CAR T-CELL THERAPY: A ROAD MAP FOR NURSES

Thursday, September 10, 2020
9 AM -10 AM ET

A presentation timeslot has been assigned to provide a symposium supported by The Leukemia & Lymphoma Society during the Oncology Nursing Society's (ONS) Bridge Virtual Event. The Oncology Nursing Society's assignment of a presentation timeslot does not imply product endorsement.

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WELCOME AND INTRODUCTIONS

Valarie Leishman, RN, BSN, MBA
Senior Manager
Professional Education
The Leukemia & Lymphoma Society
Rye Brook, NY

www.LLS.org/CE

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OUR SUPPORTERS

This program is supported by Bristol Myers Squibb Company; Kite, A Gilead Company and Novartis Pharmaceuticals Corporation.

CE DESIGNATION

Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under Provider Number CEP 5832 to award 1.0 continuing education contact hour through the California Board of Registered Nursing.

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LEARNING OBJECTIVES

At the conclusion of this program, participants will be able to:

- Provide an overview of chimeric antigen receptor (CAR) T-cell therapy and the blood cancers and solid tumors under study for treatment
- Explain the nurse's role in assessment, monitoring for and managing side effects of treatment
- Describe the nurse's role in preparing patients and family members about the CART process and potential side effects of treatment
- Address the need for communication with a patient's community oncologist and healthcare team to transition care after CAR T-cell therapy

Our Mission:
Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.

HCP Resources

Online and in-person CME/CE webinars, symposia & rounds
Free CME & CE www.LLS.org/CE

Podcast series for healthcare professionals
Listen as we speak with experts about diagnosing and treating patients with blood cancer, including survivorship issues
www.LLS.org/HCPpodcast

HCP Palm Card - resources for you & your patients

CART Fact Sheet for HCPs

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Resources For Patients and Caregivers

Patient Financial Aid www.LLS.org/PatientAid

Webinars, videos & in-person programs
www.LLS.org/Programs **and** www.LLS.org/Educationvideos

Podcast series (The Bloodline With LLS)
www.LLS.org/Podcast

CART resources
www.LLS.org/CART

Booklets on disease, treatment, & support
www.LLS.org/Booklets

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Resources For Patients and Caregivers

- **Information Specialists** – Provide patients and caregivers with personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges.
  - They can also send you free materials to distribute to your patients.
- **Clinical Trial Nurse Navigators** – RNs help patients find a clinical trial and assist throughout the trial process.
- **Expert Nutrition Consultations** – One-to-one patient consultations from a certified dietician.

These specialists can serve as an additional resource for your HCP team.
M - F, 9 am to 9 pm ET:

- Phone: (800) 955-4572
- Live chat: www.LLS.org/InformationSpecialists
- Email: infocenter@LLS.org

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FACULTY

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FACULTY DISCLOSURES

Sherry Adkins RN, MSN, ANP-C
Advisory Board: Celgene/Bristol Meyers Squibb

Heather Difilippo MSN, CRNP
Janssen Preceptor
CART T Advisory Board: Celgene/Janssen
Novartis Speaker Bureau

Ilene Galinsky, BSN, MSN, ANPc
Consultant: AbbVie, Celgene, Pfizer, Merus, Jazz

Kathleen McDermott, RN, BSN
CAR T Speaker Bureau: Gilead/ KITE
CAR T Advisory Board: Celgene

ND53
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Slide 12

ND53 video

Nicole Dane, 9/4/2020

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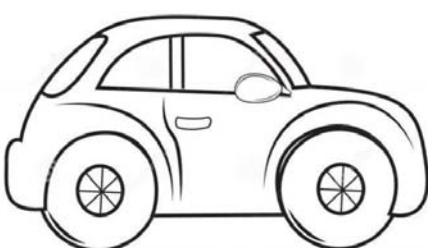
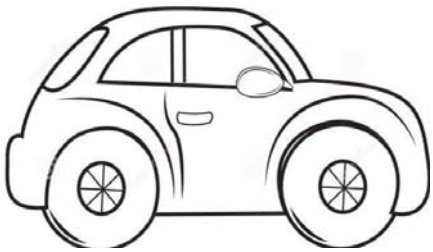
CAR-T Directory

Ilene → Heather → Kathleen → Sherry





CAR T Navigation Overview → Screening → Apheresis → Manufacturing Bridging therapy → Lympho-depletion → CAR T infusion → Acute toxicity period → Long-term monitoring

How Many Of You Have Experience With CAR T's?

- YES
- NO

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CAR T-cell Therapy

- Where we were
- Where we are
- Where are we going

What are CAR T cells?

- Chimeric antigen receptor T cells – genetically engineered to produce an artificial T cell receptor→ immunotherapy
- CARs= proteins that have been engineered to give T cells new ability to target a specific protein
- To be effective- recruitment, activation and expansion and persistence of the T cells at the tumor site[1]
- First generation CARs- contained a single cd3domain lacked costimulatory and cytokine signaling, second, third generation, and now fourth generation- third combine the signaling potnetial of two costimulatory domains(cd28 and 4-1BB) and fourth generation called TRUCKs (T cells redirected for universal cytokine-mediated killing[2]

[1] British Journal of Cancer 120,26-37(2019) [2]NCBi.nlm.nih.gov

What Makes a Cancer a Good CAR T-cell Candidate?

Tumor antigen that is present on all, or most, of the cancer cells and is necessary for that cancer cell's survival

+

Tumor antigen that is not present on normal healthy cells such that immune attack on those normal healthy cells would lead to unacceptable toxicity

=

A Good CAR T-cell Candidate

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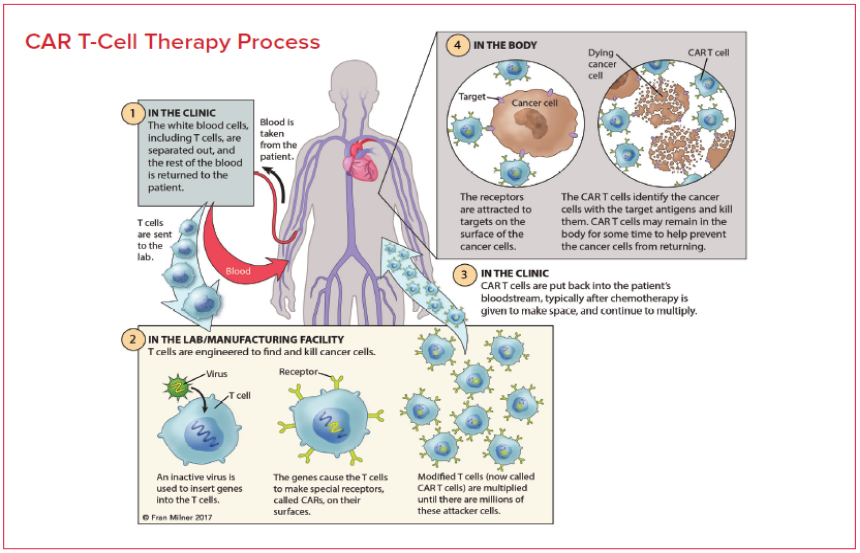
How Are CAR T-Cells Manufactured/Engineered?



4) Patient Monitoring

Disease response

- CT scans
- Bone marrow biopsies
- Peripheral blood flow cytometry

CAR T-cell persistence

- IHC of bone marrow biopsy
- RT-PCR and flow cytometry of blood and bone marrow aspirate

The Leukemia & Lymphoma Society Patient CART Fact Sheet.

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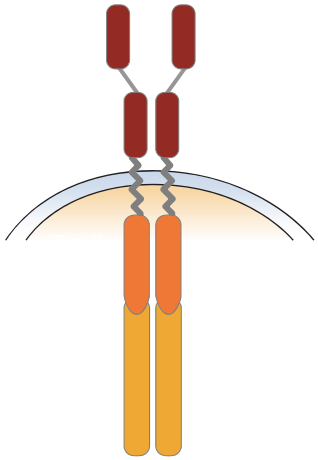
CAR T-Cell Therapy: Tisagenlecleucel (CTL019)[1-3]



- **First approved CAR T-cell therapy in the United States**
  - August 2017: for patients up to 25 years of age with B-cell precursor ALL refractory or in second or later relapse
  - May 2018: for adult patients with r/r DLBCL after ≥ 2 lines of systemic therapy
- Also approved in the EU, Canada, and Switzerland
- **Updated results of the ELIANA study are presented**
  - Median follow-up, 24 months (max, 35 months)
  - Additional 11 months of follow-up from the previous report in *NEJM*[1]

Receptor; DLBCL, diffuse large B-cell lymphoma; EU, European Union; peds ALL, pediatric acute lymphoblastic leukemia; r/r, relapsed/refractory.

1. Milone MC, et al. *Mol Ther*. 2009;17:1453-1464.

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FDA-Approved CAR T-Cell Therapies

Therapy	Target	Indications
Tisagenlecleucel (KYMRIAH®)	CD19	▪ **Patients aged up to 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse** ▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including**: • DLBCL NOS or arising from follicular lymphoma • High-grade B-cell lymphoma
Axicabtagene ciloleucel (YESCARTA®)	CD19	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including**: • DLBCL NOS or arising from follicular lymphoma • High-grade B-cell lymphoma • Primary mediastinal large B-cell lymphoma

Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: Dr. Daniel DeAngelo

FDA-Approved CAR T-Cell Therapies Continued

Therapy	Target	Indications
brexucabtagene autoleucel (TECARTUS™)	CD19	▪ TECARTUS™ (brexucabtagene autoleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
Approved July 24,2020		

Brexucabtagene autoleucel PI

Key Anti-CD19 CAR T-Cell Therapy Trials: B-ALL

	ELIANA[1] (N = 75)	MSKCC[2] (N = 53)	ZUMA-3[3] (N = 45)
CAR T-cell agent	**Tisagenleucel**	**JCAR015**	**KTE-X19**
Study phase	II	I	I/II
Study population	Pediatric/young adults with R/R B-ALL	Adults with relapsed B-ALL	Adults with R/R B-ALL
CR, %	MRD negative: 81	Overall: 83	Overall: 68 RP2D: 84
Median OS, mos	19.1	12.9	--
Median EFS, mos	NR	6.1	--
Median DoR, mos	NR	--	RP2D: 12.9
Median follow-up, mos	13.1	29	16
	FDA approved	**Halted**	**Phase 2 completed September 2019**

1. Maude. NEJM. 2018;378:439. 2. Park. NEJM. 2018;378:449. 3. Shah. ASCO 2019. Abstr 7006.

Key Anti-CD19 CAR T-Cell Therapy Trials: DLBCL

	ZUMA-1[1,2]	JULIET[3]	TRANSCEND NHL 001[4]
CAR T-cell agent	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Study phase	II	II	I
Patient population	Adults with refractory DLBCL	Adults with R/R DLBCL	Adults with R/R DLBCL
Patients pheresed/ treated, n	111/101	165/111	344/269
ORR, %	82	52	73
▪ 6 mo	78	33	--
CR, %	54	40	53
▪ 6 mo	--	29	--
	FDA approved	**FDA approved**	**In clinical trials**

1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. ASH 2019. Abstr 241.

Slide credit: Dr. Daniel J Deangelo

Select Ongoing Trials With CAR T-Cell Therapy for Patients With Lymphoma

Trial	Phase	Treatment	Population	1° Endpoint(s)
TRANSFORM (NCT03575351)	III	Lisocabtagene maraleucel vs SoC	Transplant-eligible R/R aggressive B-cell NHL	PFS
BELINDA (NCT03568461)	III	Tisagenlecleucel vs SoC	R/R aggressive B-cell NHL	EFS
ZUMA-12 (NCT03761056)	II	Axicabtagene ciloleucel	High-risk large B-cell lymphoma; no prior treatment	CRR
ZUMA-5 (NCT03105336)	II	Axicabtagene ciloleucel	Indolent B-cell NHL; R/R after 2 lines of therapy	ORR
TRANSCEND-PILOT-017006 (NCT03483103)	II	Lisocabtagene maraleucel	R/R aggressive B-cell NHL after first-line immunochemotherapy	ORR
ELARA (NCT03570892)	II	Tisagenlecleucel	R/R FL	CRR

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Select Ongoing and Recent Studies of BCMA-Targeted CAR T-Cell Therapies for R/R Multiple Myeloma

Study	CAR T-Cell Therapy	Phase	Key Findings
KarMMa-3 (NCT03651128)	**Idecabtagene vicleucel**	**III**	▪ **Ongoing; RCT vs standard triplet therapy**
KarMMa-2 (NCT03601078)	Idecabtagene vicleucel	II	▪ Ongoing
KarMMa (NCT03361748)	Idecabtagene vicleucel	I/II	▪ Ongoing; positive results reported in press release
CARTITUDE-1 (NCT03548207)	LCAR-B38M/JNJ-4528	I/II	▪ Ongoing; ORR 91% (n = 21)[1]
CARTIFAN-1 (NCT03758417)	LCAR-B38M/JNJ-4528	I/II	▪ Ongoing
CRB-402 (NCT03274219)	bb21217	I	▪ Ongoing; ORR 83% (n = 18)[2]
EVOLVE (NCT03430011)	JCARH125	I/II	▪ Ongoing
UPenn study	4-1BB CAR	I	▪ Complete; ORR 64% (n = 11)[3]
NCI study	CD28 CAR	I	▪ Complete; ORR 81%, VGPR/CR 63% (N = 16)[4]

1. Madduri. ASH 2019. Abstr 577. 2. Berdeja. ASH 2019. Abstr 927. 3. Cohen. JCO. 2019;129:2210. 4. Brudno. JCO. 2018;36:2267.

Slide credit: Dr. Daniel J Deangelo

Select Ongoing and Recent Studies of CAR T-Cell Therapies for Other Hematologic Malignancies

Study	CAR T-Cell Therapy	Target	Setting	Key Findings
TRANSCEND-CLL-004 (NCT03331198)	Lisocabtagene maraleucel	CD19	▪ Relapsed/refractory CLL/SLL	▪ Ongoing; 82% ORR (n = 22)[1]
ZUMA-8 (NCT03624036)	KTE-X19	CD19	▪ Relapsed/refractory CLL	▪ Ongoing
RELY-30 (NCT02917083)	CD30.CAR-T	CD30	▪ Relapsed/refractory HL	▪ Ongoing; 66% ORR (N = 37)[2]

1. Siddiqi. ASH 2019. Abstr 503. 2. Ramos. Unpublished.

Slide credit: Dr. Daniel J Deangelo

CAR T-Cell Therapy in Solid Tumors

- Responses to CAR T-cell therapy in solid tumors (including glioblastoma, neuroblastoma, NSCLC, mesothelioma, renal cell carcinoma, sarcoma, and ovarian, prostate, head and neck, and breast cancers) have been **suboptimal or mixed** in small clinical studies[1]

Obstacle	Rationale and Potential Solutions
Tumor antigen	▪ Not all appropriate tumor antigens are universally expressed or vital for cell survival; many tumor antigens that meet these criteria are also present on normal cells ▪ Potential solutions: CARs targeting dual antigens, armored CARs engineered to secrete immunostimulatory cytokines to enhance epitope spreading
T-cell trafficking	▪ Potential solutions: engineer T-cells to express chemokine receptors necessary for tissue trafficking and localization (in addition to the CAR) or that target the tumor vasculature
Tumor microenvironmental effects on T-cells	▪ Myeloid suppressor cells and tumor associated macrophages, inhibitory cytokines ▪ Potential solutions: combine CAR T-cells with immune checkpoint blockade inhibitors, engineer armored CARs to express immunostimulatory cytokines, target tumor associated macrophages and myeloid suppressor cells

1. Yeku. ASCO Edu Book. 2017;37:193.

Slide credit: Dr. Daniel J DeAngelo

What is Next?

- Adding checkpoint inhibitors
- Bispecific Car T
- Off the shelf products
- “Kill” switch

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We Can't Afford the Drugs That Could Cure Cancer

Customized immunotherapies are ready to revolutionize care and save lives—if drug companies stop charging so much for them.

By Ezekiel Emanuel
Sept. 20, 2018 11:35 am ET

PRINT TEXT 144

When I was training as an oncologist nearly three decades ago, we dreamed of curing cancer. Today, advances in cellular immunotherapy make it no longer a dream: A cure for cancer has become possible, even probable. But tragically, the costs of these drug therapies are so

Unanswered Questions and Ongoing Research in CAR T-Cell Therapy

- Overcoming resistance
  - T-cell exhaustion and combining PD-1 blockade with CAR T-cell therapy
  - Antigen loss and dual antigen targeting (eg, CD19 and CD20)
  - Use of CAR T-cells in earlier lines of tx, pretreatment with immunomodulatory drugs (eg, ibrutinib in CLL)
  - Evading a hostile tumor microenvironment: armored CARs (IL-12, CD40L, 4-1BBL)
- Toxicity management: safer CARs, prophylactic strategies, new treatments
- Overcoming issues of cost and manufacturing inefficiencies: universal (off the shelf) CARs, NK cell CARs
- Expanding indications
- Identifying new targets: eTCRs and CARs, TILs (engineered T cell receptors, looking for different cancer antigens, tumor infiltrating lymphocytes)

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The New CAR T Patient

Heather DiFilippo, RN, MSN, CRNP

Kathleen McDermott, RN, BSN, OCN, BMTCN

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CAR-T Directory

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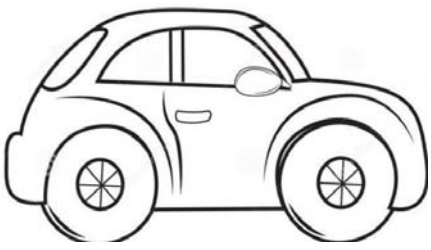
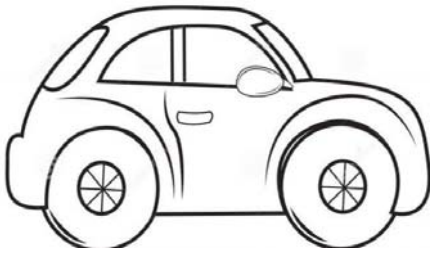
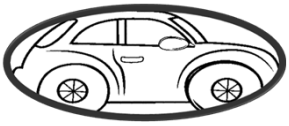




CAR T Navigation Overview › Screening › Apheresis › Manufacturing Bridging therapy › Lympho-depletion › CAR T infusion › Acute toxicity period › Long-term monitoring

Which of the following patients with diffuse large B-cell lymphoma would be eligible for a currently approved CAR T-cell therapy?

1. Newly diagnosed
2. Refractory to R-CHOP, eligible for ASCT
3. Refractory to R-CHOP, PR with salvage RICE, ongoing CR after HDT/ASCT
4. Relapsed after R-CHOP and R-GDP + HDT/ASCT



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Clinical Case: Dana Penn (D.P.)

Baseline factors and diagnosis

Diagnosis: Follicular Lymphoma 2009
Transformed DLBCL 2014
Age: 68 years
Sex: Male

Support system: Wife and adult children
ECOG performance status: 1
Demographics: Home >3.5 hours from CART Facility

Treatment history

- Number of prior systemic therapies: **2**
  - **Therapy 1: 2014: R-CHOP X6 -- CR**
  - **Therapy 2: Relapse 2019 RICE 2-- PD**
- Prior autologous stem cell transplant: **No**
- Refractory status: **Refractory to 2nd-line chemotherapy**
- Best response to last prior therapy: **Progressive disease**

Relevant medical history

- **Prior to enrollment: Hypertension**
  Barrett's Esophagus
  Hernia
- **Refractory Disease: Enlarging neck mass**

DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group;

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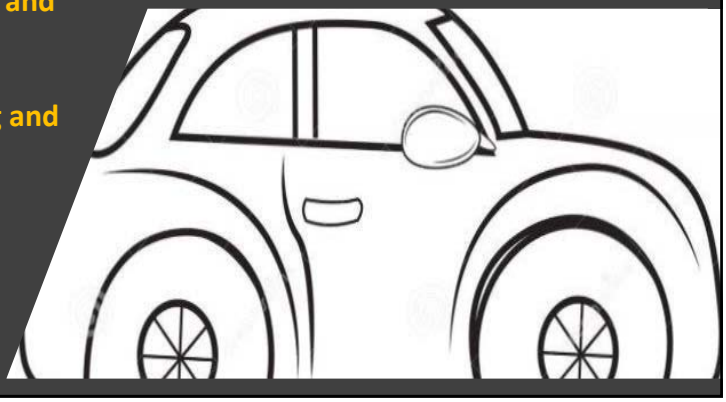
Referral and Evaluation

Certified CAR-T Treatment Facility

- FDA requires (REMS) Risk Evaluation and Mitigation Strategy
- Staff trained: prescribing, dispensing and administering
- Safety: Tocilizumab availability and tracking



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Screening

Multidisciplinary Team

- MD
- Nurse Practitioner/ Physician Assistant
- Nurse Navigator
- Social Worker
- Clinical Coordinator
- Financial Coordinator

Dear Mr. Dana Penn,

Listed below are your upcoming appointments at THR CAR T Clinical Program in preparation for your CAR T therapy. Please check in at the front desk before each appointment with your photo ID.

Tuesday August 27,2019

08:30 a.m.	Vein check assessment
09:15 a.m.	Chest X-Ray
10:00 a.m.	**Teaching session with Nurse Navigator**
11:10 a.m.	Blood draw
12:00 p.m.	EKG and Echocardiogram
12:30 p.m	**Exam & Consents with CART MD**
2:30 p.m.	**Consult with Social Worker**

Please feel free to contact me directly if you have any questions or concerns regarding this schedule.

Sincerely,

Cellular Therapy Clinical Coordinator

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Which CAR T-Cell Product-commercial or trial ?

Patients are considered for trial based on slot availability and meeting eligibility criteria

	Axicabtagene Ciloleucel Kite, a Gilead Company	Tisagenlecleucel (CTL019) Novartis
US FDA Indication	Adult DLBCL	Ped/young adult ALL Adult DLBCL
CAR Type	CD19/CD28/CD3z	CD19/4-1BB/CD3z
Costimulatory Domain	CD28	4-1BB (CD 137)
Vector	Retrovirus	Lentivirus

Kite, a Gilead Company. (2017). Yescarta® (axicabtagene ciloleucel) package insert. Retrieved from https://www.yescarta.com/files/yescarta-pi.pdf,

Novartis Pharmaceuticals Corporation. (2018). Kymriah® (tisagenlecleucel) package insert. Retrieved from https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf

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Patient Navigation

Comprehensive Team Assessment:

- Medical evaluation
- Functional health patterns
- Demographics
- Family and social supports

Patient and Caregivers:

Needs and Expectations

- Assess
- Develop plan collaboratively
- Clearly communicate action plan and responsible party: patient, caregiver or the health care team

Patient and Caregivers Education:

- Leukapheresis
- Manufacturing
- Bridging Therapy
- Lymphodepletion chemotherapy
- Admission for infusion and monitoring
- Potential side effects: CRS, neurotoxicity and management techniques
- Possible need for ICU Transfers and Rehabilitation on Discharge
- Patient ID card
- Emergency Contacts and when to call

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- Prior autologous stem cell transplant: **No**
- Refractory status: **Refractory to 2nd-line chemotherapy**
- Best response to last prior therapy: **Progressive disease**

CAR-T treatment plan

Leukapheresis for Tisagenlecleucel (Kymriah®) manufacturing

Bridging Therapy:

- **Dexamethasone steroid pulse X 4 days**
- **XRT to neck mass**

Lymphodepletion

Tisagenlecleucel (Kymriah®) Infusion

DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group;

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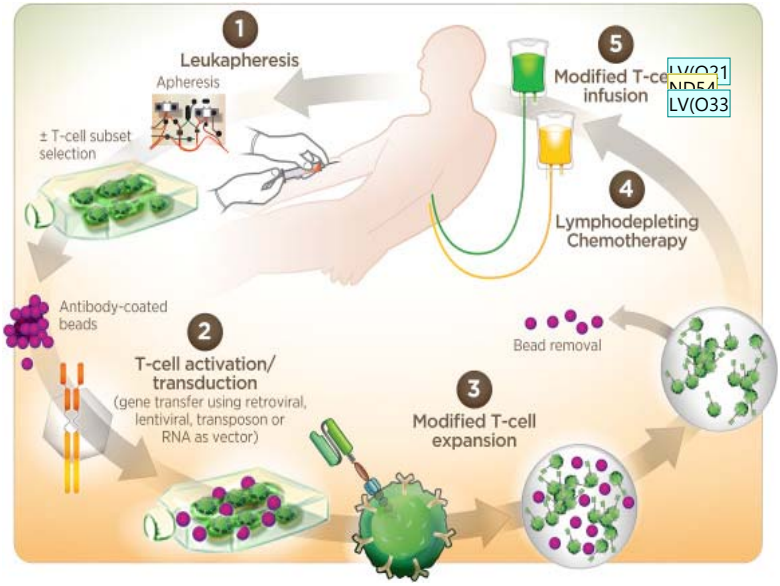
Leukapheresis and Manufacturing



Leukapheresis

- Peripheral or Central line
- Length of procedure
- Preparing for procedure
- Side effects
- Instructions post-procedure

Manufacturing

- Description of process
- Chain of Identity
- Anticipated return date
- Possible manufacturing delays/problems
- Instructions who to call
- When to call

Slide 40

LV(O21 Is there a reference for this graphic?
Leishman, Valarie (National Office), 8/14/2020

ND54 never sent...
Nicole Dane, 9/4/2020

LV(O33 no
Leishman, Valarie (National Office), 9/4/2020

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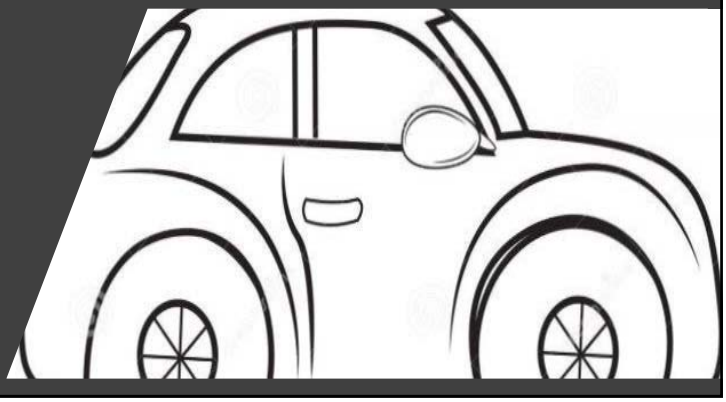
Bridging Chemotherapy

- Chemotherapy, Radiation Therapy, and/or steroids administered during the CAR T-cell product manufacturing time to control disease progression.
- Currently no standard treatment regimen
- Regimen chosen must allow adequate time for hematologic recovery prior to starting lymphodepletion chemotherapy



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Lymphodepletion Chemotherapy

- NP visit day prior to or day of LD chemotherapy
  - Chemotherapy is per drug label or at physician's discretion
  - Establish relationship and contact information
  - Educate patient on what to anticipate the day of the infusion
  - Review chemotherapy side effects (nausea)

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Day of infusion

- Evaluate patient day of and prior to infusion
  - Insure appropriate candidate
    - Free of infection
    - Resolved toxicity from chemotherapy
    - Ongoing patient education
    - Document that it is okay for the infusion to proceed-
      - The patient has been assessed and is free of: unresolved serious adverse reactions from preceding chemotherapies (including pulmonary reactions, cardiac reactions or hypotension), active uncontrolled infection, active graft vs host disease, or worsening disease burden following lymphodepleting chemotherapy. This has been discussed and confirmed by the attending physician and we will proceed with the infusion of the cells

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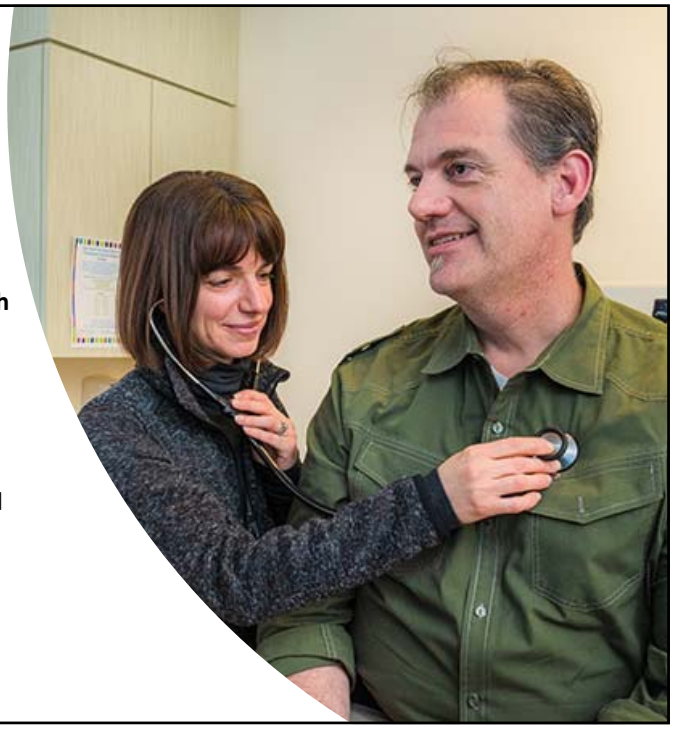
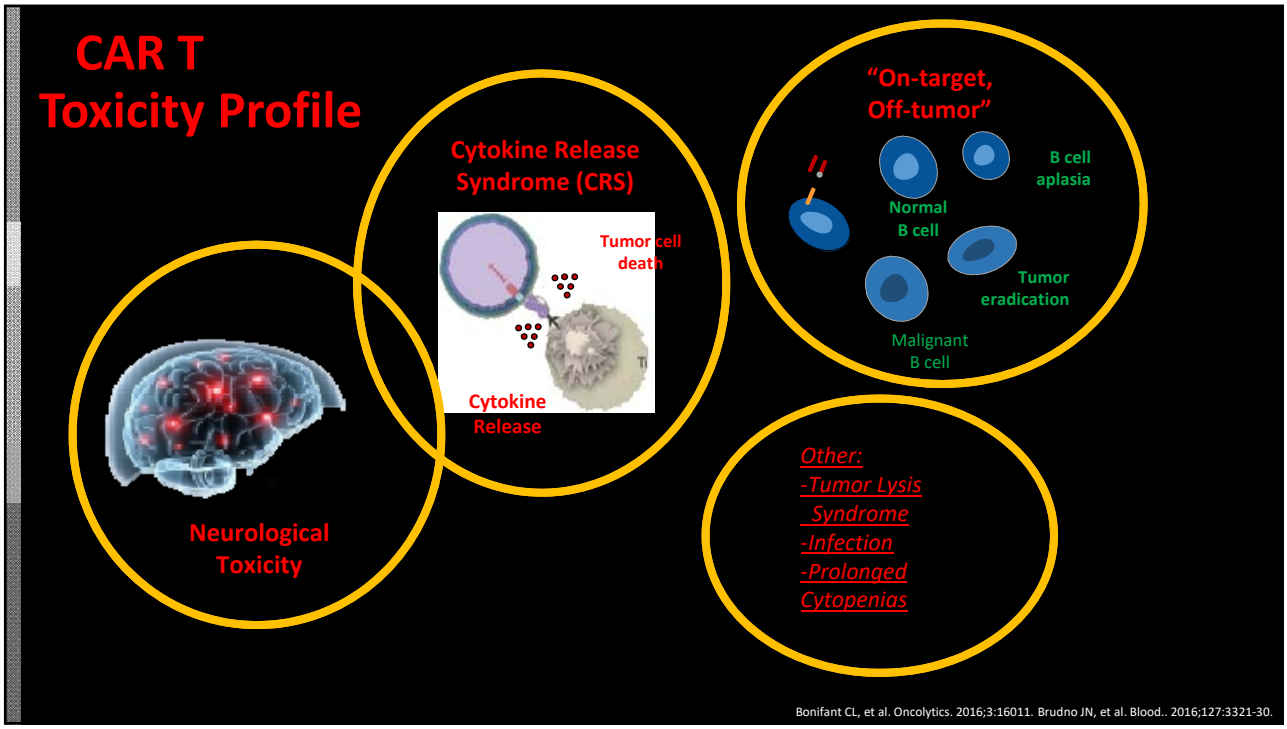
Patient Management

- **On the day of infusion:**
  - **Reassurance**
  - **Allopurinol if appropriate for tumor lysis which can be a complication**
  - **Baseline blood work**
    - **CRP/Ferritin baseline and then weekly. They can elevate during CRS**
    - **CBC Plts > 20 for T cell infusion**
  - **Contact information during working hours and after hours/on weekends**
  - **Prophylactic antibiotics for infection risk**
  - **Review respiratory viral swab**
  - **Free of infection**





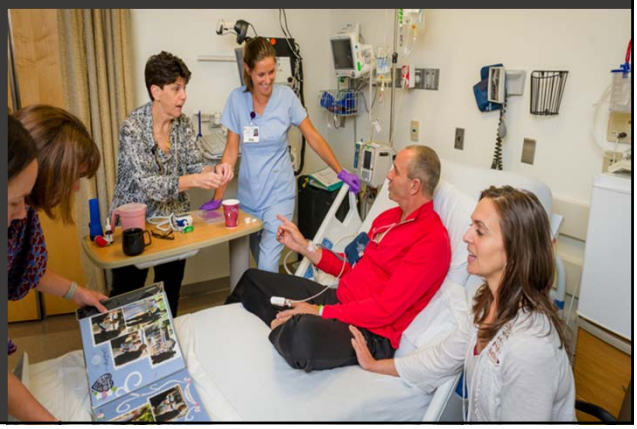
Cytokine Release Syndrome (CRS)

Cytokine release syndrome is a systemic inflammatory response associated with CAR T-cell therapy

- Symptoms : fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, fast breathing, rapid heartbeat, low blood pressure

Cytokine release syndrome typically occurs between day 2-14 following the CAR T cell infusion

Frequent monitoring/ surveillance required



ASTCT Consensus Grading for CRS Associated with Immune Effector Cells (IEC)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	$T_m \geq 100.4°F$	$T_m \geq 100.4°F$	$T_m \geq 100.4°F$	$T_m \geq 100.4°F$
With either:				
Hypotension	None	Responsive to fluids	Requiring 1 vasopressor (w/ or w/o vasopressin)	Requiring multiple vasopressors (excluding vasopressin)
And/ Or				
Hypoxia	None	Low-flow nasal cannula or blow-by	High-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask	Requiring positive pressure (CPAP, BiPAP Intubation and mechanical ventilation)

- Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading
- Low-flow nasal cannula: O2 delivered at <6 L/minute.

ASTCT, American Society for Transplantation and Cellular Therapy

Lee DW, et al. Biol Blood Marrow Transplant. 2018 Dec 25. pii: S1083-8791(18)31691-4.

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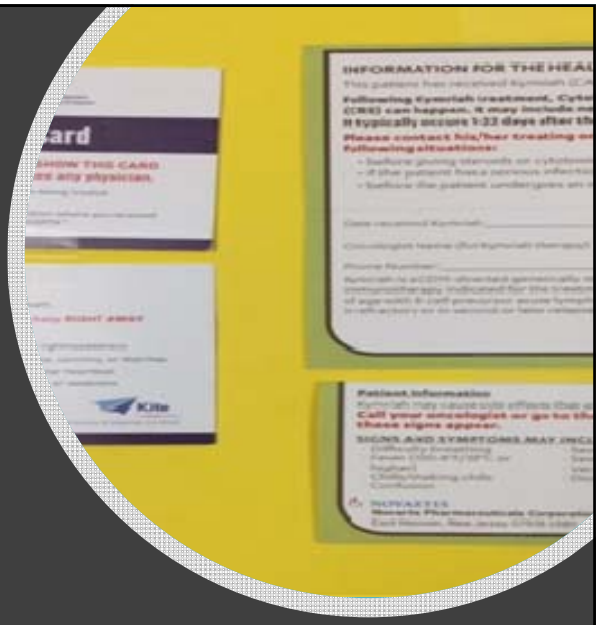
Post CAR T Infusion: Monitoring

- If outpatient: patients are evaluated day 2 and 4 following infusion and weekly out through day 28
- We confirm patient has contact information for symptom management
- Reiterate signs and symptoms of CRS and neurotoxicity
  - There is no such thing as too much education
- Physical exam
- Evaluate for CRS/ infection / neurotoxicity



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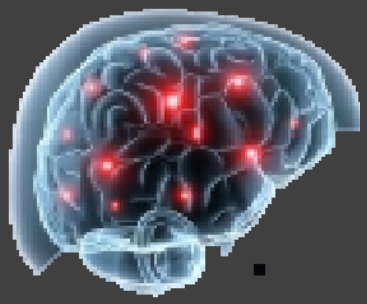

Neurotoxicity

IEC - Associated Neurotoxicity Syndrome (ICANS)

- Less well defined; less defined management
- Symptoms
  - Expressive aphasia (esp naming objects/people); can progress to perseveration, global aphasia
  - Often alert and oriented
  - Tremors, myoclonus, seizures
  - Apraxia/dysgraphia
  - Encephalopathy
- Onset: within days to 2-3 weeks post CAR T
  - During or after systemic CRS
- Rare cases of cerebral edema and death

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Immune Effector Cell-Associated Encephalopathy

- ICE Score
- How many of the following is the patient oriented to: year, month, city, hospital ?
- Identify 3 objects. How many can the patient name?
- Can follow commands ?
- Can write a standard sentence ?
- Can count backwards from 100 by 10 ?

Score 10: No impairment
Score 7-9: Grade 1
Score 3-6: Grade 2
Score 0-2: Grade 3

***Combine with other ICANS assessments if applicable for final grade**

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Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

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 (attributed to no other cause)	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 Non-convulsive 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
Raised 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

Lee DW, et al. Biol Blood Marrow Transplant. 2018 Dec 25. pii: S1083-8791(18)31691-4.

Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care	Supportive care	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

MD Anderson. CAR cell therapy toxicity assessment and management. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

LEUKEMIA & LYMPHOMA SOCIETY BEATING CANCER IS IN OUR BLOOD.

Clinical Case: Dana Penn (D.P.)

Diagnosis: Transformed DLBCL
Age: 68-year-old male

Received chemotherapy followed by his T cell infusion
Tolerated chemotherapy and T cells without any complications

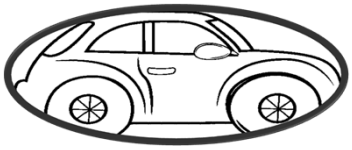
On day 3, DP was seen in the office; temp 101.3, hypotension, back pain and flu-like symptoms

Evaluated by NP in outpatient infusion center
- **Started on IVF's for low blood pressure**
- **O2 on arrival was 97% and within 30 mins dropped to 90% on RA, placed on 2 liters NC**
- **Infectious work up initiated**

Patient transported to ER; admitted to the hospital

Which of the following management approaches would you consider most appropriate for this patient?

A. Continue supportive care only
B. Administer tocilizumab
C. Administer dexamethasone
D. Administer tocilizumab + high-dose methylprednisolone and admit to the ICU
E. Uncertain



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Clinical Case: Dana Penn (D.P.)

Diagnosis: Transformed DLBCL
Age: 68-year-old male

Admitted : Treatment intravenous fluids, antibiotics and antipyretics
Infectious work up negative

Day 5: DP developed new fevers and low blood pressure- not responsive to fluid boluses

Grade 2 CRS -> Tocilizumab administered

12 hours following Tocilizumab-> blood pressure normalized and fevers resolved

LEUKEMIA & LYMPHOMA SOCIETY BEATING CANCER IS IN OUR BLOOD.

Clinical Case: Dana Penn (D.P.)

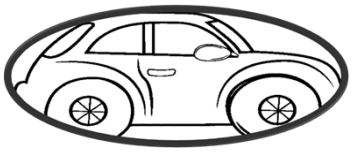
Diagnosis: Transformed DLBCL
Age: 68-year-old male

Day 7: DP developed word finding difficulty with somnolence.

Afebrile and Vital signs within normal limits

Which of the following management approaches would you consider most appropriate for this patient?

A. Continue supportive care only
B. Administer tocilizumab
C. Administer dexamethasone
D. Administer tocilizumab + high-dose methylprednisolone and admit to the ICU
E. Uncertain



LEUKEMIA & LYMPHOMA SOCIETY
BEATING CANCER IS IN OUR BLOOD.

Clinical Case: Dana Penn (D.P.)

Diagnosis: Transformed DLBCL
Age: 68-year-old male

Day 7: DP developed word finding difficulty with somnolence.

Grade 2 Neurotoxicity -> receive corticosteroids (dexamethasone)

U. of Penn has an online reference tool that is available to all health care providers CRS and neurotoxicity management pathways readily accessible LV(O32 LV(O34

Slide 58

LV(O32 Can you add the URL to ge to the tool?
Leishman, Valarie (National Office), 9/3/2020

ND55 heather mentioned on call yesterday she cannot...
Nicole Dane, 9/4/2020

LV(O34 right
Leishman, Valarie (National Office), 9/4/2020

LEUKEMIA & LYMPHOMA SOCIETY BEATING CANCER IS IN OUR BLOOD.

Clinical Case: Dana Penn (D.P.)

Diagnosis: Transformed DLBCL
Age: 68-year-old male

Day 10: neurological status returned to baseline
CBC and chemistry within normal ranges

Day 12: Discharge to local accommodations with caregiver

- **Instructed to stay within the immediate area to day 28 with caregiver**
- **Seen in the office weekly for the next two week**

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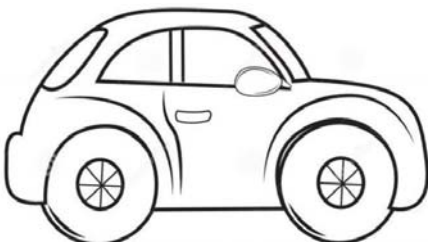
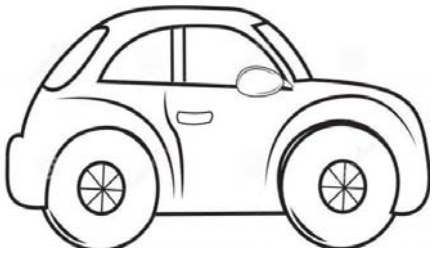
CAR-T Directory

Ilene › **Heather** › **Kathleen** › **Sherry**





CAR T Navigation Overview › Screening › Apheresis › Manufacturing Bridging therapy › Lympho-depletion › CAR T infusion › Acute toxicity period › Long-term monitoring

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Heading Home

- The majority of patients receive CAR T-cells (commercial and on clinical trials) at specialized centers and then return home for care with local oncologist
- As this is a relatively new therapy, communication with community oncologists regarding potential adverse events and follow-up care is vital

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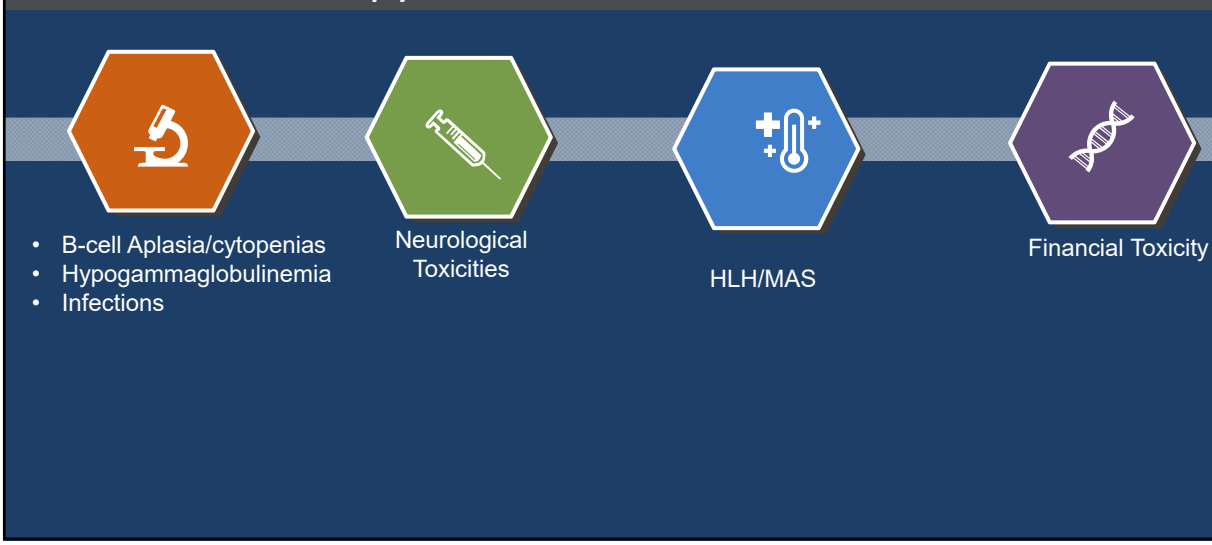
Potential Late (Post 30 days) Toxicities Associated with CAR T-cell Therapy



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Cytopenias/Infections/B-cell Aplasia/Hypogammaglobulinemia

- Cytopenias are common; related to lymphodepleting chemotherapy as well as an immune-mediated mechanism related to the CAR T-cells
- A study by Hill (2018) indicated that 14% of patients developed infections 29-90 days after cell infusion. A 2018 study (Park, et al) of patients with ALL, 31% of patients developed infections from days 31-180
- Low CD4 counts increase the risk of opportunistic viral, fungal, parasitic and bacterial infections including *Pneumocystis jiroveci* pneumonia (PJP)
- B-cell aplasia due to "on-target, off-tumor" effect resulting in hypogammaglobulinemia
- However, long-lived plasma cells which produce the majority of antibodies (in adults) may not be affected by anti-CD19 targeted therapy due to low expression of CD19

MD Anderson

Antimicrobial Prophylaxis

- Treatment guidelines for cancer-related immunosuppression have been used to guide prophylaxis
- A team of clinicians from across the country developed guidelines for antimicrobial prophylaxis in patients receiving immune-effector cells
  - -CARTOX algorithm/CARTOX mobile app
- Recent publication in *Blood* addresses infection prevention in patients receiving CD19-targeted CAR T-cell therapy.
  - Hill, J. and Seo, S. (2020) https://doi.org/10.1182/blood.2019004000

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General Recommendations

- Monitor blood counts weekly through day 60 or until counts recover
- Myeloid growth factors can be used with most products although some restrict it the first 3 weeks post cell therapy
- Antiviral therapy (valacyclovir, acyclovir) for at least 6 months to a year post cell infusion
- PJP prophylaxis for at least 6 months to a year post cell infusion but should be continued beyond those time points if CD4 count is less than 200 cells/mcL.
- Anti-fungal and anti-bacterial prophylaxis in patients with prolonged neutropenia.
- High risk patients (recent allo SCT, prolonged use of corticosteroids, etc) may require mold prophylaxis.

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General Recommendations

- History of Hepatitis B (positive HBsAg or HBcAb positive):
  - Entecavir or tenofovir for 12-24 months post cell infusion.
  - Monitor HBV titer once a month while on prophylaxis and monthly for a year after discontinuing the drug.
- Infectious Disease specialists should follow patients with an history of Hepatitis C/HIV.
- Immunoglobulin G infusions may be helpful in patients with levels of IgG less than 400 mg/dL and/or patients who develop frequent infections.

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Neurological toxicities (encephalopathy, seizures, tremor, aphasia, headache, dizziness, etc.)

	ZUMA-1 (Axicabtagene Ciloleucel)	Juliet (Tisagenlecleucel)
Median time to onset, days (range)	5 (1-17)	6 (1-17)
Median Duration, days (range)	17	14

Jain, T, et al (2019) *Biol Blood Marrow Transplant* 25 (2019)

- Patients receiving axicabtagene ciloleucel (YESCARTA®) and tisagenlecleucel (KYMRIAH®) are at risk for altered or decreased consciousness or coordination in the 8 weeks following infusion. (Yescarta®, Kymriah®)
- Data regarding long-term neurologic sequelae is limited.

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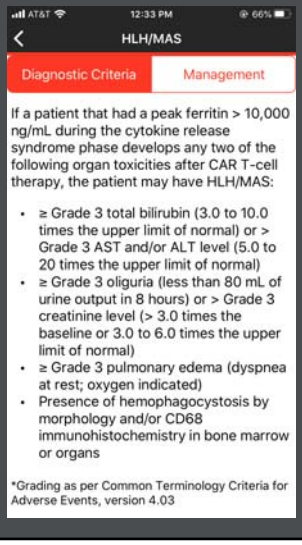
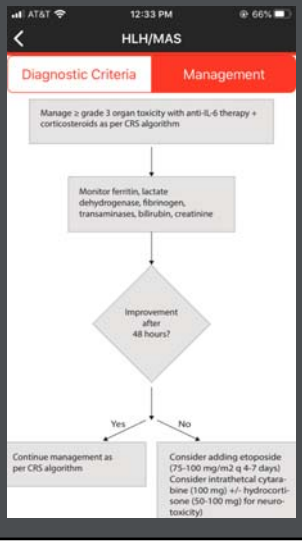
Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS)—Hyperactivation of the Immune System





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Financial Toxicity

CANCER CARE PATIENT FINANCIAL ASSISTANCE RESOURCES

The Leukemia and Lymphoma Society (LLS) Co-pay Assistance Program

The LLS Susan Lang Pay-it-Forward Travel Assistance Program

Cancer Care Financial Assistance Program

Cancer Financial Assistance Coalition

Headstrong Foundation Financial Assistance Program

HealthWell Foundation Financial Assistance Program

Perillo-Stafford Leukemia Foundation Financial Assistance Program

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Clinical Case: Dana Penn (D.P.)

Seen by social worker on day 20 for financial concerns and received assistance with co-pays from the Leukemia and Lymphoma Society.

On day 30 he had a PET scan which showed a complete response to therapy. He remained cytopenic but did not require transfusion or growth factor support.

He received additional reinforcement of education regarding potential long-term and late effects of therapy including when to seek urgent/emergent care. His clinic nurse verified that he had a wallet card and reminded him to carry it and present it to medical personnel in case of an emergency.

He subsequently returned to Colorado and was followed by his local oncologist.

His local oncologist was provided with a letter detailing his treatment course, potential adverse events, recommendations for monitoring and antimicrobial prophylaxis.

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CAR T-cell Therapy: A Road Map for Nurses

Thank you for your attention

QUESTIONS ?