CAR T-cells: A New Era of Cancer Therapy

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Objectives

At the conclusion of this session, participants should be able to:

- Describe what CAR T-cell therapies are and how they target cancer cells
- Identify which cancers can be treated with CAR T-cells
- Recognize both acute and long-term complications/side effects of CAR T-cell therapies

Cancer Therapy

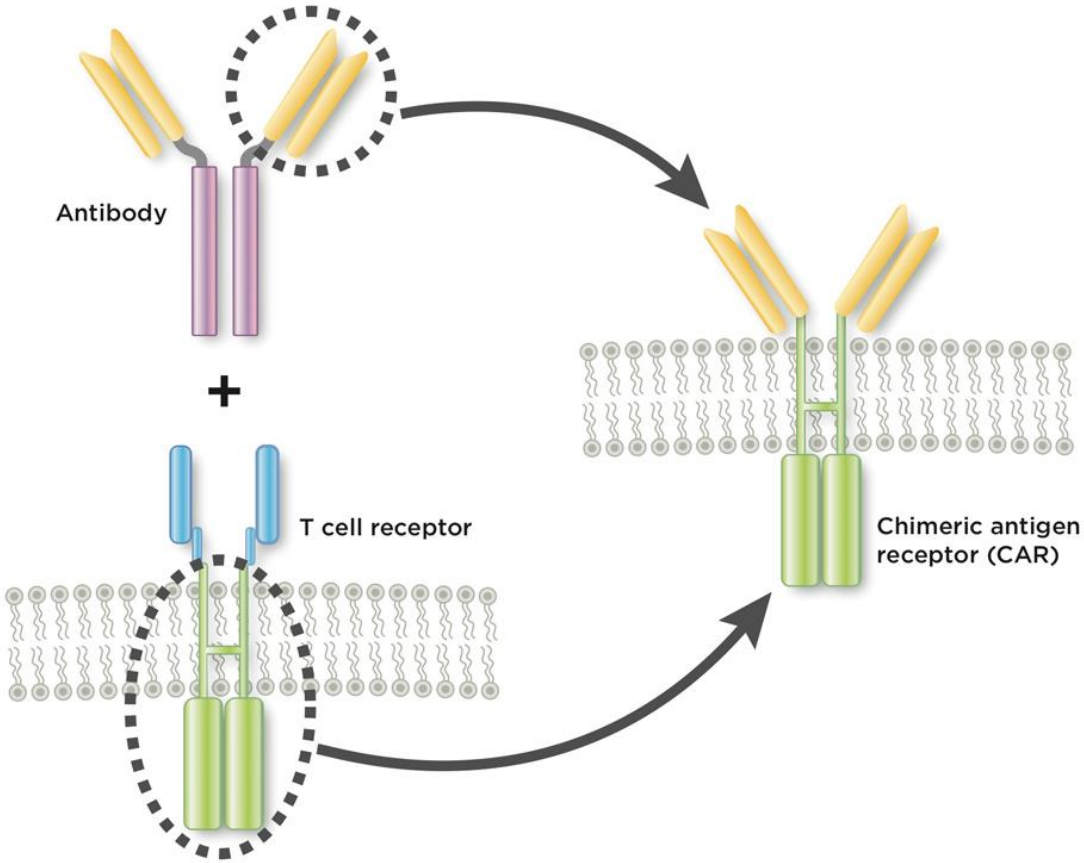
- Surgery
- Radiation
- Chemotherapy
- **Immunotherapy**

CAR T-cells:

T-lymphocytes that are genetically modified to produce chimeric antigen receptors that target antigens found on the surface of tumor cells

Chimeric Antigen Receptor

Combines antibody derived antigen recognition domain with T-cell receptor intracellular domain



https://www.mskcc.org/news/model-ts-fda-approves-first-car-t-cells-cancer

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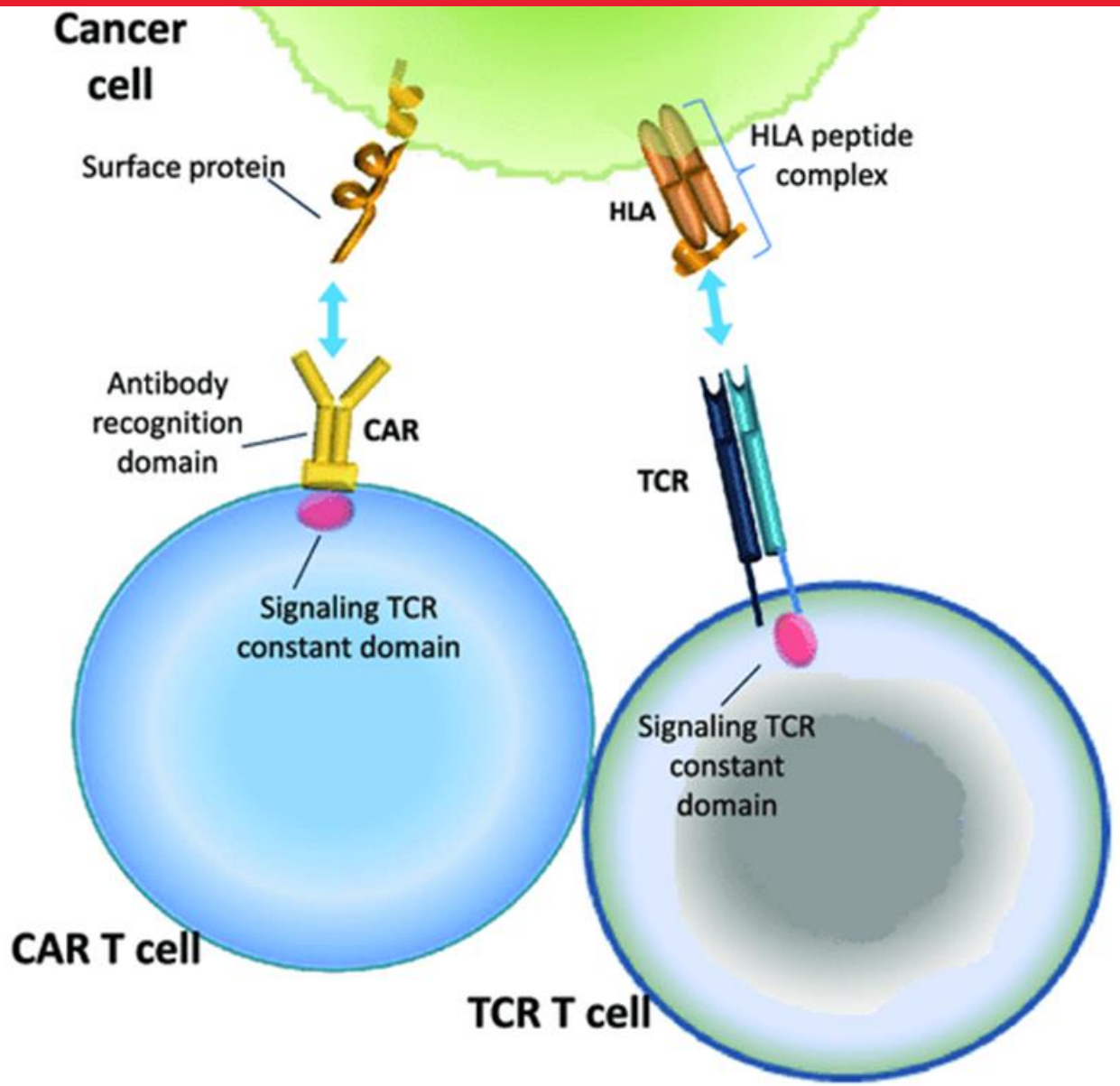

Farkona S, *BMC Medicine*.

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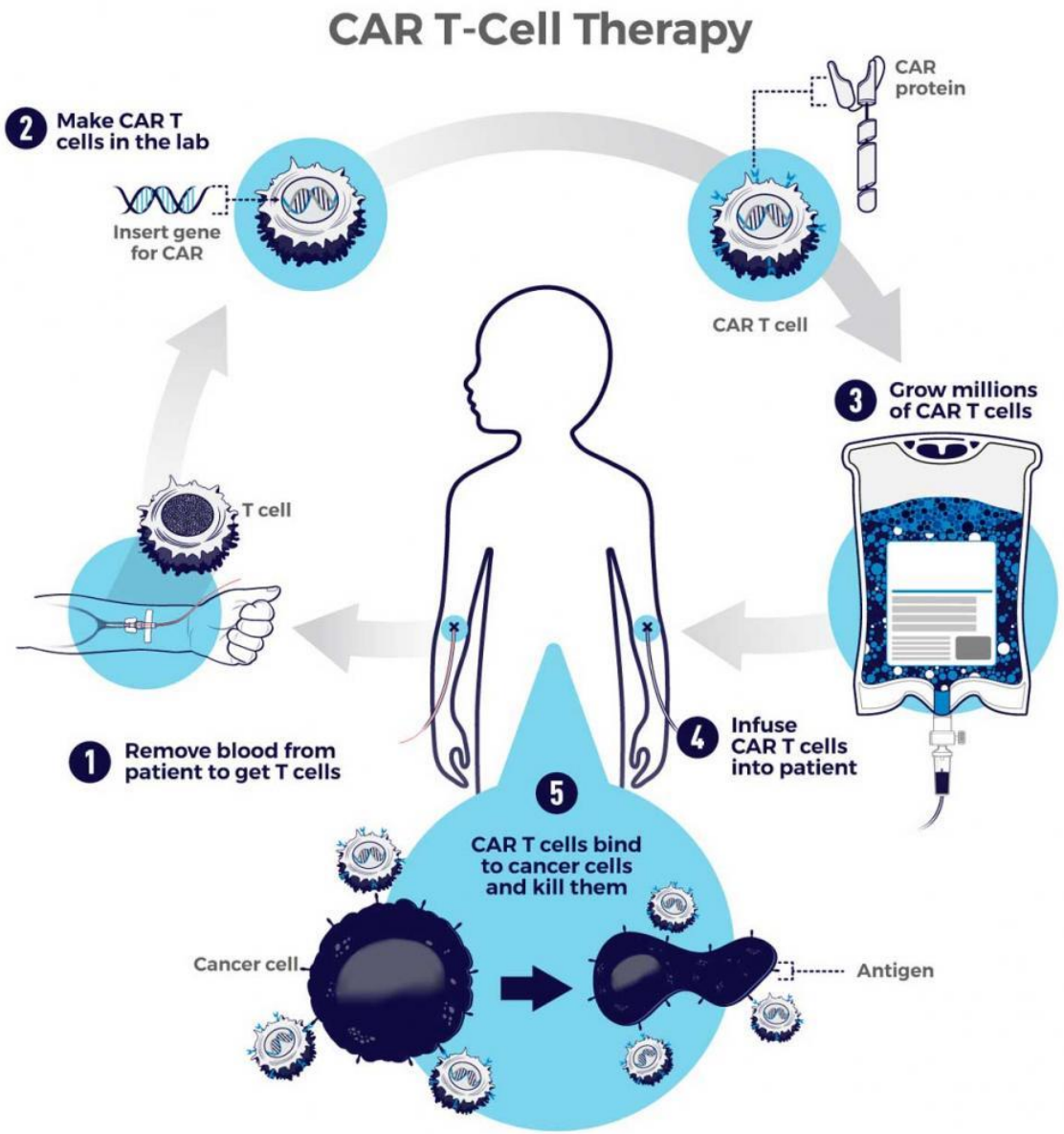
Chimeric **Antigen** Receptor Target Antigens

- Must be present on the surface of cancer cell
- Ideally present on all cancer cells
- Ideally not present on normal cells



CAR T-Cell Therapy Infographic. National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/research/car-t-cell-therapy-infographic. Accessed July 30, 2020.

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CAR T-cell Products

FDA NEWS RELEASE

FDA approval brings first gene therapy to the United States

For Immediate Release:

August 30, 2017

This release was updated on Aug. 30, 2017 to correctly identify the FDA designations granted to Kymriah.

Español (/news-events/comunicados-de-prensa/primera-terapia-genetica-en-los-estados-unidos-es-aprobada-por-la-fda)

The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).

FDA Approved CAR T cells

CAR T-cell Product	Target	Indications	Approved	ORR	CR
Tisagenlecleucel (tisa-cel)	CD19	Children and adults up to 25 years with R/R B-cell ALL Adults with R/R B-cell lymphoma	2017, 2018	81% 52%-85%	60% 40%-65%
Axicabtagene ciloleucel (Axi-cel)	CD19	Adults with R/R B-cell Lymphoma Adults with R/R follicular lymphoma	2017	82% 94%	54% 79%
Brexucabtagene autoleucel (Brex-cel)	CD19	Adults with R/R Mantle Cell Lymphoma	2020	93%	67%
Lisocabtagene maraleucel (Liso-cel)	CD19	Adults with R/R B-cell Lymphoma	2021	73%	53%
Idecatagene vicleucel (Ide-cel)	BCMA	Adults with R/R multiple myeloma	2021	72%	28%
Ciltacabtagene autoleucel (Cilta-cel)	BCMA	Adults with R/R multiple myeloma	2022	97%	65%

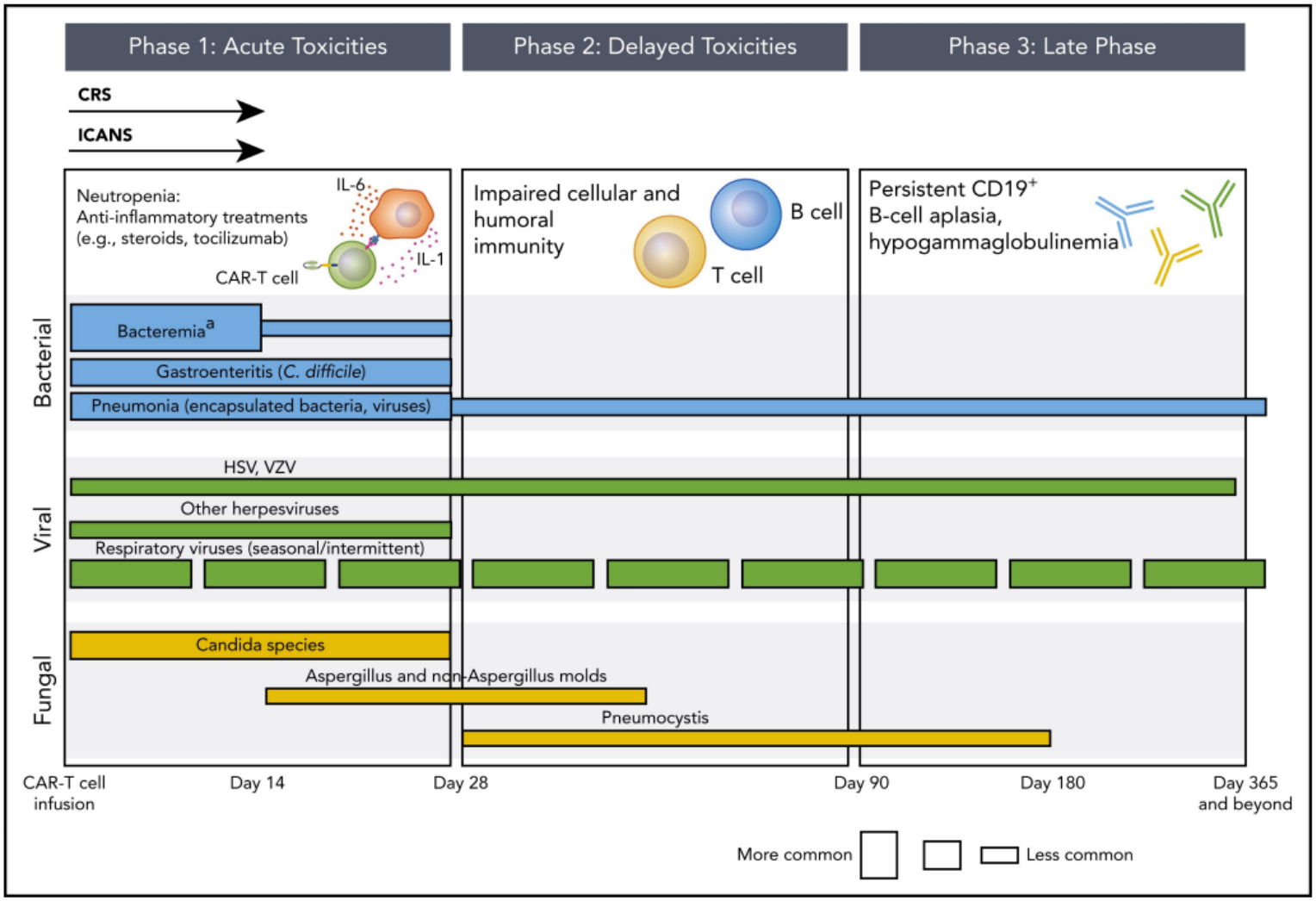
BCMA=B-cell maturation antigen; R/R=relapsed/refractory; ORR=overall response rate; CR=complete response rate

CAR T-cell Toxicities

Lymphodepletion

- Prior to receiving CAR T-cells, patients receive lymphodepleting chemotherapy to create a favorable environment for CAR T-cell proliferation
- Chemotherapy side effects:
  - Nausea, vomiting, decreased appetite
  - Prolonged cytopenias
  - Infection

Infectious Complications



Hill JA, Seo SK. *Blood*

Cytokine Release Syndrome (CRS)

Acute systemic inflammatory response due to T-cell activation and elevated cytokine levels

ASTCT Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a 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, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Lee et al. *Biol Blood Marrow Transplant*

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CRS Treatment

- Supportive care
  - Exclude infection: blood cultures and empiric antibiotics
  - Antipyretics, IVFs, oxygen, vasopressers, mechanical ventilation
- Tocilizumab (anti IL-6)
- Corticosteroids

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ASTCT Consensus Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point

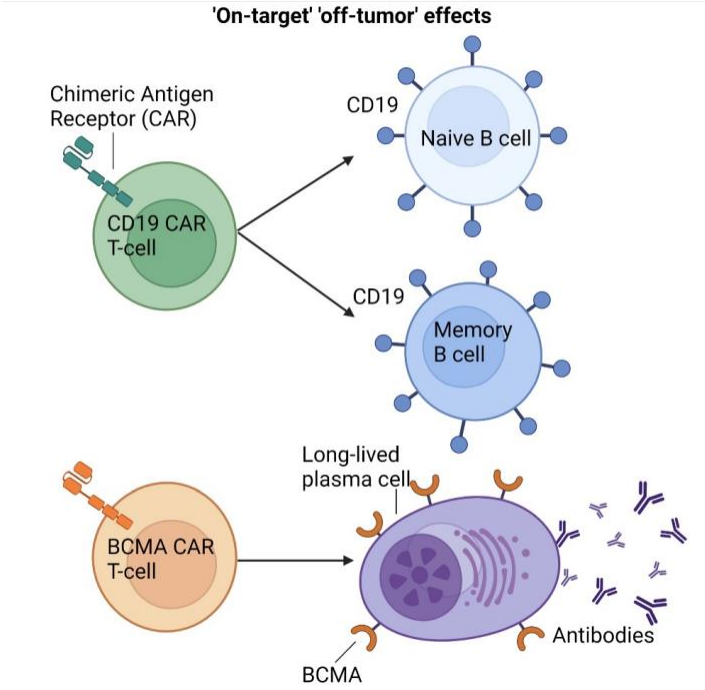
Lee et al. *Biol Blood Marrow Transplant*

ICANS Treatment

- Supportive care
- Corticosteroids
- Anakinra (IL-1 receptor antagonist) *

Hypogammaglobulinemia

- Due to B-cell aplasia
- “On target, off tumor” toxicity
- Treatment: IVIG q4-8 weeks
- Vaccination



Kampouri et al. *Expert Rev Hematol*

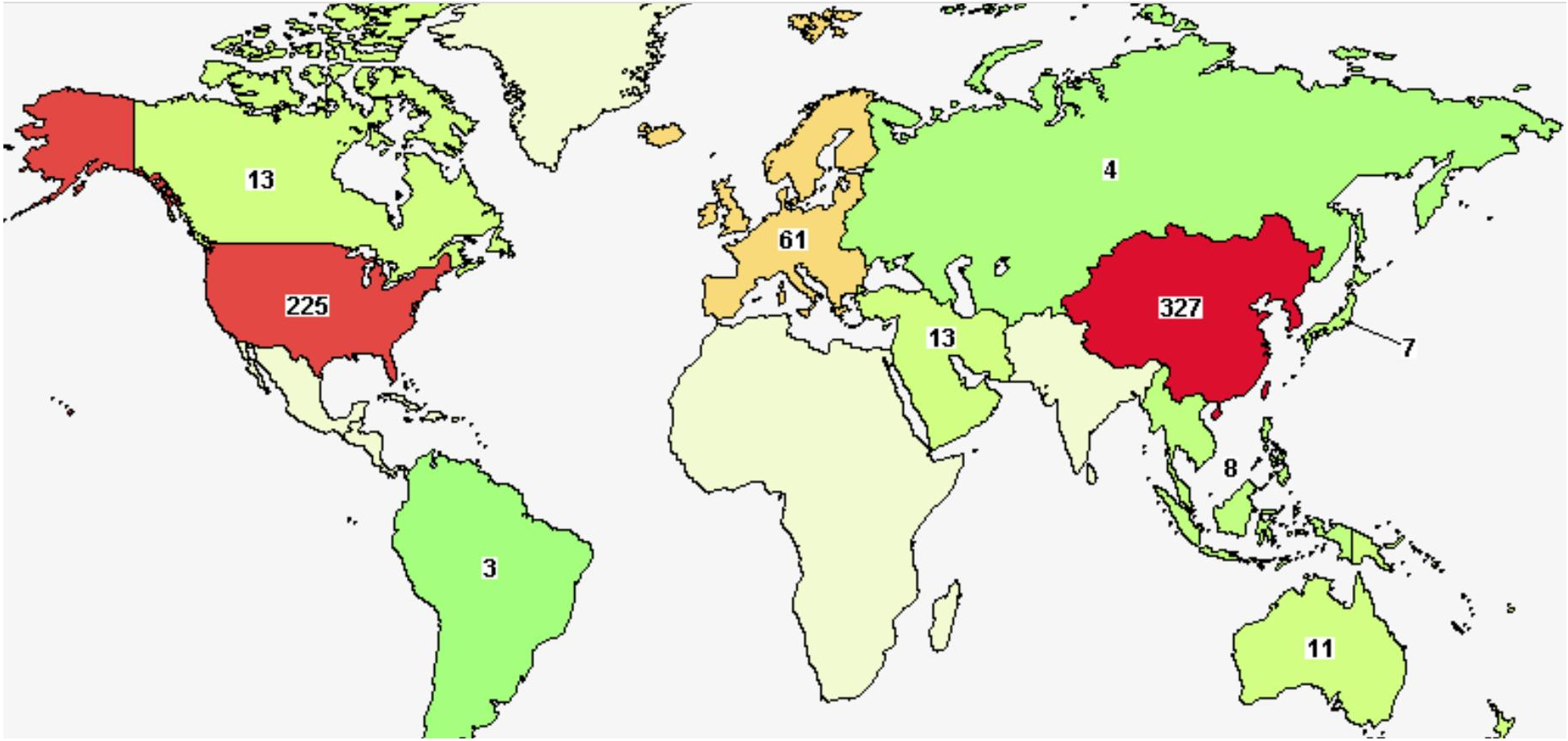
Relapse

- Relapse can be due to:
  - loss of CAR T-cell persistence
  - Antigen escape (i.e. CD 19 negative relapse)

Other Side Effects

- Secondary malignancies
- False positive HIV testing

Investigational CAR T-cells



Clinicaltrials.gov

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Barriers to Success

- Target antigens
- Tumor antigen heterogeneity
- Trafficking
- Physical barriers/microenvironment
- Proliferation/persistence
- Antigen escape
- Manufacturing time

Future Directions

- Targeting different antigens
- Bispecific CARs
- Allogeneic CARs
- CAR T-cells as first line therapy

Conclusions

- CAR T-cells are genetically modified T-cells used to target specific tumor antigens
- There are many toxicities associated with current CAR T-cell products including CRS, ICANS, and hypogammoglobulinemia
- Though there is still much to be learned about and improved on with CAR T-cell therapies, they can provide prolonged remission in patients who otherwise may not have achieved remission

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