Educator Module

Introduction to CAR T-Cell Therapy

Agenda

- Objectives
- Introduction to chimeric antigen receptor T (CAR T)–cell therapy
- Current CAR T-cell products and clinical trials
- CAR T-cell therapy availability
- CAR T-cell treatment process
- Common adverse events associated with CAR T-cell therapy
- Conclusions

Objectives

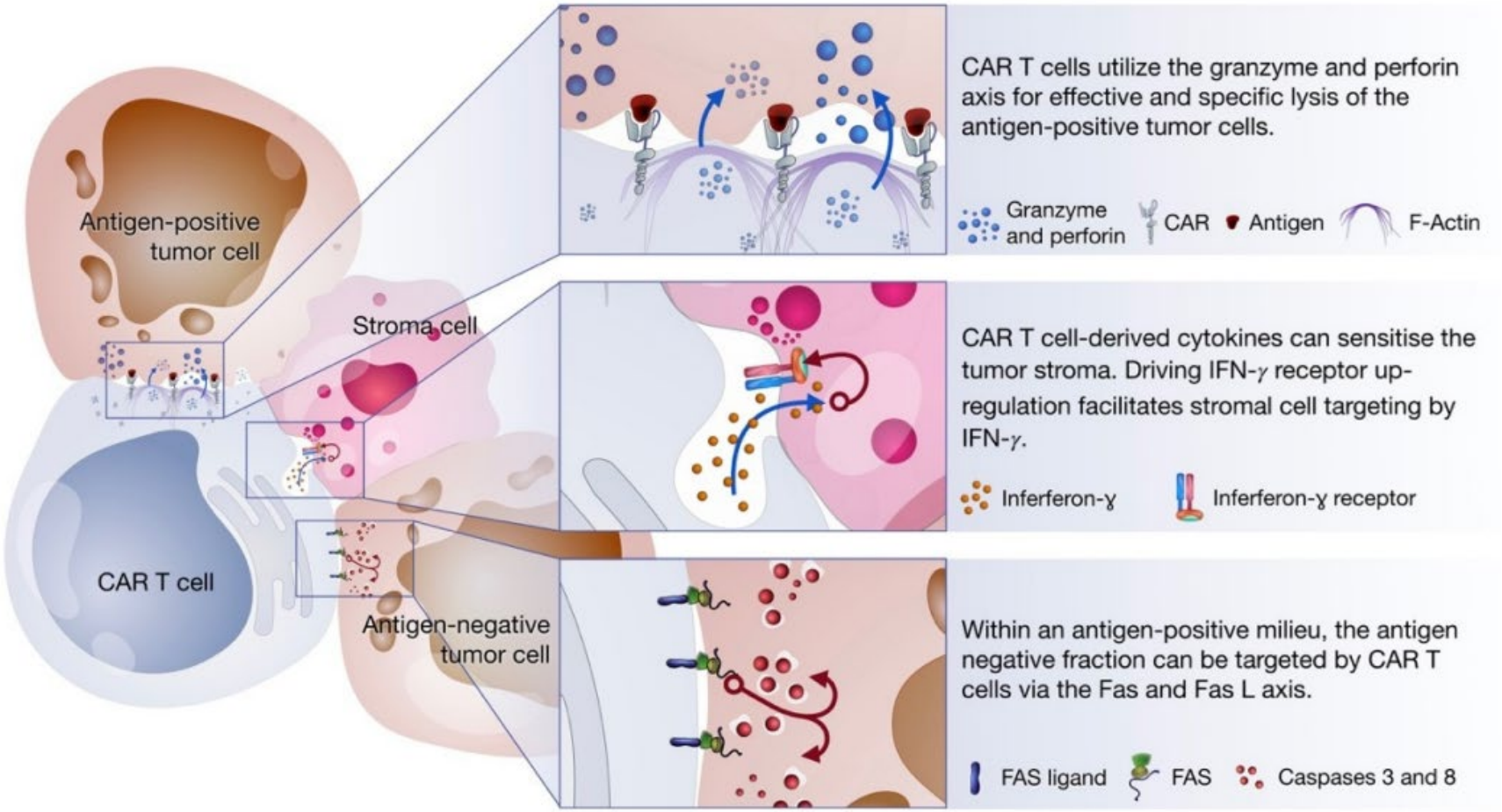
- Review the definition and mechanism of action of CAR T-cell therapy
- Compare and contrast CAR T-cell therapy to conventional chemotherapy and other immunotherapy modalities
- Review current CAR T-cell options and emerging CAR T-cell therapies in late stages of clinical development
- Understand the CAR T-cell treatment process for patients
- Identify common treatment-related toxicities associated with CAR T-cell therapy

What Is CAR T-Cell Therapy?

- Autologous T cells engineered to express a specific T-cell receptor, which enables the T cells to recognize tumor cells and initiate cytotoxic activity[1]
- A cellular therapy that is entirely different from conventional chemotherapy (e.g., doxorubicin, cytarabine, etoposide, fluorouracil, etc)[2,3]
- CAR T-cell therapy is more similar to existing antibody therapies (e.g., immune checkpoint inhibitors)[4]
  - Similar mechanism of action because they both have antigen targets and cause immune activation
- Also can be compared to bispecific T-cell engager (BiTE) therapies (e.g., blinatumomab)[3]
  - Both therapies rely on the engagement of T cells with malignant cells
  - Adverse events can be similar to those associated with CAR T cells

1. Miliotou A, Papadopoulou LC. *Curr Pharm Biotechnol*. 2018;19:5-18. 2. NIH. Chemotherapy to Treat Cancer. 2015. www.cancer.gov/about-cancer/treatment/types/chemotherapy. Accessed October 10, 2019. 3. NIH. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. 2019. www.cancer.gov/about-cancer/treatment/research/car-t-cells. Accessed October 10, 2019. 4. NIH. Immunotherapy to Treat Cancer. 2019. www.cancer.gov/about-cancer/treatment/types/immunotherapy. Accessed October 10, 2019. 5. Slaney CY, et al. *Cancer Discov*. 2018;8:924-34.

CAR T-Cell Therapy Mechanism of Action



Benmebarek M-R, et al. *Int J Mol Sci.* 2019;20:1283.

CAR T-cell therapy:

1. Causes lysis of antigen-positive tumor cells
2. Modulates tumor microenvironment by sensitizing tumor stroma
3. Causes lysis of antigen-negative tumor cells through apoptotic mechanisms

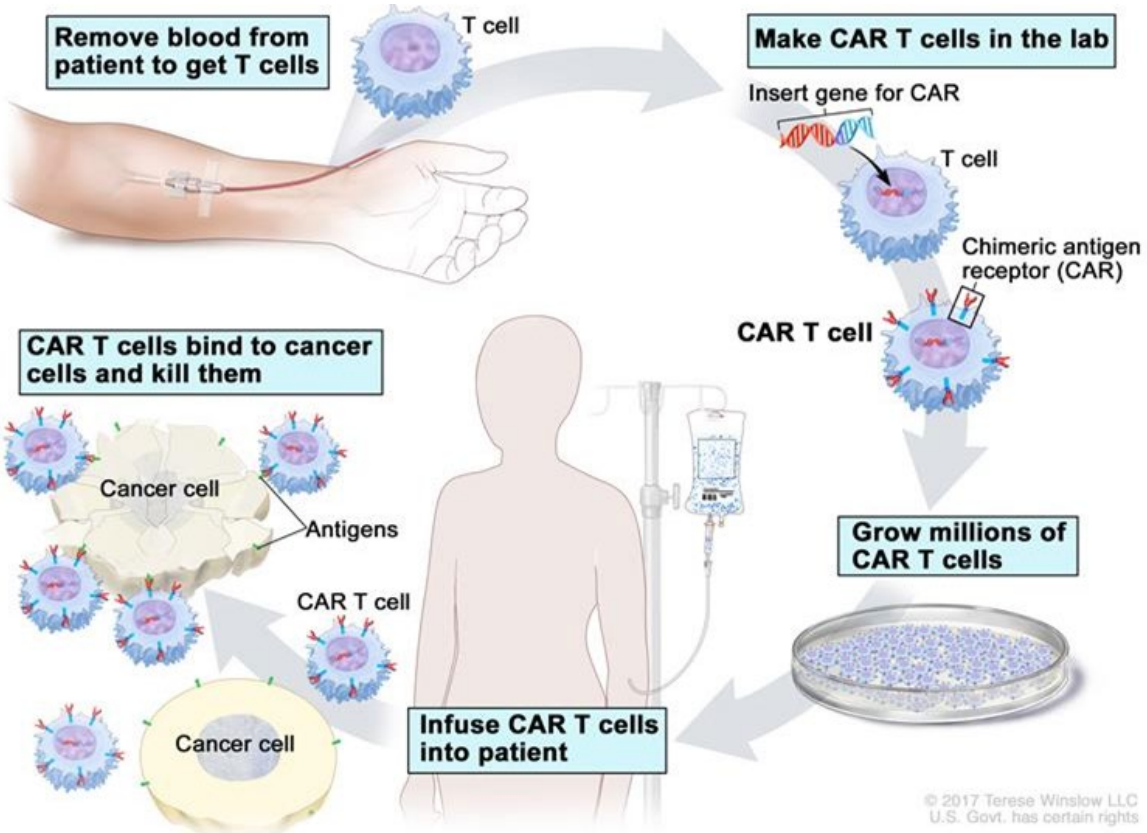
Unique Benefits of CAR T-Cell Therapy

- Biological therapy that often requires shorter treatment courses than many other conventional regimens[1]
- Can be useful against disease that is refractory to chemotherapy[1]
- Can be used independent of or in addition to bone marrow transplant (BMT)[2]
- Because it utilizes the patient's own cells, there are no graft-versus-host complications
    - However, CAR T cells retain a "graft"-versus-tumor effect[3]

1. Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56. 2. Shalabi H, et al. *Biol Blood Marrow Transplant*. 2018;24:S20-4. Abstract 6. 3. Bonifant CL, et al. *Mol Ther Oncolytics*. 2016;3:16011.

CAR T-Cell Treatment Is Individualized

CAR T Cells Produced From the Patient's Own Cells[1]



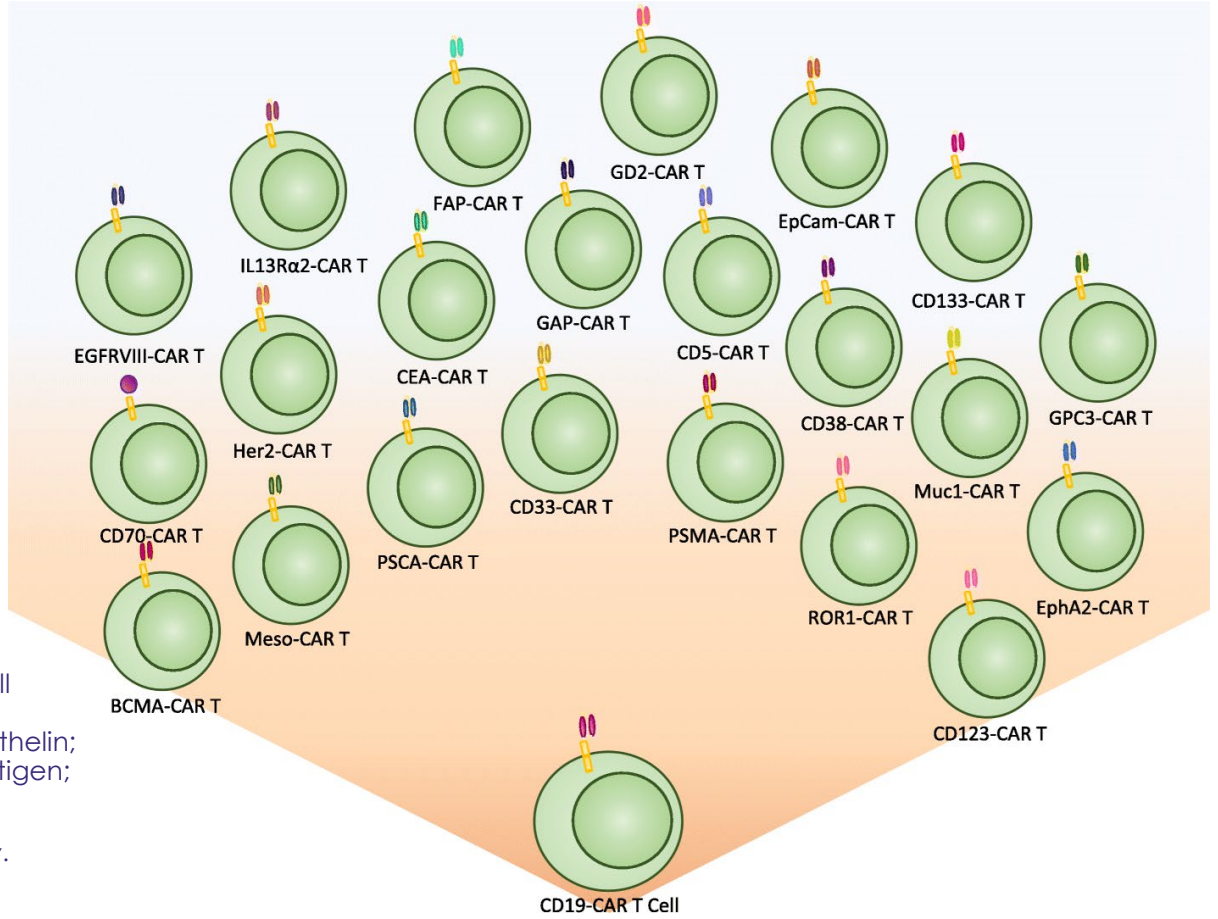
- Current CAR T-cell therapies are engineered for each individual recipient
  - Research is ongoing to create "off-the-shelf" CAR T-cell products, but are not yet available[2,3]
- To create CAR T cells, T cells must be collected from the patient's tissue, tumor, or blood
  - FDA-approved products are collected from blood
- T cells are then processed in manufacturer's lab to add an engineered antibody that is specific to the disease target

1. NIH. CAR-T cell therapy. www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy. Accessed October 7, 2019. 2. Zhao J, et al. *J Hematol Oncol*. 2018;11:132. 3.Ruella M, Kenderian SS. *BioDrugs*. 2017;31:473-81.

What Targets Are Possible?

- FDA-approved products target CD19
  - CD19 is an antigen expressed primarily on B cells
  - Therefore, CD19 is heavily expressed by B-cell and precursor B-cell malignancies
- Other studies focused on a range of targets for multiple cancer types[1]
  - ROR1 (i.e., NTRKR1) for lung and breast cancer
  - BCMA and CD38 for multiple myeloma
  - HER2 for breast cancer and sarcoma
  - PSMA for prostate cancer
- Each CAR T cell is effective only against its target antigen and therefore ineffective against antigen-negative or -downregulated targets[2]

Multiple Targets Pursued for CAR T-Cell Therapy[1]



BCMA, B-cell maturation antigen; CEA, carcinoembryonic antigen; EpCam, epithelial cell adhesion molecule; EphA2, erythropoietin-producing hepatocellular carcinoma A2; FAP, fibroblast activation protein; GAP, goblet cell–associated antigen passages; Meso, mesothelin; Muc1, mucin 1; PSCA, prostate stem cell antigen; PSMA, prostate-specific membrane antigen; ROR1/NTRKR1, neurotrophic tyrosine kinase receptor-related 1.

1. Townsend MH, et al. *J Exp Clin Cancer Res*. 2018;37:163. 2. Majzner R, Mackall CL. *Cancer Discov*. 2018;8:1219-26.

FDA-Approved CAR T-Cell Products

CAR T-Cell Product	FDA Approval	Target	Indication(s)	Efficacy
Axicabtagene ciloleucel (Yescarta)[1]	10/2017	CD19	Adults with relapsed/refractory large B-cell lymphoma, including DLBCL-NOS, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from FL, after ≥2 lines of systemic therapy	ORR: 82%[2] 6-mo PFS: 49%
Tisagenlecleucel (Kymriah)[3]	8/2017	CD19	• Adults with relapsed/refractory large B-cell lymphoma, including DLBCL-NOS, high-grade B-cell lymphoma, and DLBCL arising from FL, after ≥2 lines of systemic therapy • Patients age ≤25 with B-cell precursor ALL that is refractory or in second or later relapse	ORR: 52%[4] 12-mo PFS: 65% (79% in patients with CR)

ALL, acute lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ORR, objective response rate; PFS, progression-free survival; PMLBCL, primary mediastinal B-cell lymphoma; NOS, not otherwise specified.

1. Yescarta (axicabtagene ciloleucel) package insert. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf. 2. Jain MD, et al. *Ther Clin Risk Manag*. 2018;14:1007-17. 3. Kymriah (tisagenlecleucel) package insert. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf. 4. Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56.

Becoming an Authorized Center

- To administer CAR T-cell therapy, institutions must be enrolled with the manufacturers' REMS programs

Includes review of:
- Full prescribing information
- REMS live training
- Adverse reaction management guide

Resources and complete steps required for enrollment are available at manufacturers' REMS websites:

yescartarems.com
kymriah-rems.com

- All relevant staff trained on REMS program requirements and complete knowledge assessment
- Maintain training records
- Maintain ≥2 vials tocilizumab per patient on-site and ready to be administered within 2 hr
- Provide patients/caregivers with Patient Wallet Card
  - Instruct to remain within 2 hr for 4 wk after infusion
- Maintain training and retraining program

Kite. Risk Evaluation and Mitigation Strategy (REMS). www.yescartarems.com/. Accessed 10/7/19.

The CAR T-Cell Treatment Process

Cost of Treatment

- Axicabtagene ciloleucel is priced at $373,000 and tisagenlecleucel at $373,000-$475,000, depending on indication[1,2]
  - Does not include associated cost of treatment (i.e., hospitalization, clinic visits, follow-up)[3]
  - Approved indications are covered by many major insurance carriers and Medicare[4]
- CAR T-cell therapy may be available at no cost to the patient in clinical trials
  - Careful consideration is required for non-study–related costs, for which patients may be liable

1. Lash A. *Xconomy*. 2019. https://xconomy.com/national/2019/01/03/for-car-t-cancer-fighters-in-the-real-world-two-roads-diverge/. Accessed October 10, 2019. 2. Santomasso B, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:433-44. 3. Kahl KL. *Cure*. 2019. www.curetoday.com/articles/medicare-coverage-of-cart-cell-therapy-opens-patient-access-to-lifesaving-treatment. Accessed October 10, 2019.

Patient Eligibility for CAR T-Cell Therapy

- Per FDA guidelines for approved indications[1,2] or insurance criteria[3]
  - May vary based on clinical trial protocols

- ECOG 0-1*
- Neurological, cardiac, pulmonary, hepatic, and renal function per oncologist approval
- No uncontrolled infections
- Cannot have acute GVHD
- Bulky disease, disease impacting organ function, or ECOG >1 may benefit from debulking with chemotherapy prior to initiation of CAR T-cell products
- Patients must have sufficient organ reserve to tolerate lymphodepleting therapy, typically cyclophosphamide and fludarabine
- Because neurotoxicity and delirium are components of CAR T-cell toxicity, some institutions consider psychiatric screening, DPOA, and advanced directives prior to CAR T-cell therapy enrollment
  - Active depression, suicidal ideation, schizophrenia, paranoia

* Or Karnofsky score of ≥70%[4]

DPOA, durable power of attorney; ECOG, Eastern Cooperative Oncology Group; GVHD, graft-versus-host disease

1. KYMRIAH (tisagenlecleucel) suspension for intravenous infusion. [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 5/2018. 2. Yescarta (axicabtagene ciloleucel) package insert. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf. 3. Amerigroup RealSolutions in Healthcare. Axicabtagene ciloleucel (Yescarta). Medical Policy. Reviewed 6/6/2019. https://medicalpolicies.amerigroup.com/medicalpolicies/policies/mp_pw_d052641.htm. Accessed October 10, 2019. 4. Hayden PJ, et al. *Curr Res Transl Med*. 2019;67:79-88.

Patient Disposition

- Patients enrolling in CAR T-cell therapy should have a reliable caregiver(s) able to provide 24/7 supervision during and following CAR T-cell treatment[1,2]
- Product guidelines for both FDA-approved products currently require that patients remain within 2 hr of a treatment center for at least 4 wk following CAR T-cell infusion
    - Due to significant risk of delayed toxicity with neurotoxicity or cytokine release syndrome (CRS)
- Following mandatory observation period, patients will need long-term follow-up either at treating institution or with a local oncologist

1. Kite. How Will I Receive Treatment? https://www.yescarta.com/car-t-treatment-process#leukapheresis. Accessed October 10, 2019. 2. Kymriah (tisagenlecleucel) package insert. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf.

CAR T-Cell Creation and Treatment Process

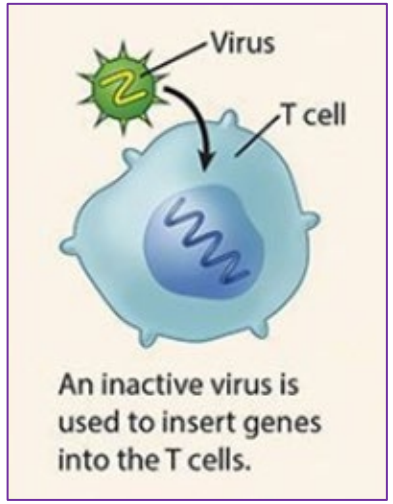
T-Cell Harvest

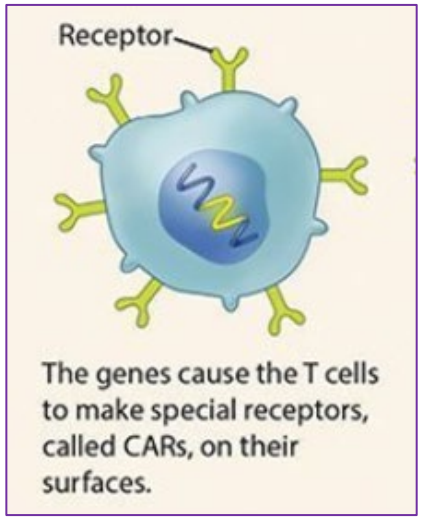
- Patient must first enroll with eligible center to establish care
  - Pretreatment workup will be conducted to establish patient reserve
  - May include: PFT, stress testing, echo, MRI/CT, BMA, LP, etc
- T cells harvested either by biopsy or apheresis
  - Sample may be found to be insufficient at various times in harvest and creation process
    - Insufficient quantity of T cells recovered
    - Insufficient expansion after modification
  - Sample quality may depend on prior chemotherapy exposure and degree of immunodeficiency[1,2]
- After isolating endogenous T cells from patient, cells are delivered to manufacturing lab for cell engineering and processing

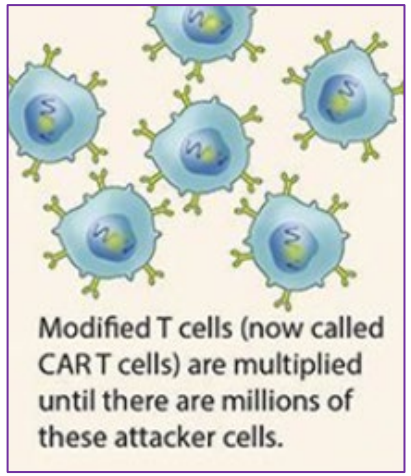
BMA, bone marrow aspirate; echo, echocardiogram; LP, lumbar puncture; PFT, pulmonary function testing.

1. Zou Y, et al. *J Hematol Oncol*. 2018;11:130. 2. Das RK, et al. *Clin Res*. 2018;78(suppl);abstr 1631.

Cell Engineering and Expansion







- Manufacturing process involves use of modified viral vector, such as lentivirus or γ-retrovirus, to insert specific genetic sequences to produce antibody expression[1,2]
  - Each viral vector is manufactured specifically for the product of interest
  - Viral vectors are incapable of causing disease, though long-term observation is lacking
- T cells are also modified to expand population in vitro and in vivo
- Different products are expanded to different specifications
  - Clinical trials may target specific cell populations
  - Development of regulations on cell count and viability has led to "generic" product[3,4]

1. Leukemia & Lymphoma Society. CAR T-Cell Therapy. www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy. Accessed 10/7/19. 2. Zhang C, et al. *Biomark Res*. 2017;5:22. 3. NCT03601442. CTL019 Out of Specification MAP for ALL or DLBCL Patients. Novartis Pharmaceuticals. Updated October 10, 2019. https://clinicaltrials.gov/ct2/show/NCT03601442. 5. Pagliarulo N. *Biopharma Dive*. 2018. www.biopharmadive.com/news/in-car-t-manufacturing-a-hurdle-novartis-has-yet-to-clear/543624/. Accessed October 10, 2019.

Cell Delivery

- Once expanded using cellular growth medium in the lab, final CAR T cells are isolated and packaged
- Currently takes 3 to 4 wk "vein-to-vein"[1,2]
  - But manufacturers are targeting 2-wk expansion times
- Can be stored if complications or delays prevent immediate infusion if cells have not been thawed
- CAR T cells are thawed at time of infusion and must be infused within 2 to 3 hr
- Careful attention to chain of custody due to biological nature of therapy[3]

1. Kite. Rapid and Reliable Manufacturing. www.yescartahcp.com/car-t-technology. Accessed October 10, 2019. 2. Novartis. Kymriah Fact Sheet. https://novartis.gcs-web.com/static-files/a2272924-bf6c-47e4-9ece-14fb5547ab47. Accessed October 10, 2019. 3. Yescarta (axicabtagene ciloleucel) package insert. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf.

Debulking

- Debulking can be performed prior to collection of cells, during cell processing, or prior to lymphodepletion depending on product approval
  - Typically use a standard regimen (e.g., ICE, EPOCH, hyper-CVAD), even if disease was previously refractory or chemotherapy-resistant
- Debulking is separate from lymphodepletion

Goal

Not remission, but to decrease disease burden

→ To decrease circulating cells to reduce likelihood of tumor lysis syndrome or CRS because patients with bulky disease or excessive blasts in marrow are significantly at higher CRS risk[1]
→ To decrease disease burden to improve end organ function in order to safely receive CAR T-cell therapy

EPOCH, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride; ICE, ifosfamide, carboplatin, and etoposide; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

Yáñez L, et al. *HemaSphere*. 2019;3:e186.

Lymphodepletion

- Lymphodepletion is a chemotherapy step prior to infusion of cell product, usually within 2 wk of administering CAR T cells
  - Can be repeated if necessary due to delays
- Utilizes conventional chemotherapy
  - Both FDA-approved CAR T-cell products utilize a combination cyclophosphamide and fludarabine
  - Bendamustine approved as alternative
  - May be omitted if pancytopenic under specific product guidelines
- Not a myeloablative regimen, as this is not a stem cell transplant

Goal

To reduce endogenous nonengineered T cells and improve response to CAR T-cell therapy[1,2]

1. Enblad G, et al. *Clin Trials Cancer Immunother*. 2016;4(suppl);abstr A041. 2. Zou Y, et al. *J Hematol Oncol*. 2018;11:130.

Infusion

- Depending on product or study design, may be infused inpatient or outpatient
- Mandatory inpatient stay versus monitoring in outpatient setting is the current standard of care
  - Currently, tisagenlecleucel allows outpatient infusion, whereas axicabtagene ciloleucel mandates hospital admission[1,2]
  - Clinical trial requirements vary
- Current CAR T-cell products mandate the availability of tocilizumab prior to infusion[3,4]
- Premedication with diphenhydramine/H1 blocker & acetaminophen is required[3,4]
- Product infused over relatively short infusion times of <15 min
- For multibag dosing, bags are thawed individually until successful completion of prior bag[3,4]

1. Novartis. Treatment Process. www.hcp.novartis.com/products/kymriah/acute-lymphoblastic-leukemia-children/dosing-and-administration/. Accessed October 10, 2019. 2. Kite. Where Can Yescarta be Received? www.yescarta.com/treatment-centers. Accessed 10/7/19. 3. Yescarta (axicabtagene ciloleucel) package insert. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf. 2. Jain MD, et al. *Ther Clin Risk Manag*. 2018;14:1007-17. 4. Kymriah (tisagenlecleucel) package insert. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf.

Common Adverse Events Associated With CAR T-Cell Therapy

Common Adverse Events

- Toxicity associated with classical cytotoxic chemotherapy in debulking and lymphodepleting regimens
  - Nausea, vomiting, alopecia, anorexia, myelosuppression, etc
- Unique side effect profiles due to cytokine release and neurotoxicity

Neurotoxicity

- Occurred in 40% to 57% within 8 weeks of infusion[1,2]
- Typically occurred during or shortly after CRS[1]
- Considered manageable and reversible, but can be life-threatening or fatal[2]

Cytokine Release Syndrome

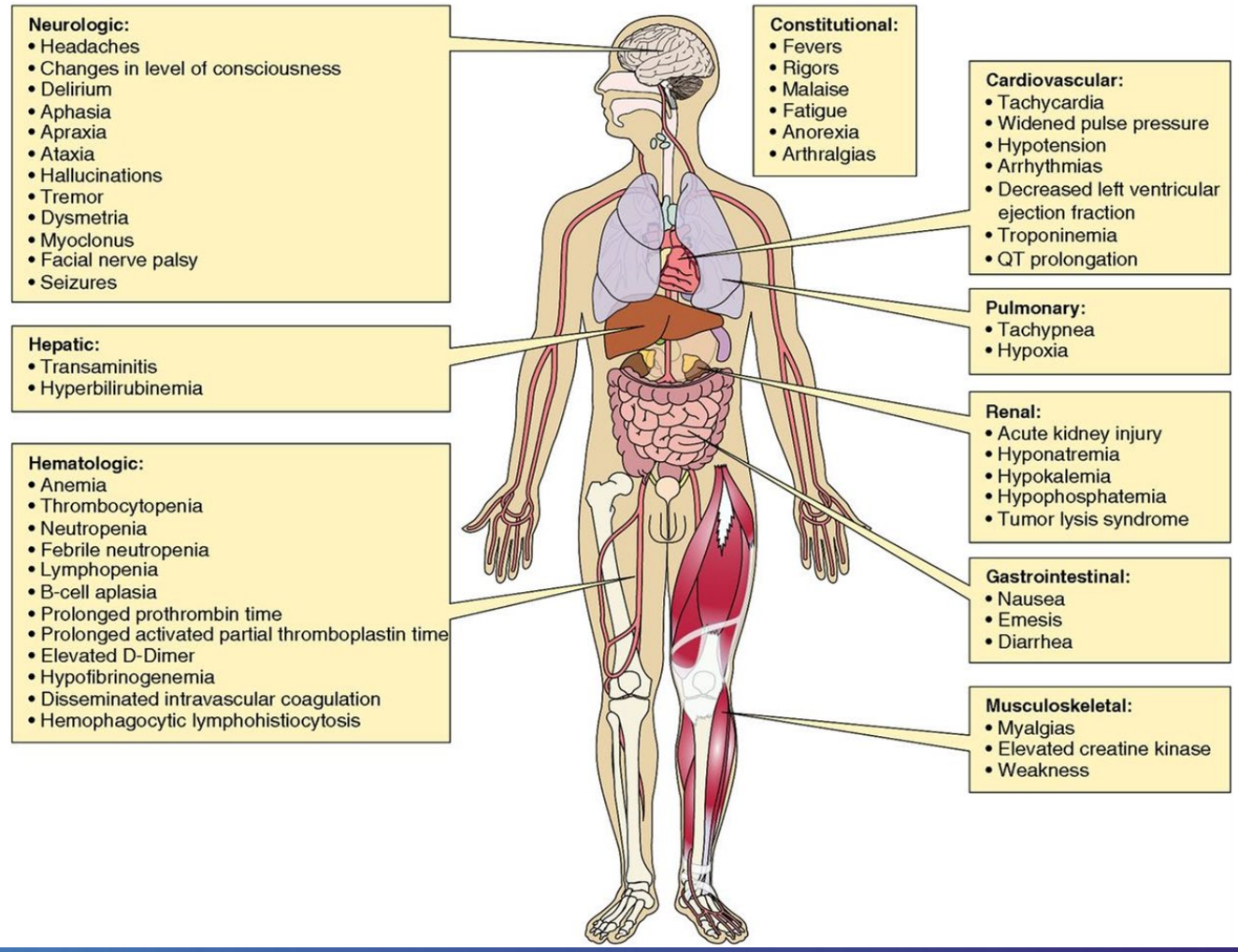
- Occurred in 77% to 94% of patients in clinical trials[1,2]
- Median time to onset was 3 days[1]
- Median duration was 8 days[1]
- Considered manageable and reversible with early recognition and intervention, but potentially fatal

1. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. 2. Maude SL, et al. 2018. *N Engl J Med*. 2018;378:439-48.

CRS: Symptoms

Common symptoms of CRS

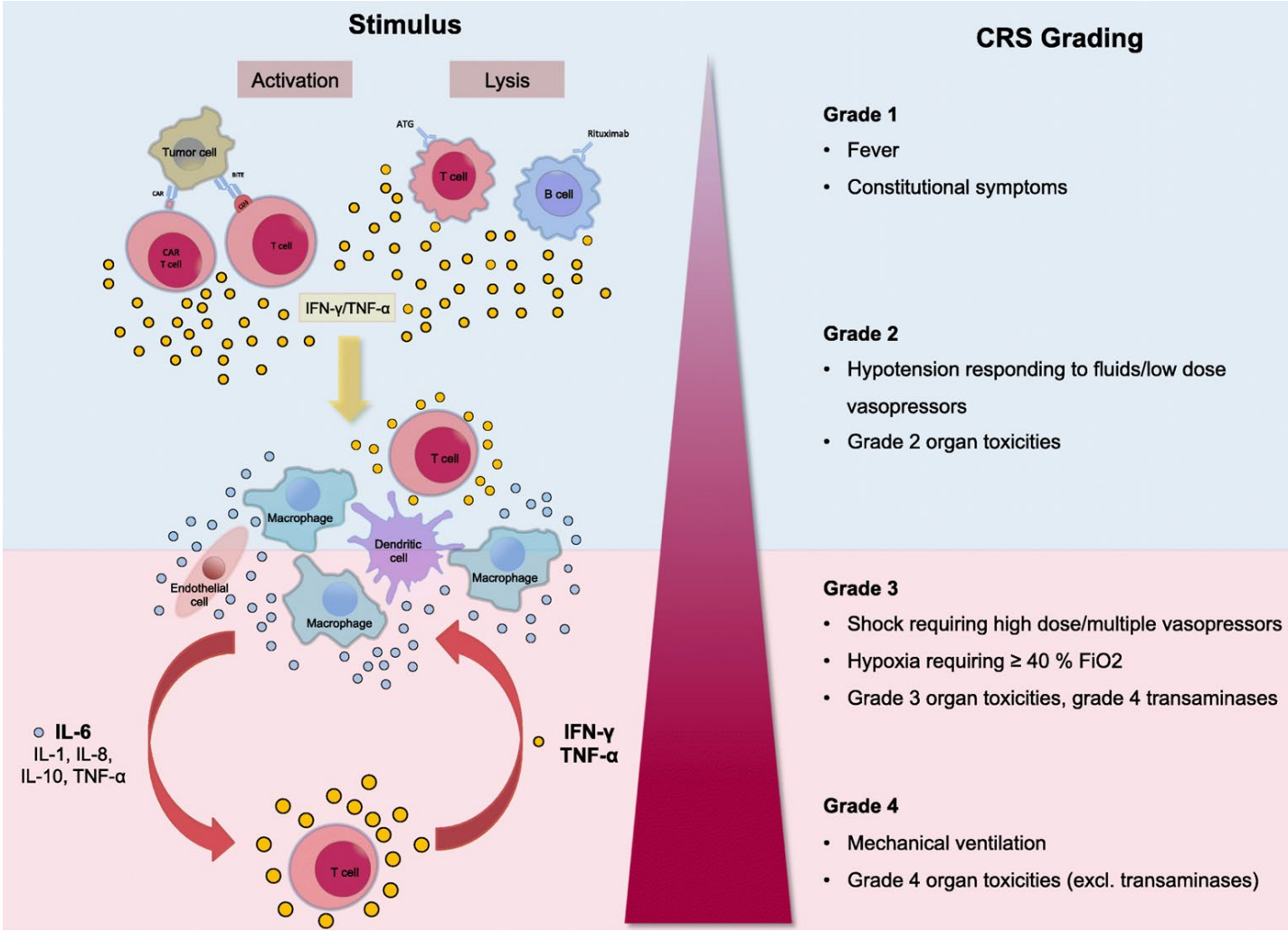
- Fever
- Chills
- Hypotension
- Tachypnea and shortness of breath
- Acute kidney injury
- Hepatoxicity
- Myelosuppression
    - Beyond 28 days in approximately 30% of patients
- Coagulopathy



Brudno JN, Kochenderfer JN. *Blood*. 2016;127:3321-30.

CRS: Mechanism and Grading

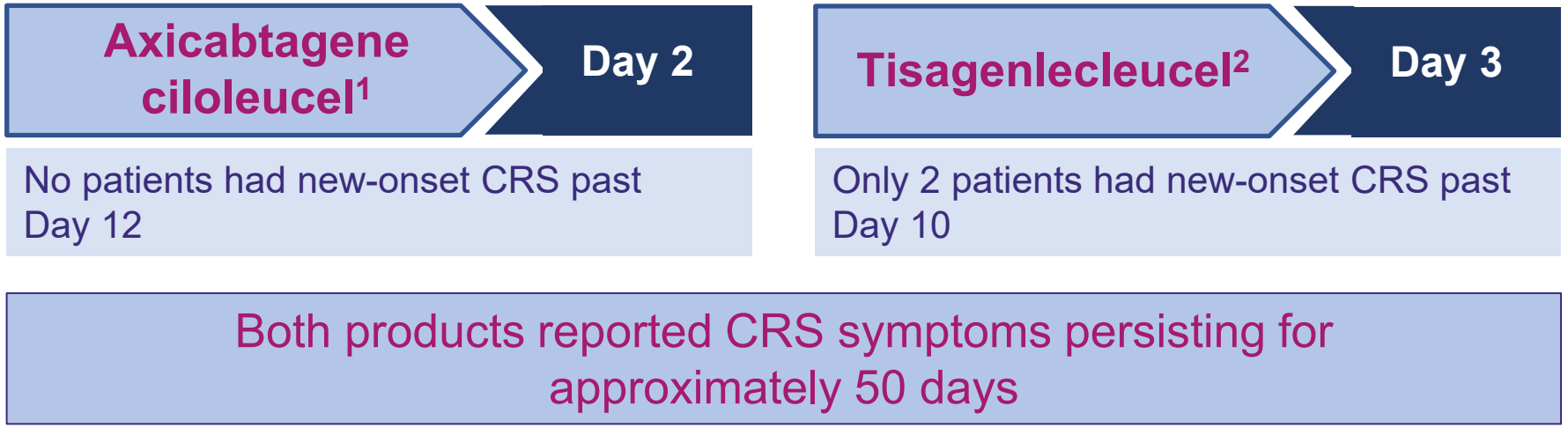
- Systemic inflammatory response associated with immune activation[1]
  - High degree of circulating IL molecules, specifically IL-6
- Grading currently based on symptoms, organ toxicities, and supportive care required[1]
- Currently, there are multiple grading systems, but there is work toward creating a consensus grading[2]



1. Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6:56. 2. Riegler LL, et al. *Ther Clin Risk Manag*. 2019;15:323-35.

Onset of CRS

- Onset of CRS is typically early, but can persist for long periods
  - Median time to onset in clinical trials:



1. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. 2. Novartis. Treatment Process. www.hcp.novartis.com/products/kymriah/acute-lymphoblastic-leukemia-children/dosing-and-administration/. Accessed October 10, 2019.

Diagnosis of CRS

- Commonly based on trend of IL-6, DIC (fibrinogen, PTT/INR, haptoglobin, platelets), ferritin, CRP[1]

Clinical Diagnosis, NOT a Laboratory Diagnosis

- Trends may have value for anticipating worsening, stabilizing, and improving CRS
- Supportive care with antipyretics, cardiovascular and respiratory support, symptom management, and end organ optimization
- Often must be managed in tandem with neutropenic fever algorithms
  - Neutropenic fever occurs in 10% to 20% of patients[2]

CRP, C-reactive protein; DIC, disseminated intravascular coagulation; INR, international normalized ratio; PTT, partial thromboplastin time.

1. Wang Z, Han W. *Biomark Res*. 2018;6:4. 2. Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56.

Treatment of CRS

- Tocilizumab is the only FDA-approved agent for the treatment of CRS[1]
  - Both FDA-approved CAR T-cell products require that 2 vials of tocilizumab per patient are on hand prior to CAR T-cell infusion[2-4]
  - Blocks IL-6 receptor
  - Used to treat moderate to severe CRS
- Dexamethasone or methylprednisolone for severe CRS or failure of tociluzumab[5]
- Siltuximab[6]
  - Less extensively studied and not part of REMS
  - Binds to circulating IL-6
- Anakinra[7]
  - Even less studied than siltuximab
  - Binds to IL-1 receptor

1. Riegler LL, et al. *Ther Clin Risk Manag*. 2019;15:323-35. 1. Kite. Risk Evaluation and Mitigation Strategy (REMS). www.yescartarems.com/. Accessed October 7, 2019. 2. Novartis Risk Evaluation and Mitigation Strategy (REMS). www.kymriah-rems.com/. Accessed October 7, 2019. 3. Mahmoudjafari Z, et al. *Biol Blood Marrow* Transplant. 2019;25:26-33. 4. Santomasso B, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:433-44. 5. Norelli M, et al. *Nature Med*. 2018;24:739-48. 6. Brudno JN, Kochenderfer JN. *Blood*. 2016;127:3321-30.

Neurotoxicity

- Encompasses a spectrum of CNS toxicity
  - Including: confusion or delirium, paranoia, aphasia, somnolence, seizures, insomnia, encephalopathy, and death[1,2]
- Wide range of time to onset
  - 48 hr to 4 wk[3,4]
- Treated with supportive care through management of any concurrent CRS
- Dexamethasone or methylprednisolone per product algorithms or clinical trial design[3,4]
- Tocilizumab when concurrent with CRS
- Lack of imaging does not rule out CAR T-cell neurotoxicity
  - Cerebral edema a late sign with very poor prognosis
- Limit driving, heavy machinery, dangerous activities, etc for approximately 4 to 6 wk
  - Can be individualized based on concern for CNS toxicity
- Provide extensive caregiver education

CNS, central nervous system.

1. Prudent V, Breitbart WS. *Palliat Support Care*. 2017;15:499-503. 2. Gust J, et al. *CNS Drugs*. 2018;32:1091-101. 3. Kite. Risk Evaluation and Mitigation Strategy (REMS). www.yescartarems.com/. Accessed October 7, 2019. 4. Novartis Risk Evaluation and Mitigation Strategy (REMS). www.kymriah-rems.com/. Accessed October 7, 2019.

Long-Term Follow-Up

- Monitoring by caregivers for delayed CRS and neurotoxicity
- Clinic and laboratory follow-up for prolonged or delayed cytopenias
- Antibiotic prophylaxis for neutropenia and trimethoprim-sulfamethoxazole for pneumocystis jiroveci pneumonia prophylaxis
- Hypogammaglobulinemia, secondary to B-cell depletion by CD19-targeted CAR-T products, may be treated per clinic preference or reserved for patients with recurrent infections or other risk factors
- Antiepileptic prophylaxis per clinic protocols
- Disease specific monitoring for relapse
- T cell–specific monitoring, albeit unclear significance at this time

Doan A, Pulsipher MA. *Pediatric Blood Cancer*. 2018;65:e26914.

Conclusions

- CAR T-cell therapy represents new and novel management strategy for the treatment of B-cell malignancies, as well as a range of hematologic and solid tumors.
- Awareness of the current treatment landscape, including the clinical trial landscape, is critical to effectively manage patient expectations and direct patients to appropriate therapy.
- Although CAR T-cell treatment is neither a conventional chemotherapy nor a hematopoietic stem cell transplant, it can be used in conjunction with either or both to manage aggressive disease.
- The side effects of CAR T cells are unique and require practitioner and institution experience and expertise to provide early and effective intervention.