OVERVIEW OF RECENT CBER CANCER PRODUCT APPROVALS

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Medical Officer

Office of Tissues and Advanced Therapies

Center for Biologics Evaluation and Research

FDA Regulation of Oncology Products

Oncology Center of Excellence (OCE)

CDER

Office of Hematology and Oncology Drug Products (OHOP)

- Drugs (small molecules)
- Biologics
  - Monoclonal Antibodies
  - T cell engagers
  - Therapeutic Proteins
  - Cytokines

CBER

Office of Tissues and Advanced Therapies (OTAT)

- **Cell therapies**
- **Gene Therapies**
- Oncolytic viruses
- Therapeutic vaccines and immunotherapies

CDRH

Office of In Vitro Diagnostics and Radiological Health (OIR)

- Devices
- Companion Diagnostics

FDA

The New York Times (OCT. 15, 2014)
Cell Therapy Puts Leukemia Patients in Extended Remission

The Washington Post

Aug 30, 2017

FDA clears first gene-altering therapy — 'a living drug' — for childhood leukemia

Oct 18, 2017

US regulators approve 2nd gene therapy for blood cancer

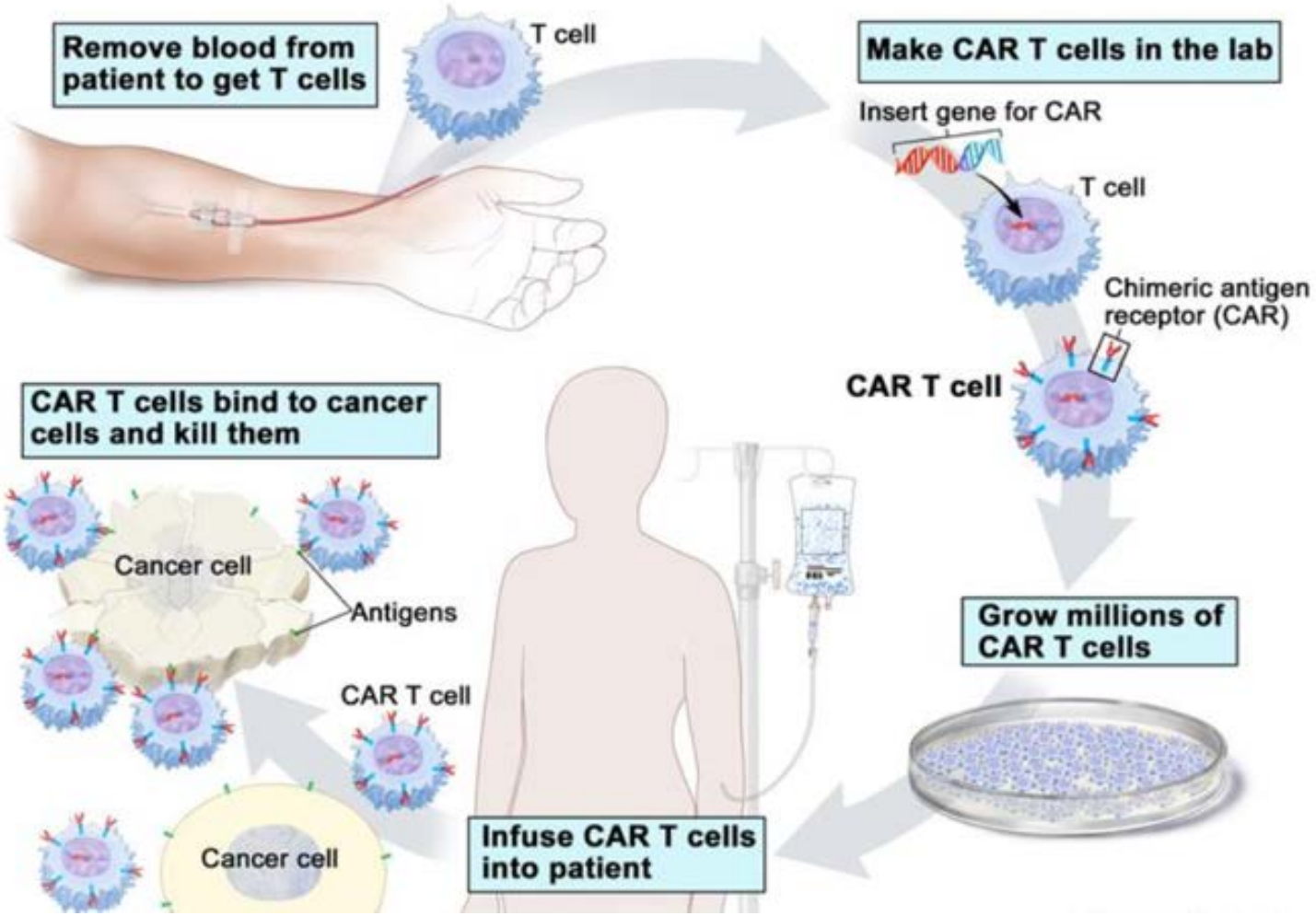
What is Chimeric Antigen Receptor (CAR) T-Cell Therapy?

- Novel type of cancer immunotherapy
- Involves training patients' own immune cells (T cells) to attack cancer cells

The Washington Post

Emily Whitehead, shown with her parents, was the first child treated with CAR T-cell therapy

CAR T-Cell Therapy



Source: National Cancer Institute at the National Institutes of Health

CAR T-Cell Therapy Approvals:

Developed under FDA's expedited programs

- **Kymriah** (tisagenlecleucel)
  - CAR T-cells (target – CD19)
  - Refractory/relapsed childhood acute lymphoblastic B cell leukemia (2017)
  - Adult patients with relapsed or refractory large B cell lymphoma (2018)
  - Oncology Drugs Advisory Committee meeting
  - Novartis

- **Yescarta** (axicabtagene ciloleucel)
  - CAR T-cells (target – CD19)
  - Adult patients with relapsed or refractory large B cell lymphoma (2017)
  - Gilead (Kite)

Efficacy:

- Single arm studies
- Approval was based on:
  - Overall Response Rate (ORR)= Complete Response (CR) + Partial Response (CR)
  - Duration of response
- Pediatric and young adult leukemia
  - CR = 63%
- Adult large B cell lymphoma
  - CR = 32-52%
  - ORR = 50-72%

CAR T-Cell Therapy Can Cause Severe Side Effects

- Side effects can be fatal or life-threatening
- Majority of patients experienced:
  - **Cytokine Release Syndrome (CRS)**:
    - Systemic response to T-cell activation: flu-like symptoms, difficulty breathing, body organ toxicities
    - FDA expanded the approval of Actemra (tocilizumab) to treat CRS
  - **Neurologic toxicities**:
    - Confusion, inability to talk, seizures, brain swelling

FDA's Measures To Reduce The Risks of CAR T-Cell Products

- Boxed warning for CRS and neurologic toxicities
- Approval with a Risk Evaluation and Mitigation Strategy (**REMS**)
  - To ensure the benefits of the drug outweigh the risks
  - Protective measures in place to ensure patients' safety:
    - Hospitals must be certified
    - Education of physicians, hospital staff and patients about the recognition and management of CRS and neurologic toxicity

Summary

Tisagenlecleucel (Kymriah)
Axicabtagene ciloleucel (Yescarta)

- Compelling efficacy in highly refractory or resistant population
- Major safety issues: fatal and life-threatening CRS, neurologic toxicity
  - Black box warning
  - Approval with REMS
- Concern for long-term safety issues and secondary malignancies
  - Approval with post-marketing studies

Long-Term Safety Concerns

- Theoretical risk:
  - Secondary malignancies
- Post-marketing requirement (PMR)*:
  - Observational study to collect safety and survival information
  - 15 year follow-up for known and anticipated adverse reactions

*Note: post marketing requirements (PMRs) are distinct from REMS programs

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Questions?

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
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- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber

FDA Headquarters

Useful FDA Information

- References for the Regulatory Process for the Office of Tissues and Advanced Therapies
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- OTAT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- Cell and Gene Therapy Guidances
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/

- Expedited Programs Guidance:
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf