Health Economics in CAR-T: Patient, Provider, and Policy Implications

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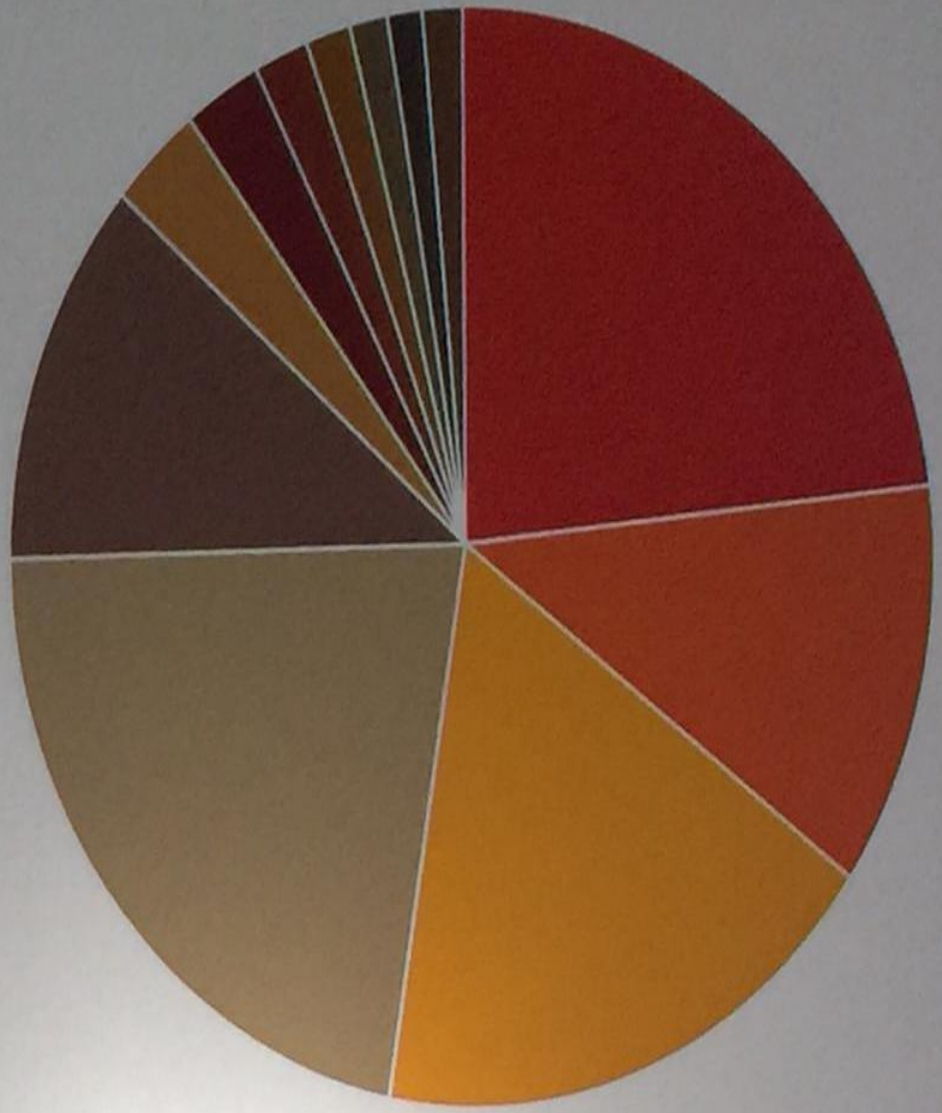
- Two CAR-T cell therapies approved by the U.S. Food and Drug Administration (FDA) for the treatment of lymphoma:
  - Axicabtagene ciloleucel (Yescarta) approved for the treatment of patients with large-B-cell lymphomas whose cancer has progressed after receiving at least two prior treatment regimens
  - Tisagenlecleucel (Kymriah) is approved for adult patients with relapsed or refractory large B-cell lymphomas after two or more lines of systemic therapy
- These mark the first CAR-T cell products to be approved by the FDA
- CAR-T cell therapies being studied in hundreds of clinical trials for numerous disease states

- Diffuse large B-cell lymphoma (DLBCL) most common form of non-Hodgkin lymphoma
- Accounts for almost ¼ of newly diagnosed cases of non-Hodgkin lymphoma
- Occurs in men and women, though slightly more common in men
- Incidence generally increases with age
- Roughly half of patients are over age 60

2016 U.S. Lymphoid Malignancy Statistics by World Health Organization Subtypes



- Treatment options for DLBCL:
- Typically requires immediate treatment
- Initial treatment usually includes chemo-immunotherapy, with or without radiation therapy; can lead to cure or disease remission in a large number of patients (60%)
- High-dose chemotherapy followed by stem cell transplantation can be used to treat patients whose disease is refractory/resistant to treatment or relapsed following initial chemotherapy
- Relapsed/refractory patients who are not candidates for stem cell transplant, or who choose not to have a stem cell transplant, have various combination chemotherapy regimens that can sometimes be used for treatment

- *Blood* literature review to assess the prognosis for patients who relapse after first line treatment and to assess the impact of patient age on outcomes
- Prognosis for patients with DLBCL who relapse is poor, with median survival of less than one year and less than half of patients who relapse still alive at one year post relapse
- Despite the use of SCT treatment, less than half of patients who met the eligibility criteria for and underwent SCT were alive at 5 years post transplant
- Age was seen to be an important prognostic indicator in DLBCL patients who relapse, with poorer prognosis in patients aged ≥65 years than in those aged <65 years

Table 1. Median overall survival, 1-yr and 5-yr survival rates

	Median overall survival		1-yr survival		5-yr survival	
	N of patients	Median months (range)	N of patients	Median % (range)	N of patients	Median % (range)
Relapse	565	10 (4-22)	625	41 (20-68)	92	27 (12-42)
Treatment initiation post relapse	569	13 (9-28)	760	60 (41-70)	160	30 (14-100)
ASCT in 2nd line	549	40 (36-44)	821	73 (70-75)	65	45
<65 years	1,082	24 (10-44)	1,320	67 (34-75)	129	43 (40-45)
≥65 years	510	10 (4-11)	570	41 (20-49)	152	22 (14-30)

Source: Andrew McMillan et al., Blood 2016;128:4204

- The cost of cancer care in the United States is increasing at a higher rate than any other sector in health care
- Upon approval in 2017, CAR-T therapies were at that time among the most expensive anti-cancer therapies on the market
- Led to widespread national conversation on cost-effectiveness, reimbursement policy and patient access
- Patient exposure to out of pocket expenses and non-medical resource utilization often overlooked
- Evidence suggests increased patient cost-sharing results in indiscriminate reductions in health service utilization and delayed treatment decision-making, not simply curtailment of low-value services

Source: Gusmano MK et.al, Health Affairs; 38:368-3
2019

- As many as 40% of cancer patient report financial difficulty after their diagnosis
- Several elements of CAR-T therapy the economically impact the patience experience
  - High deductable plan/ co-insurance
  - Transportation
  - Lodging
  - Caregiver burden/ logistics
  - Child/spousal/parent care
  - Employment
- Financial concerns and related/limited access to an accredited institution can add delay for patients whose disease may progress during the period of treatment decision-making

Source: PDQ® Adult Treatment Editorial Board. PDQ Fina
Toxicity and Cancer Treatment. Bethesda, MD: National C

Economics in CAR-T: The Patient Experience

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Institute. Accessed 01/15/20 [PMID: 27583328]

Economics in CAR-T: Systemic Impact

- Current federal reimbursement policy is inadequate to cover both costs associated with drug acquisition and expense related to inpatient care
- Acute issues for Medicare population (highly relevant for DLBCL patients)
  - Even with hospital specific adjustments and additional payment opportunities, Medicare's inpatient payment for CAR-T is not financially viable for hospitals
  - Hospital billed charges fundamentally impact the Medicare payments hospitals receive but have nothing to do with what patients pay out of pocket but can impact availability of treatment and proximity to patients in need of treatment
- Inadequate reimbursement could limit patient access due to the high costs of care if a limited number or institutions can offer the therapy or if capacity is restricted – impacting both commercially insured patients and beneficiaries of federal entitlement programs
- Reimbursement policy and systems must be adaptable: more than 400 cellular therapies in development

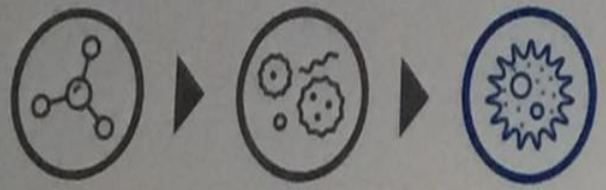
- Patient experience and access key issues:
- Impacted patient population experiences poor outcomes and have limited treatment options
- In some cases, no other treatment options exist
- Patients are seriously ill and cannot afford the time delay which may accompany a lack of clarity in coverage for their treatment and care
- Economics of CAR-T therapy directly impact patients
- Coverage policy should reflect FDA approvals AND be adaptable to reflect future scientific advancements
  - Follow data and invest in longer-term follow-up to understand efficacy, durability and potential late toxicities of CAR-T cell therapy
  - Greater investment in understanding patient financial burden and treatment decision-making

Car T Is a Breakthrough in Cellular Therapy That Is The Epicenter of a Tsunami

The Basics of CAR T Therapy

CAR T is a breakthrough Cellular Therapy

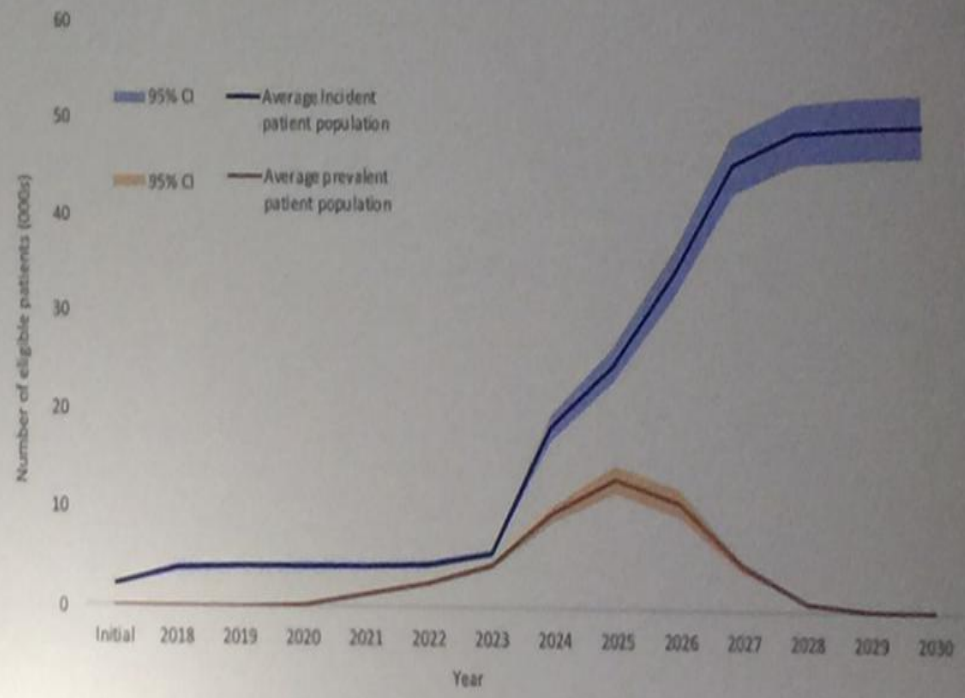
Chemistry → Biologics → Cellular Therapy



CAR Ts are a next-generation evolution in drug development toward true personalized medicine in oncology

- Next frontier of Oncology innovation; true "n=1" personalized medicine
- **Two CAR T products currently approved in** in ALL and NHL
- **400+ cellular therapy trials** on-going
- The FDA has **>800 active** cell-based or directly administered gene therapy **INDs** currently on file
- The FDA expects to **approve 10 to 20 cell** / gene therapy products per year by 2025
- **CAR-T will cause significant erosion of HCT**

Predicted Cumulative Product Launches and Annual Patient Treatments 2018-2030



Quinn, et al. Value Health 2019; 22(6):621-626

 Sources: Clinicaltrials.gov; FDA

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Unsolved Cellular Therapy Commercialization Challenges Tie Back to the Provider

1

Healthcare Delivery Infrastructure

- Care delivery network setup one site at a time: apheresis → infusion
- Long-term patient monitoring / follow up

Resource-intensive process

+

2

Individualized Patient Approvals

- Individualized authorization process
- C-level approval often required by the provider

Elongated approval

+

3

Therapy Delivery Economics

- Government reimbursement
- In-patient procedure billed at a fixed case rate

Unprofitable care delivery

+

4

Supply Chain Orchestration

- Coordination of manufacturing and patient treatment timelines
- Lengthy production cycle time

Delayed care delivery

=

5

Access to Care

- Academic centers have limited reach
- Minimal sites available in the community setting

Unintended access barriers

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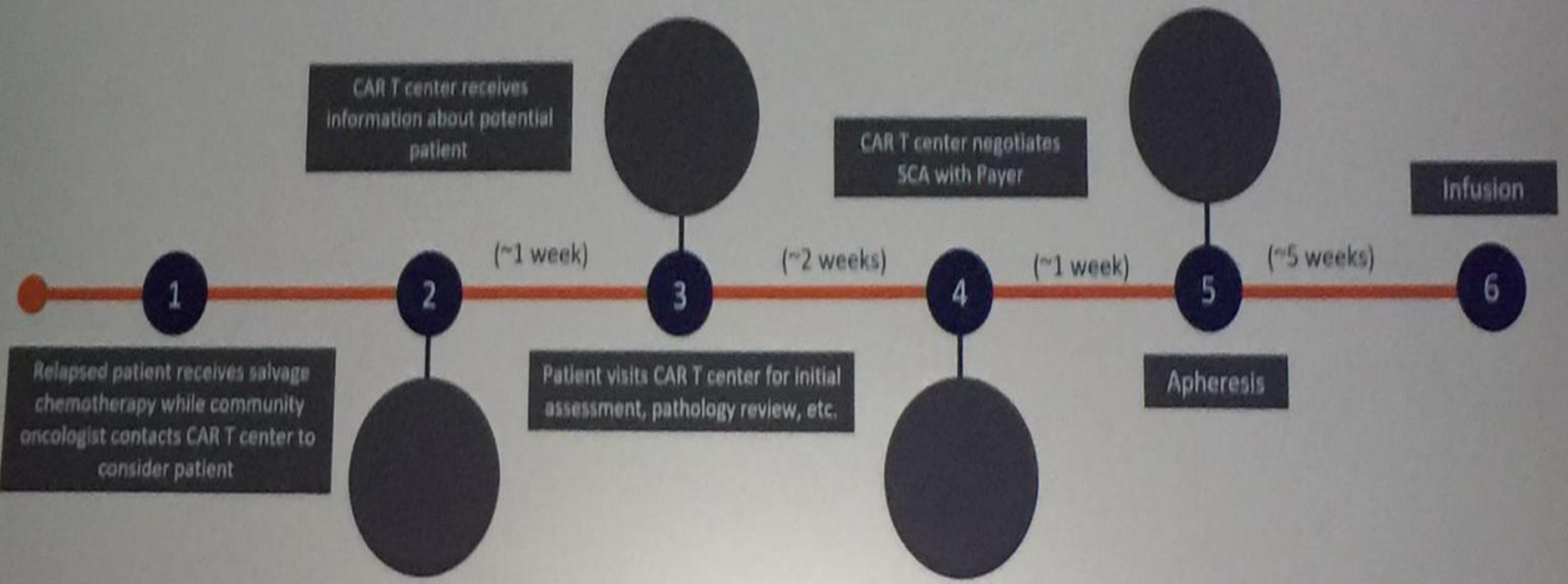
Patient Journey and Logistics



Due to the characteristics of patients who are treated with CAR T therapy,
the time pressure from patient identification to apheresis is expected to be a significant constraint

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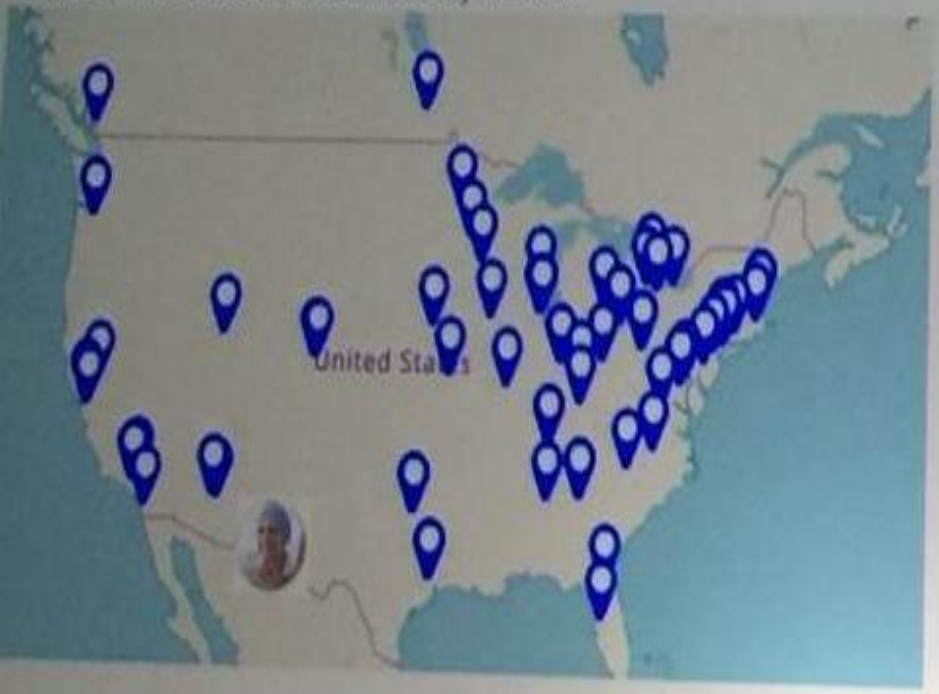
Adult REMS Certified Centers in the US

FACT Accredited Centers; n=84



REMs Certified Centers; n=90

- Novartis: n=72; 9 not Kite
- Kite: n=81; 18 not Novartis

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Where Do We Go From Here?

1

Healthcare Delivery Infrastructure

- Outpatient structure
- Standard certification
- CIBMTR

+

2

Individualized Patient Approvals

- Pre-negotiate case rate
- Improve time to approval

+

3

Therapy Delivery Economics

- CMS reform
- Classification as cells not drug
- Reimbursement agnostic to site of care
- Decrease cost of cells
- Financial toxicity

+

4

Supply Chain Orchestration

- Streamline ordering
- Standardize collection

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5

Access to Care

- Increase clinical capacity
- Clinical trials

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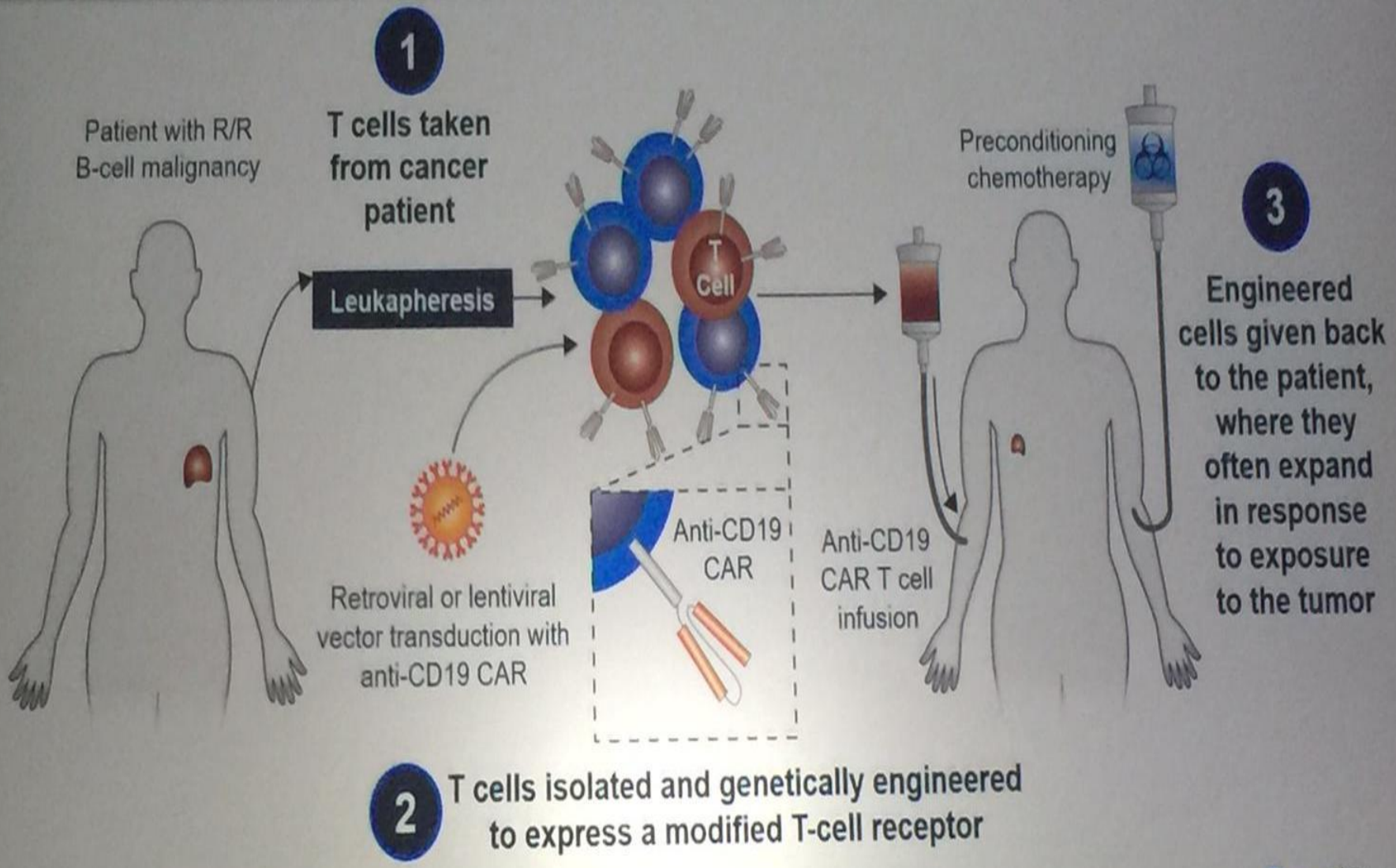
Overview of CAR T Cell Therapy[1,2]



1. https://labiotech.eu/immuno-oncology-history-car-t-nyt/. Accessed March 7, 2019. 2. Levine BL. *Cancer Gene Ther*. 2015;22:79-84.

The Regulatory Status (As of February 2020)

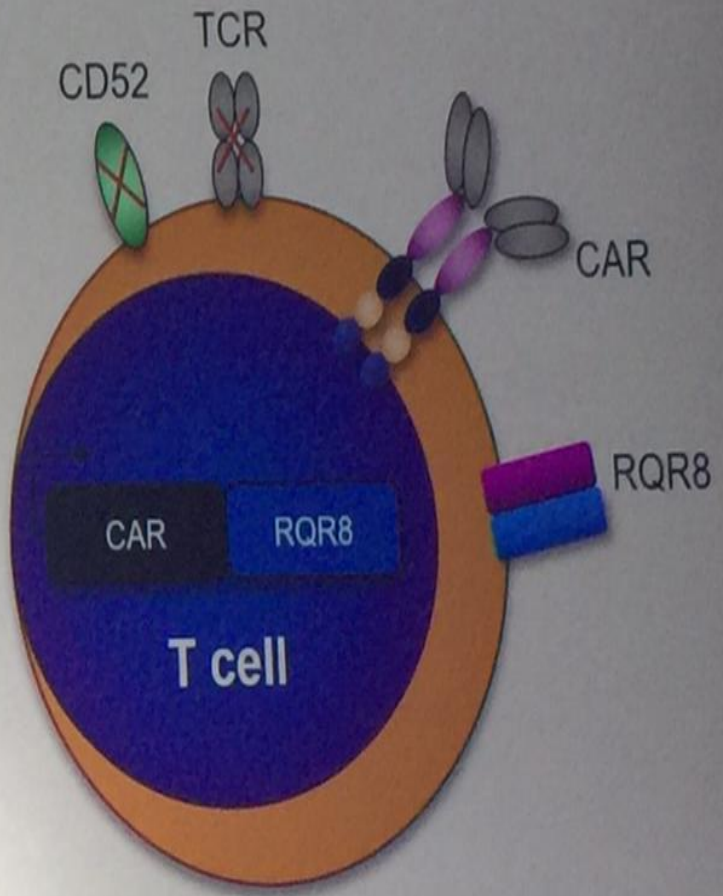
- **Tisagenlecleucel (CTL019)**
  - **August 30, 2017:** Approved for R/R B-cell precursor ALL (pediatric or young adult patients aged ≤25 y)
  - **May 1, 2018:** Approved for adult patients with R/R large B-cell lymphoma after ≥2 lines of systemic therapy
- **Axicabtagene ciloleucel (KTE-019)**
  - **October 18, 2017:** Approved for adult patients with R/R large B-cell lymphoma after ≥2 lines of systemic therapy
- **Lisocabtagene maraleucel (JCAR017)**
  - **February 13, 2020:** FDA priority review for R/R large B-cell lymphoma

Universal CAR T Cell: UCART19[1]

- Universal donor "off-the-shelf"
- 2nd generation CAR T cell
- CD19 scFv (4G7), 4-1BB, CD3z
- Allogeneic engineered with TALEN® (transcription activator-like effector nuclease) gene knock-out technology
- TCRαβ (TRAC) deleted to prevent graft-vs-host disease

Phase 1 clinical trials

- N = 7 pediatric (PALL study: NCT02808442)
- N = 14 adult (CALM study: NCT02746952)
- 67% (14/21) CR/CRi
- 71% (10/14) MRD-



1. Benjamin R et al. *Blood*. 2018;132(suppl 1):896.

The Overall Shape of DLBCL Management (2019)