Safety Considerations for *CAR T* Gene Therapy

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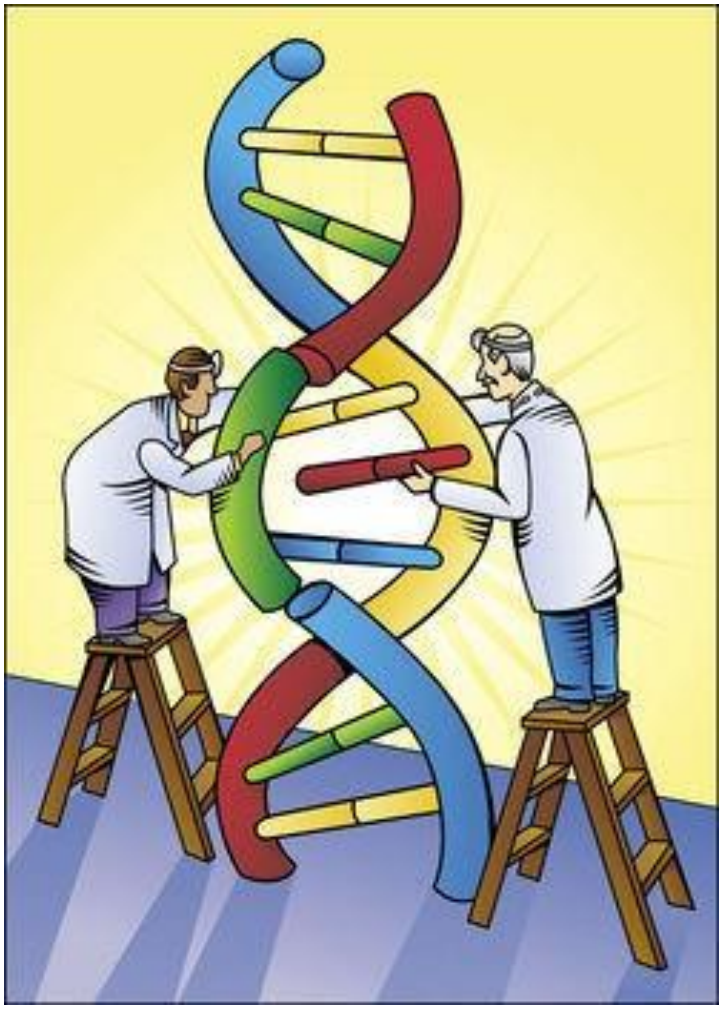
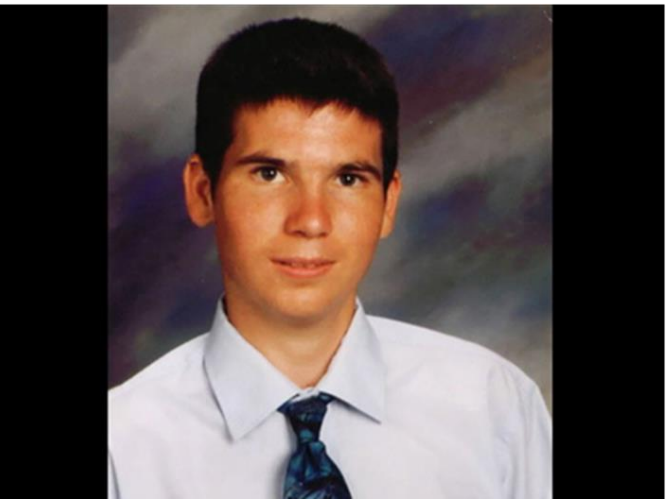
What is Gene Therapy?

- Using genes to treat or prevent disease
  - Replacing a mutated gene with a healthy copy
  - Inactivating a mutated gene that is not functioning properly
  - **Introducing a new gene into the body to fight a disease**



Regulatory History of Gene Therapy



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BUSINESS

FDA Approves Pioneering Cancer Treatment With $475,000 Price Tag

Novartis's Kymriah gets nod for some leukemia patients; uses body's own cells to fight cancer

T-cells from cancer patients arrive at Novartis's New Jersey facility to be turned into super cells as part of a new type of cancer treatment. PHOTO: BRENT STIRTON/ASSOCIATED PRESS

By Denise Roland and Peter Loftus

71 COMMENTS

Updated Aug. 30, 2017 3:48 p.m. ET

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August 30, 2017

Kymriah background

Breakthrough Therapy designation for this genetically modified autologous immunotherapy

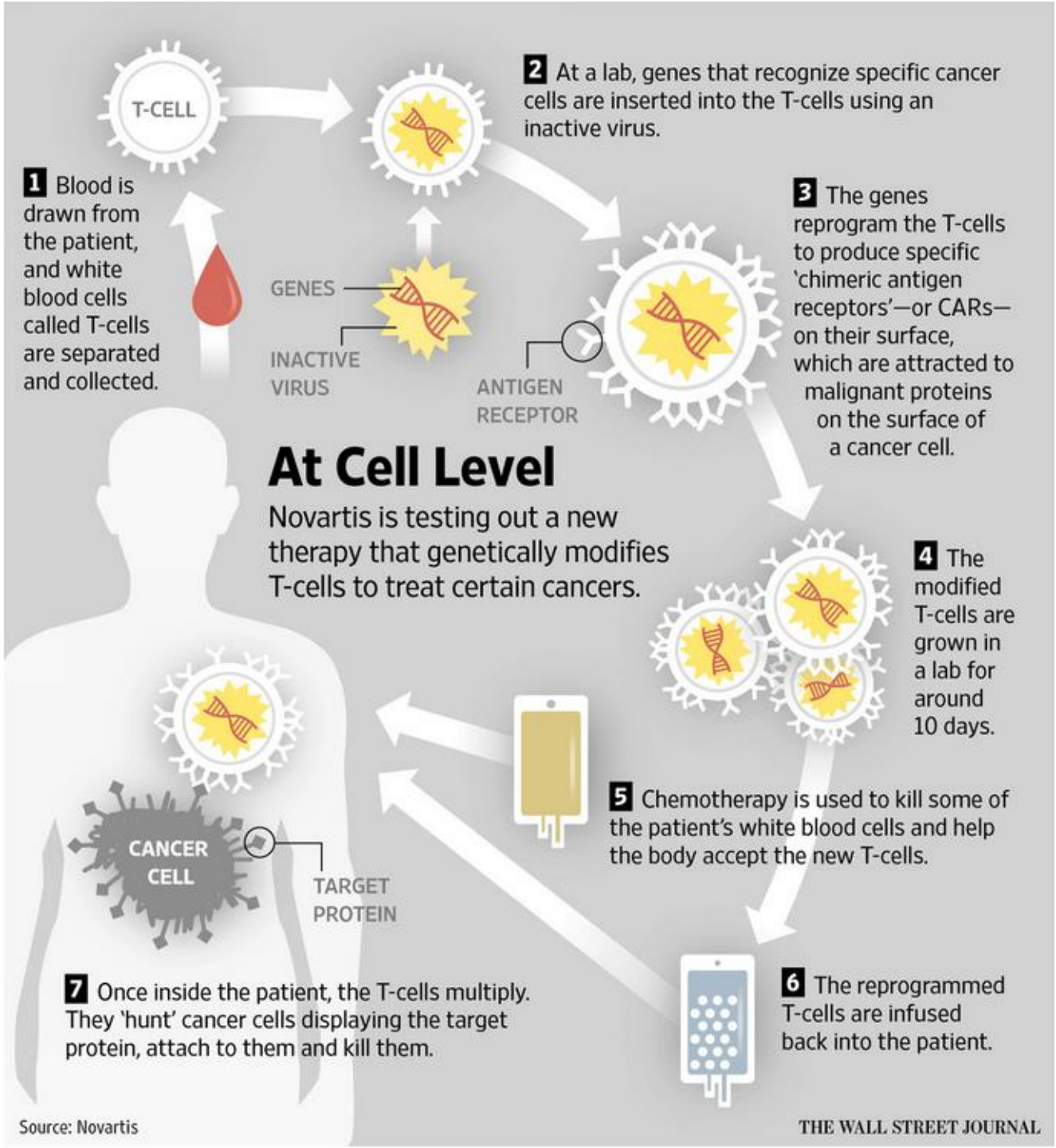
- A lentiviral vector is used to encode an anti-CD19 chimeric antigen receptor T cell (CAR-T)

- *Indication:*
  Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in secondary or later relapse.

Oncologic Drugs Advisory Committee Meeting, July 12, 2017:

- voted **10 to 0** for overall favorable benefit-risk profile

Approved on August 30, 2017


T-CELL
1 Blood is drawn from the patient, and white blood cells called T-cells are separated and collected.
2 At a lab, genes that recognize specific cancer cells are inserted into the T-cells using an inactive virus.
GENES
INACTIVE VIRUS
ANTIGEN RECEPTOR
3 The genes reprogram the T-cells to produce specific 'chimeric antigen receptors'—or CARs—on their surface, which are attracted to malignant proteins on the surface of a cancer cell.
At Cell Level
Novartis is testing out a new therapy that genetically modifies T-cells to treat certain cancers.
4 The modified T-cells are grown in a lab for around 10 days.
5 Chemotherapy is used to kill some of the patient's white blood cells and help the body accept the new T-cells.
CANCER CELL
TARGET PROTEIN
6 The reprogrammed T-cells are infused back into the patient.
7 Once inside the patient, the T-cells multiply. They 'hunt' cancer cells displaying the target protein, attach to them and kill them.
Source: Novartis
THE WALL STREET JOURNAL

Safety Data

Cytokine Release Syndrome (CRS)

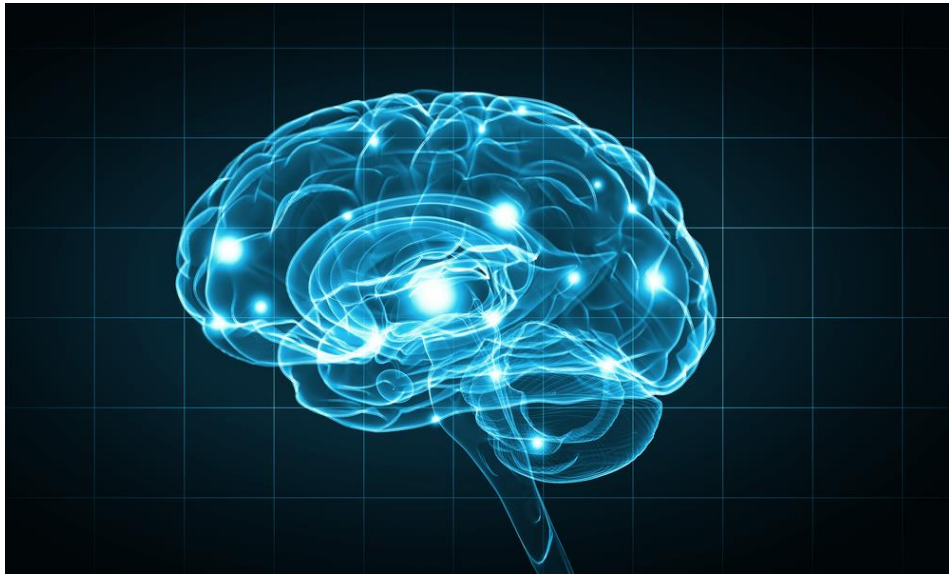
- 54/68 (79%) experienced CRS
  - CRS 54/68 (79%)
    - Median onset - 3 days, (Range: 1-22 days)
    - Median duration 8 days (Range 1-36 days)
  - Grade 3/4 : 33/68 (49%)
    - Mean time to onset - 6 days
    - Required ICU care

Actemra (tocilizumab)

- Anti-IL 6 monclonal antibody indicated originally for rheumatoid indications
- Prior studies found tocilizumab to be the best treatment for CRS
- Kymriah pivotal study protocol specified tocilizumab treatment for CRS
- Approved on August 30 for the treatment of CAR T cell-induced CRS in patients age 2 and older

Neurotoxicity

- Encephalopathy, delirium, hallucinations, somnolence, cognitive disorder, seizure, difficulty swallowing,
- 44 (65%) experienced neurotoxicity
  - 12/68 (18%) Grade 3, no Grade 4
  - 1/10 no CRS; 6/10 Grade 3 Neuro also were Grade 4 CRS
- Reversible
- There were no events of cerebral edema on this trial



Risk/Benefit Analysis

- Benefits: efficacy; lack of alternatives
- Risks:
  - Immediate CRS/neurotoxicity and lack of treatment protocol and/or tocilizumab
  - Delayed CRS/neurotoxicity and lack of tocilizumab at outside hospital
  - Delayed CRS/neurotoxicity and further delay in diagnosis of CRS at outside hospital
  - Patient/guardian unaware of signs of CRS or neurotoxicity

Kymriah Label

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. (2.2, 2.3, 5.1)**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed. (5.2)**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. (5.3)**

Risk Evaluation and Mitigation Strategy (REMS)

- Food and Drug Administration Amendments Act of 2007 (FDAAA) provided FDA the legal authority to require a REMS for applicable drugs
- A REMS is a required risk management plan that utilizes risk mitigation strategies beyond FDA-approved professional labeling
- REMS can be required:
  - Pre-approval, if FDA determines a REMS is needed to ensure the benefits of the drug outweigh the risks
  - Post-approval, if FDA becomes aware of new safety information and determines that such a strategy is necessary to ensue that the benefits of the drug outweigh the risks

Components of a REMS

- Medication Guide or Patient Package Insert
- Communication Plan for Healthcare Providers
- Elements to Assure Safe Use

Elements to Assure Safe Use (ETASU)

A. Education and certification of healthcare providers

B. Certification of healthcare settings which dispense the product

C. Restricting product use only to specified healthcare settings

D. Documentation of safe-use condition

E. Patient monitoring

F. A patient registry

REMS Goals and Assessment

- Mitigate the risks of CRS and neurological toxicities by:
  1. Ensuring that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate access to tocilizumab.
  2. Ensuring those who prescribe, dispense, or administer Kymriah are aware of how to manage the risks of cytokine release syndrome and neurological toxicities.

- Because of ETASU, assessments submitted to FDA
  - 6 months
  - 12 months
  - Annually thereafter

For US Healthcare Professionals Only

KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion

Risk Evaluation and Mitigation Strategy

(REMS)

PDF Kymriah Prescribing Information

PDF Kymriah Medication Guide

PDF Kymriah REMS Live Training Program Slides

PDF Kymriah REMS Program Knowledge Assessment

PDF Kymriah REMS Program Patient Wallet Card

Click here to complete the Knowledge Assessment online

REMS Safety Information

A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The FDA has required a REMS for Kymriah™ (tisagenlecleucel).

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

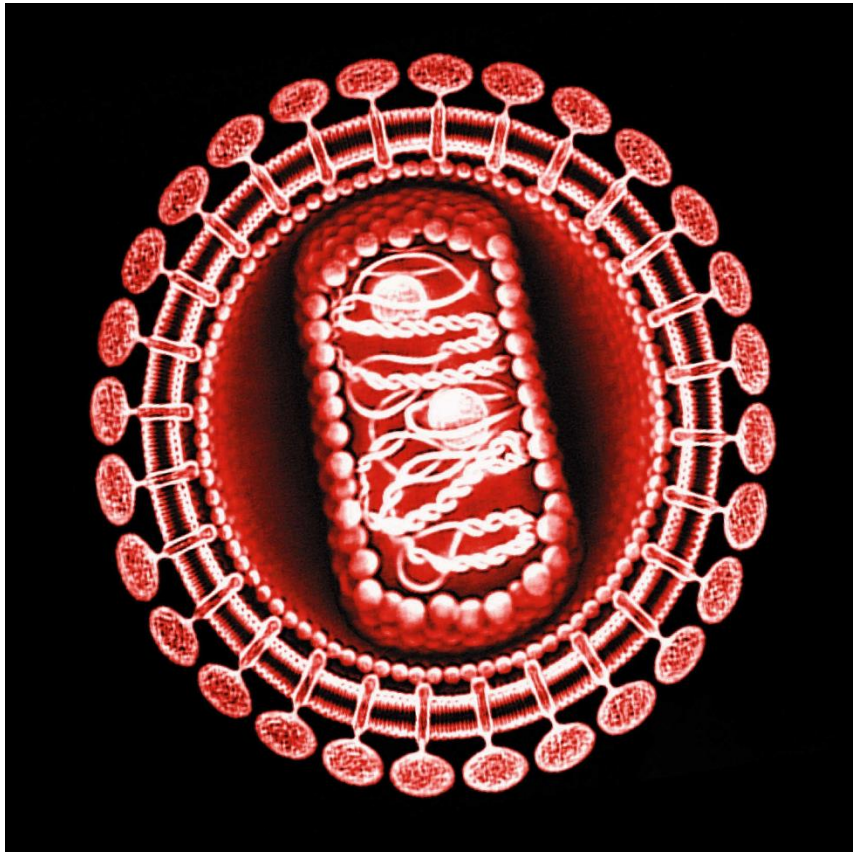
Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab.

Risk Mitigation in Clinical Trials

- Risks
  - Cytokine Release Syndrome
  - Neurological Toxicity
  - B-cell Aplasia
  - Cerebral Edema
- Strategies
  - Detailed protocols and compliance with those protocols
  - FDA Guidance for Industry

Long Term Risks

- section 505(o)(3)(B)(iii) of FDAAA, postmarketing requirement studies, "**to identify unexpected serious risk(s) when available data indicate the potential for serious risk(s)**"
- Serious risk: **secondary malignancy caused by generation of replication-competent retrovirus (RCR) or insertional oncogenesis.**



Post-Marketing Requirement

- Multi-center, prospective, observational trial with 1,000 patient enrolled in 5 years. Subjects followed for 15 years. Primary endpoint will be secondary malignancy. Secondary endpoints: other adverse events

References

- Considerations for the Design of Early Phase Clinical Trials of Cellular and Gene Therapy Products
  - https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf
- Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events
  - https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM078719.pdf
- Kymriah REMS
  - https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=368
- Yescarta REMS
  - https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=375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