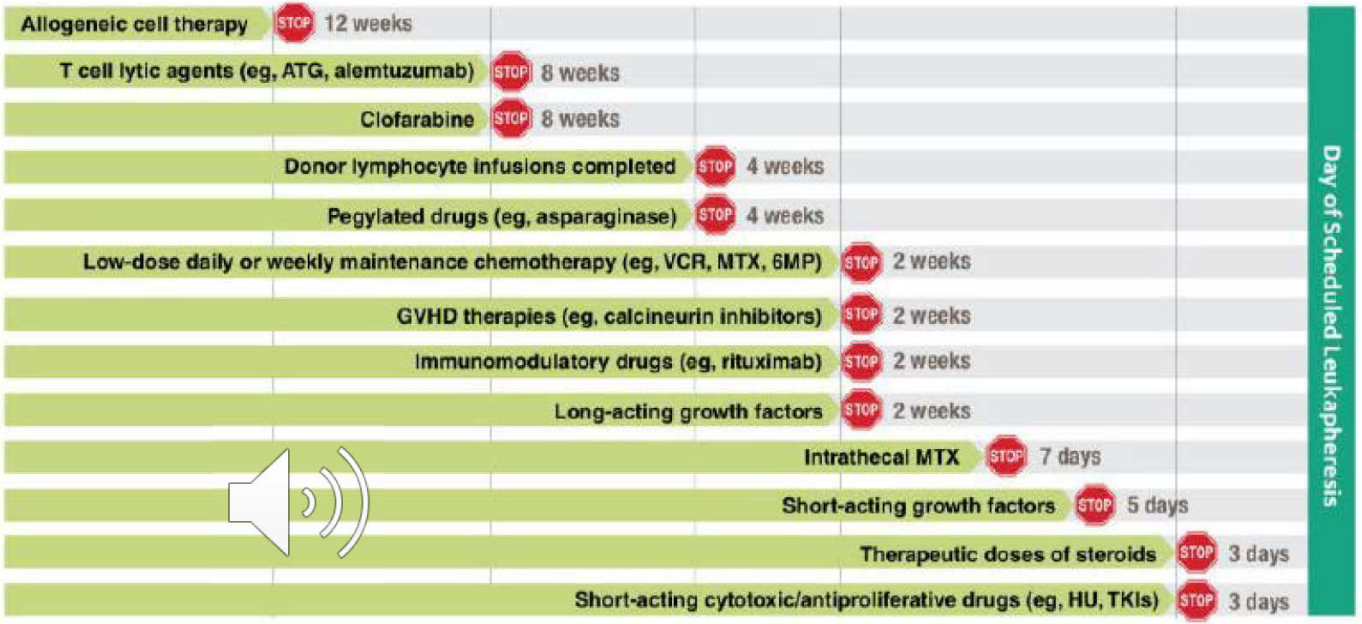

Patient Eligibility Considerations

- Adequate blood cell count for leukapheresis
- Relative disease stability
  - CART manufacturing generally 2 – 4 weeks
  - Disease not progressing rapidly through manufacturing period
- Patient ability to tolerate CAR T toxicities
  - Major organ functionality
    heart, lung, kidney, liver
  - Neurologic considerations
    Seizure risk, CVA, CNS disease

FDA Approved Therapies

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Brand	KYMRIAH®	YESCARTA®
Generic	Tisagenlecleucel	Axicabtagene ciloleucel
FDA approval	August 30, 2017	October 18, 2017
Manufacturer	Novartis	Kite Pharma (Gilead)
Signaling domain	4-1BB	CD28
REMS	Required	
Contraindications	None	
FDA Indications	ALL (≤25 years of age) DLBCL (adults)	DLBCL

ALL: acute lymphoblastic leukemia
DLBCL: diffuse large B-cell lymphoma
NHL: non-Hodgkin's lymphoma

REMS Requirements

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- Healthcare facilities that dispense and administer YESCARTA or KYMRIAH must be enrolled and comply with the REMS requirements

- Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA or KYMRIAH infusion, if needed for treatment of CRS

- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA or KYMRIAH are trained about the management of CRS and neurologic toxicities

KYMRIAH® (tisagenlecleucel)

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Indications

- Relapsed or refractory **large B-cell lymphoma** after two or more lines of systemic therapy in **adults**, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- refractory or in second or later relapse B-cell acute lymphoblastic leukemia **(ALL)** in patient **≤25 years of age**

It is **NOT** indicated for treatment of primary central nervous system lymphoma

Dosage

- Based on the number of CAR-positive viable T cells and patient weight
  - ✓ ≤25 yo ALL→ 50kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T-cells per kg body weight
    above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T-cells
  - ✓ Adult DLBCL → 0.6 to 6.0 x 108 CAR-positive viable T-cells
  - ✓ Infusion bag volume ranges 10-50mL
- IV use only: infuse at 10 to 20mL per minute

KYMRIAH Initial Approval Criteria (Centene)

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Acute Lymphoblastic Leukemia* (must meet all)**:** **Only for initial treatment dose; subsequent doses will not be covered.*

1. Age ≤ 25 years
2. Documentation of CD19 tumor expression
3. Recent (within the last 30 days) documentation of one of the following (a or b):
    a. Absolute lymphocyte count (ALC) ≥ 500/µL
    b. CD3 (T-cells) cell count of ≥ 150/µL if ALC < 500/µL
4. Request meets one of the following (a, b, or c):
    a. Refractory disease or member has had ≥ 2 relapses
    b. Philadelphia chromosome positive: Failure of 2 lines of chemotherapy that include 2 tyrosine kinase inhibitors
    c. Relapse following hematopoietic stem cell transplantation (HSCT) and must be ≥ 6 months from HSCT at the time of Kymriah infusion
5. No active or primary central nervous system (CNS) disease
6. Dose does not exceed (a or b):
    a. Weight ≤ 50 kg: 5.0×10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg
    b. Weight > 50 kg: 2.5×10^8 CAR-positive viable T cells

Approval duration: 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)*

KYMRIAH Initial Approval Criteria (Centene)

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Large B-Cell Lymphoma (must meet all)**:**

1. Age ≥ 18 years
2. Recent (within the last 30 days) ALC ≥ 300/µL
3. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes Rituxan® and one anthracycline-containing regimen (e.g., doxorubicin)
4. No active or primary CNS disease
5. Dose does not exceed 6.0 x 108 CAR-positive viable T cells

Approval duration: 3 months ***(1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)***

YESCARTA® (axicabtagene ciloleucel)

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Indications

- Relapsed or refractory **large B-cell lymphoma** after two or more lines of systemic therapy in **adults**, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma

It is **NOT** indicated for treatment of primary central nervous system lymphoma

Dosage

- Based on the number of CAR-positive viable T cells and patient weight
  - ✓ Each single infusion bag of YESCARTA contains a suspension of CAR-positive T cells in approximately 68 mL. The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells
- IV use only: the entire bag has to be infused within 30 minutes

YESCARTA Initial Approval Criteria (Centene)

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Large B-Cell Lymphoma* (must meet all)**:**

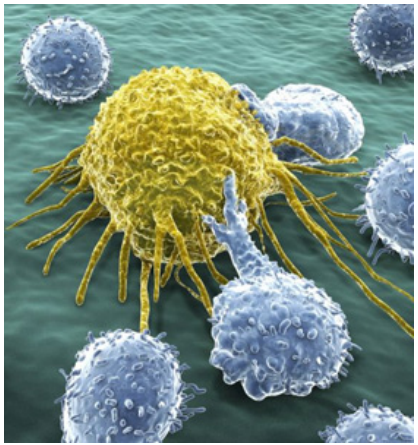
**Only for initial treatment dose; subsequent doses will not be covered.*

1. Diagnosis of LBCL
2. Prescribed by or in consultation with an oncologist or hematologist
3. Age ≥ 18 years
4. Recent (within the last 30 days) absolute lymphocyte count (ALC) ≥ 100/µL
5. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes Rituxan® and one anthracycline-containing regimen (e.g., doxorubicin)
6. No active or primary central nervous system (CNS) disease
7. Dose does not exceed 2 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells

Approval duration: 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)*

Monitoring

- Patient should be monitored daily for 7 days at a certified healthcare facility following infusion
- Patient should stay within proximity of the treatment center for at least 4 weeks after infusion to monitor
- Warning and precautions
  - Hypersensitivity reactions
  - Serious infections
  - Prolonged cytopenias: Monitor blood count
  - Hypogammaglobulinema
  - Secondary malignancies
- Routine long-term monitoring is recommended



Toxicities

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	Signs and Symptoms	Timing	Management
Cytokine release syndrome (CRS)	Fever, myalgia, hypotension, hypoxia, potential organ failure	Usually within the first 1-3 weeks postinfusion	• Tocilizumab • Corticosteroids • Severe CRS may require vasopressors, ventilatory support and supportive care in the ICU
Neurotoxicity	Confusion, delirium, hallucinations, encephalopathy, aphasia, facial paresis, mutism, myoclonus, tremors, somnolence, seizures	 May not be concurrent with CRS	• Corticosteroids • Supportive care, which may include anti-epileptic medication
Macrophage activation syndrome (MAS)	High levels of ferritin, CRP, d-dimer; hypofibrinogenemia associated with bleeding, transaminitis and elevated triglycerides	Concurrently or shortly after CRS	• Tocilizumab
B-cell aplasia	Hypogammaglobulinemia	Within first few weeks postinfusion, may last indefinitely	• Immunoglobulin replacement therapy • Prophylactic antibiotics in some cases

CRS and Neurotoxicity

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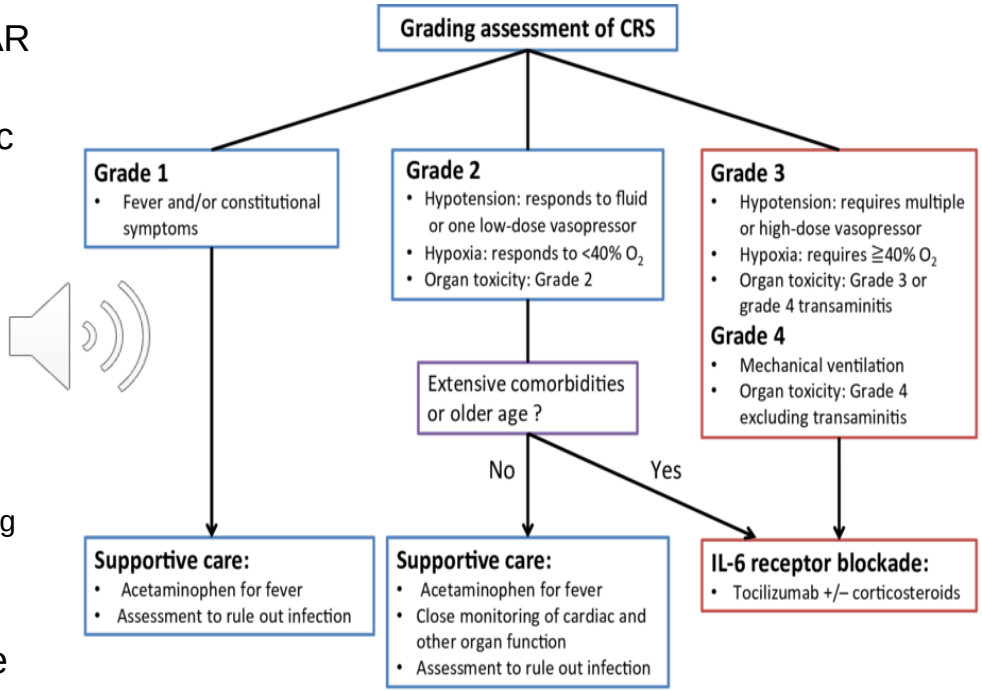
Product	Kymriah		Yescarta
	ALL (ELIANA)	DLBCL (JULIETA)	DLBCL (ZUMA1)
CRS	78%	74%	94%
CRS grade ≥3	47%	18%	13%
Median time to onset of CRS	3 days (1-51)		2 days (1-12)
Neurotoxicity	72%	58%	87%
Median time to onset of neurotoxicity	6 days	14 days	4 days (1-43)
Tocilizumab	50%	21%	45%
Steroids	26%	13%	25%

CRS Management

- The major acute toxicities associated with CAR T-cells therapy
- Symptoms and severity varies, features mimic infection
- Duration is variable, but it typically resolves within a few days to 2-3 weeks after CAR-T
- For CRT T-cell associated CRS, severe CRS (grade 3,4 maybe 2) are considered
- Tocilizumab +/- corticosteroids
  - patients <30 kg – Tocilizumab 12 mg/kg
  - patients ≥30 kg – Tocilizumab 8 mg/kg; max 800 mg
- Hydrocortisone 100 mg every eight hours, dexamethasone 10 mg up to four times daily, or methylprednisolone 1 mg/kg/day until there is improvement in CRS



ICER Analysis

Discounted Lifetime Costs

	B-ALL		B-cell Lymphoma	
Cost Category	Tisagenlecleucel	Clofarabine	Axicabtagene Ciloleucel	Chemotherapy
CAR-T Treatment Costs	$405,490	$0	$438,284	$0
Chemotherapy Treatment Costs	$15,309	$163,686	$0	$40,142
Palliative Chemotherapy Treatment Costs	$2,648	$3,973	$3,748	$6,103
Pre-Treatment Costs	$2,979	$0	$4,585	$0
SCT Costs	$47,744	$64,648	$13,345	$62,094
Adverse Event Costs*	$33,534	$0	$16,029	$7,046
Administration/ Monitoring Costs	$111,548	$93,032	$44,165	$1,045
Future Healthcare Costs	$45,901	$9,069	$95,223	$36,286
End of Life Costs	$1,602	$2,848	$1,547	$2,169
TOTAL COSTS	**$666,754**	**$337,256**	**$616,927**	**$154,884**

Discounted Lifetime Outcomes

	B-ALL		B-cell Lymphoma	
Outcome	Tisagenlecleucel	Clofarabine	Axicabtagene Ciloleucel	Chemotherapy
Life Years (responding to treatment)	9.84	2.09	6.92	2.91
Life Years (not responding to treatment)	0.51	0.34	0.43	0.32
TOTAL LIFE YEARS	**10.34**	**2.43**	**7.35**	**3.23**
QALYs (responding to treatment)	8.95	1.90	5.74	2.42
QALYs (not responding to treatment)	0.33	0.20	0.13	0.06
TOTAL QALYs	**9.28**	**2.10**	**5.87**	**2.48**

B-ALL: B-cell acute lymphoblastic leukemia, QALY: quality-adjusted life year

*for inpatient therapies, costs associated with adverse events that were expected to increase the length of stay or extend beyond discharge

ICER Analysis

B-ALL	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY
Tisagenlecleucel vs. Clofarabine	$329,498	7.91	7.18	$41,642	$45,871
B-cell Lymphoma	**Incremental Costs**	**Incremental LYs**	**Incremental QALYs**	**Incremental CE Ratio per LY**	**Incremental CE Ratio per QALY**
Axicabtagene Ciloleucel vs. Chemotherapy	$462,043	4.12	3.40	$112,168	$136,078

Base-Case Incremental Results

- ✓ The cost of KYMRIAH is $475,000
- ✓ In the United States, thresholds of $100,000 or $150,000 per QALY gained have been suggested as a reasonable upper bound for an intervention to be deemed cost effective
- ✓ The cost of YESCARTA is $368,000

Base-case payment for tisagenlecleucel assumes payment only for responders at one month.
Base-case payment for axicabtagene ciloleucel assumes payment at infusion.
CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

Outcome-Based Agreement (OBA) for KYMRIAH

- Novartis has developed OBA when administered to patients up to 25 years of age diagnosed with B-cell ALL that is refractory or in second or later relapse
- Written agreement between Novartis and participating certified centers
- Applies to patients covered by all forms of insurance, including commercial, Medicaid, Medicare, and other government plans
- Novartis will not charge for the cost of the drug when the patient does not achieve either (28 to 35 days following infusion):
  - Complete remission (CR)
  - Complete remission with incomplete blood count recovery (CRi)

The Future

- With increasing clinical experience and further technical advances with product development, it is likely that the safety profile of these agents will continue to improve with time
- Efforts are ongoing to make these cells more effective and less toxic
- Treatment for post-CAR T-cell relapse such as possible reinfusion
- Donor CAR T-cells for patients who do not have sufficient numbers of cell manufactured?
- How to sustain remission post-CAR T therapy?
- Expanded use for other hematologic malignancies

References

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