CHAMPIONING MEDICALLY INTEGRATED ONCOLOGY:

Celebrating a Decade of Impact

2025 NCODA INTERNATIONAL FALL SUMMIT

Reimagining CAR-T: The Outpatient Evolution

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OBJECTIVES

1. Identify key patient, caregiver, and product-related aspects to ensure a safe outpatient Chimeric Antigen Receptor Therapy (CAR-T) journey

2. Discuss toxicity mitigation strategies, including monitoring, management protocols, and risk-adapted approaches for outpatient CAR-T therapy

3. Outline the multidisciplinary team roles, infrastructure, workflow, and safety protocols essential for outpatient CAR-T program implementation

DISCLOSURES

The following relevant financial relationships from the past 24 months have been identified and disclosed for the following planners of this CE activity:

- Stephanie Parker, PharmD
  - o Aveo, Partner Therapeutics, Nuvation Bio

There are no relevant conflicts of interest to disclose for this presentation for the following speakers and planners of this CE activity:

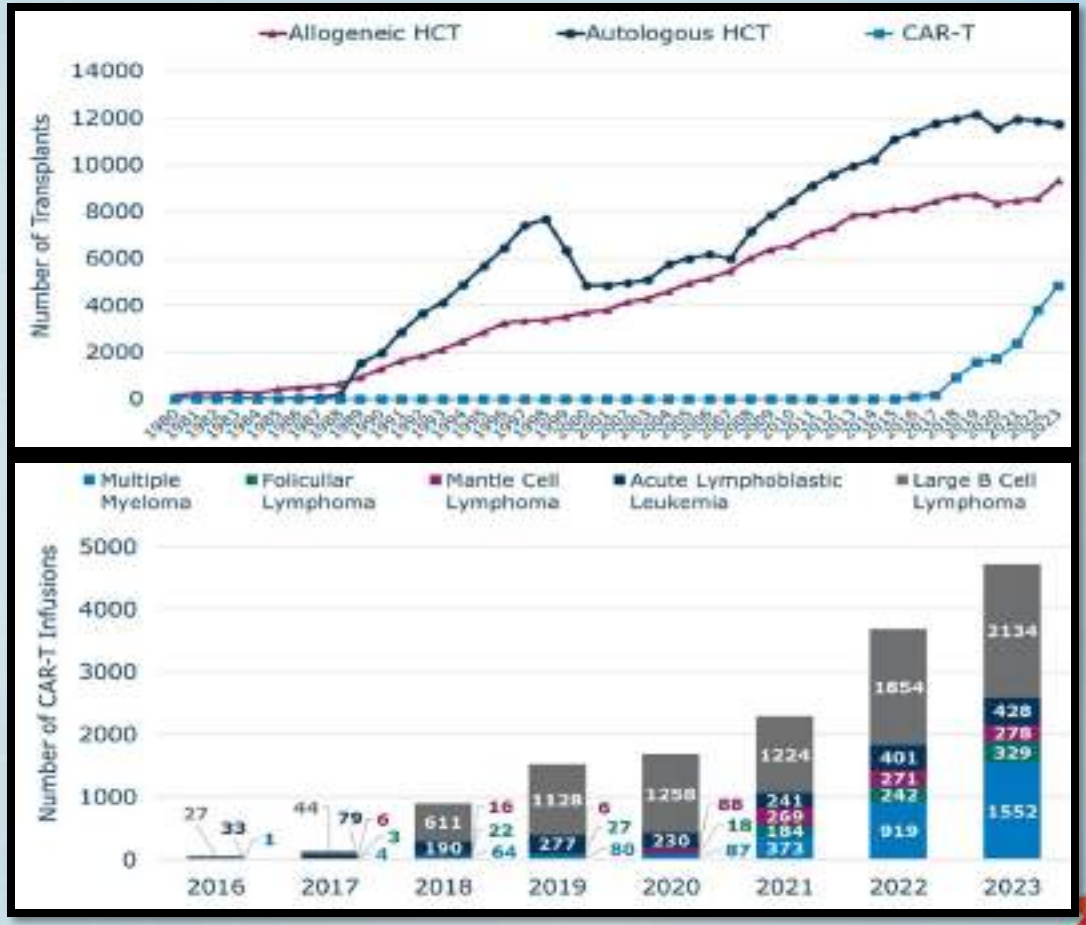
- Rebecca Gonzalez, PharmD, BCOP, FASTCT
- Tahsin Imam, PharmD

This activity may include information regarding the use of products that may be inconsistent with, or outside the approved labeling for, these products in the United States.

Current Treatment Landscape and Future Evolution of Chimeric Antigen Receptor Therapy (CAR-T)

- CAR-T is considered a major breakthrough in hematology Tx with effective and durable responses
  - Historically, focused on chemotherapy within community centers
    - ➢ Referral to certified centers for CAR-T delivery
- Success of CAR-T in early setting and in trial-ineligible patients highlights the critical need for broader access
- Shift in demand for OP CAR-T similar to aHCT
  - Driven by resource constraints and better understanding and management of toxicities
  - Comparable efficacy with reduced cost/tx burden

CIBMTR 2024 Summary Analysis: Current use of Cellular Therapy and CAR-T Infusions by Indication in the US annually



Haslam A, et al. *Blood Adv*. 2024;8(4):1032-1036. Spellman SR, et al. *Transplant Cell Ther*. 2025 Aug;31(8):505-532., Bhaskar ST, et al. *Clin Hematol Int*. 2024;6(4):93-99., Alsina M, et al. *Future Oncol*. 2025;21(10):1137-1144., Hansen DK, et al. *Cancers*. 2023;15: 5746., Mikhael J, et al. *JCO Oncol Pract 2022;* **18**, 800-807.

Tx: treatment, MM: multiple myeloma, OP: outpatient, CIBMTR: Center for International Blood and Marrow Transplant Research, US: United States, aHCT: autologous hematopoietic cell transplant

US FDA Approvals of CAR T-cell Therapy

Lymphoma (CD-19 Targeted)

2017 — Axicabtagene ciloleucel (axi-cel)
- Initial Approval: 3rd line LBCL
- Subsequent Approval: 2nd line LBCL, 3rd line FL

2020 — Tisagenlecleucel (tisa-cel)
- Initial Approval: 3rd line LBCL
- Subsequent Approval: 3rd line FL

2021 — Brexucabtagene autoleucel (brexu-cel)
- Initial Approval: as early as 2nd line for MCL

2021 — Lisocabtagene maraleucel (liso-cel)
- Intial Approval: 3rd line LBCL
- Subequent Approval: 2nd line LBCL, 3rd line for CLL/SLL, 3rd line FL, 3rd line MCL

Leukemia (CD-19 Targeted)

2017 — Tisa-cel
- Initial Approval: R/R B-ALL: peds/AYA; up to 25yo

2021 — Brexu-cel
- Subsequent Approval: R/R B-ALL: adults; 18yo+

2024 — Obecabtagene autoleucel (obe-cel)
- Initial Approval: R/R B-ALL: adults; 18yo+

Myeloma (BCMA Targeted*)

2021 — Idecabtagene vicleucel (ide-cel)
- Initial Approval: 4th line MM
- Subsequent Approval: 3rd line MM

2022 — Ciltacabtagene autoleucel (cilta-cel)
- Initial Approval: 4th line in MM
- Subsequent Approval: 2nd line MM

2026 — Arlocabtagene autoleucel (arlo-cel)
- *Initial PDUFA date February 8, 2026*
- *Note: GPRC5D-targeted CAR-T Product**

LBCL: large b-cell lymphoma, FL: follicular lymphoma, MCL: mantle cell lymphoma, CLL: chronic lymphocytic lymphoma, SLL: Small Lymphocytic Lymphoma, ALL: acute lymphocytic leukemia, R/R: relapsed/refractory, yo: years old, PDUFA: prescription Drug User Fee Act, GPRC5D: G-protein coupled receptor family C group 5 member D

Neelapu SS, et al. *N Engl J Med*. 2017;377(26):2531-2544., Maude SL, et al. *N Engl J Med*. 2018;378:439-448., Shah BD, et al. *Lancet.* 2021; 398: 491-502., Roddie C, et al. *N Engl J Med*. 2024.12;391(23):2219-2230., Jacobson CA, et al. *Lancet Oncol*. 2022;23(1), Fowler NH, et al. *Nat Med.* 2022;28(2)., Abramson JS, et al. *Lancet.* 2020;396(10254):839-852., Kamdar M, et al. *Lancet.* 2022;399(10343)., Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716., Wang M, et al. *N Engl J Med*. 2020;382(14):1331-1342., Berdeja JG, et al. *Lancet*. 2021;398(10297)., Rodriguez-Otero P, et al. *N Engl J Med*. 2023;388(11):1002-1014., San-Miguel J, et al. *N Engl J Med.* 2023;389(4)., Bal S, et al. *Blood.* 2024;144(suppl 1):922, Rakesh Popat, et al. *JCO.* 2025;43:16_suppl, TPS7564-TPS7564.

CAR-T Journey: Collection to Manufacturing

Leukapheresis

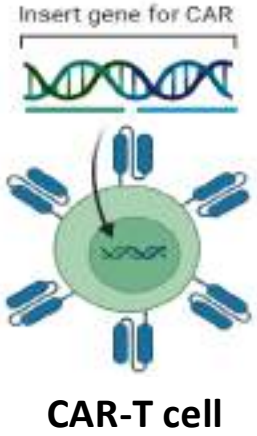
Collect patient's own WBC's

Shipped to manufacturer

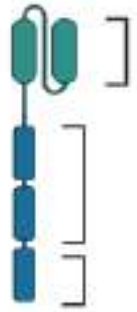
Manufacturing (Vein to Vein ~4-6 weeks)

Isolate/activate T-cells

Genetically engineered T-cells with CAR gene



CAR-T cell

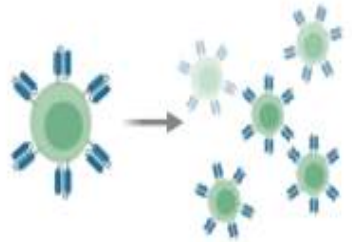


Antigen binding domain (e.g., CD19, BCMA)

Costimulatory domain (CD28 or 4-1BB)

Signaling domain (CD3ζ)

Grow and expansion of CAR-T product



Consultation and work-up	Leukapheresis	Bridging chemo/"Wash out" period
• CTNC, Provider, APP • Review labs/ VOTs • Enroll patient, sign informed consent, education	• Vein assessment +/- transfuse to collection parameters • Apheresis teaching • Collect cells, package and ship product	• Bridge to CART: palliate symptoms, debulk tumor, etc. • Preserve functional status to safely administer cells • May include chemotherapy, steroids, +/- XRT

WBC: white blood count, CTNC: Cellular Therapy Nurse Coordinator, APP: Advanced Practice Provider, VOTs: vital organ testing, XRT: radiation therapy

Mikhael J, et al. *JCO Oncol Pract*. 2022;18, 800-807. Zugasti I,et al. *Sig Transduct Target Ther* . 2025;10, 210.Image created from BioRender.com

CAR-T Journey: Lymphodepleting Chemotherapy (LD) to Adverse Events

LD Chemotherapy

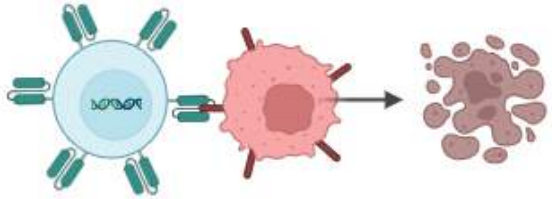
Days -5, -4, -3

Cell Infusion

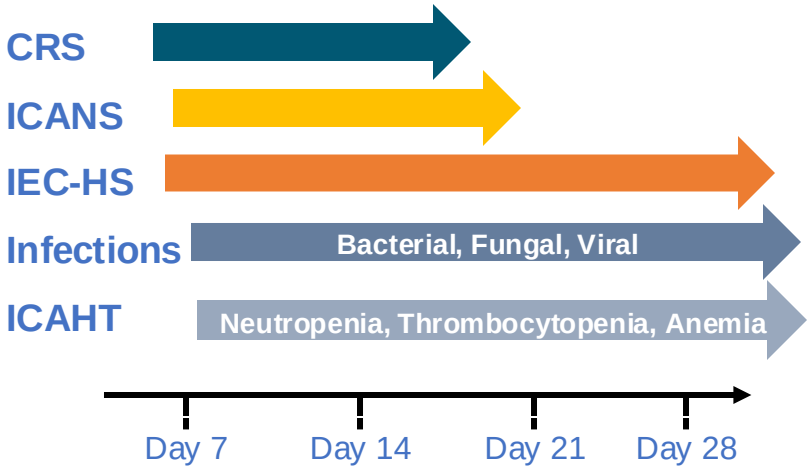
Infuse patient with engineered CAR T-cells

CAR-T Expansion/Persistence

On Target-On Tumor/On Target-Off Tumor Effects



Toxicity Spectrum



LD Chemotherapy

- Goal: deplete lymphocytes/suppressive cells to foster *in vivo* proliferation
- Composed of 3-5 days of combined agents (e.g., FluCy)
- Side effect management: pancytopenia, GI toxicity, fatigue

Cell Administration

- Clearance: central line, vitals/labs stable, no active infection
  - Product verification and wallet card provided to patient
- Infusion reaction monitoring (cryopreserved)
- Premeds & pre/post hydration

Side-effect monitoring

- CRS/ICANS/Other
- NF/Infection work-up
  - Count Recovery/Lab abnormalities
    - Need for transfusions, growth factor support, IVIG

FluCy: fludarabine, cyclophosphamide, CRS: Cytokine release syndrome, ICANS: Immune effector cell-associated neurotoxicity syndrome, IEC-HS: Immune effector cell associated hemophagocytic lymphohistiocytosis-like syndrome, ICAHT: Immune Effector Cell-Associated Hematotoxicity, GI: gastrointestinal, NF: neutropenic fever, IVIG: Intravenous immunoglobulin

Canelo-Vilaseca, M. et al. *Bone Marrow Transplant*. 2025;60: 559–567. Images created from BioRender.com., Hines MR, et al. *Transplant Cell Ther*. 2023. 29;438.e1-438.e16, Jain T, et al. *Blood*. 2023;141(20):2460-2469.

Perceived CAR-T Barriers Among US-based Large Academic and Community Practice

Barriers		Potential Solutions	

CAR-T Tx Process/ Logistics	▪ **Restriction to specialized center**
	  ▪ **Slow intake process**
	▪ Requirement for patients to **remain in specified radius of center**
	▪ Lost wages for caregivers
	▪ Bridging therapy due to vein-to-vein time
		CAR-T Tx Process/ Logistics	▪ **Authorization for both IP/OP setting administration**
			  ▪ Some OP components or reduced timing for IP stay
			▪ Remote monitoring
			▪ Collaborative follow-up with local oncologist post-CAR-T

Manufacturing	▪ Limited manufacturing slots ▪ **Manufacture failures**	**Manufacturing**	▪ In-house manufacturing ▪ **Use of OOS products**

IP: inpatient, OP: outpatient, OOS: out of specification

Atallah R, et al. *Transplant Cell Ther.* 2024;30(2S): S370S398., Gajra A, et al. *Immunotherapy*. 2020 Jul;12(10):725-732.

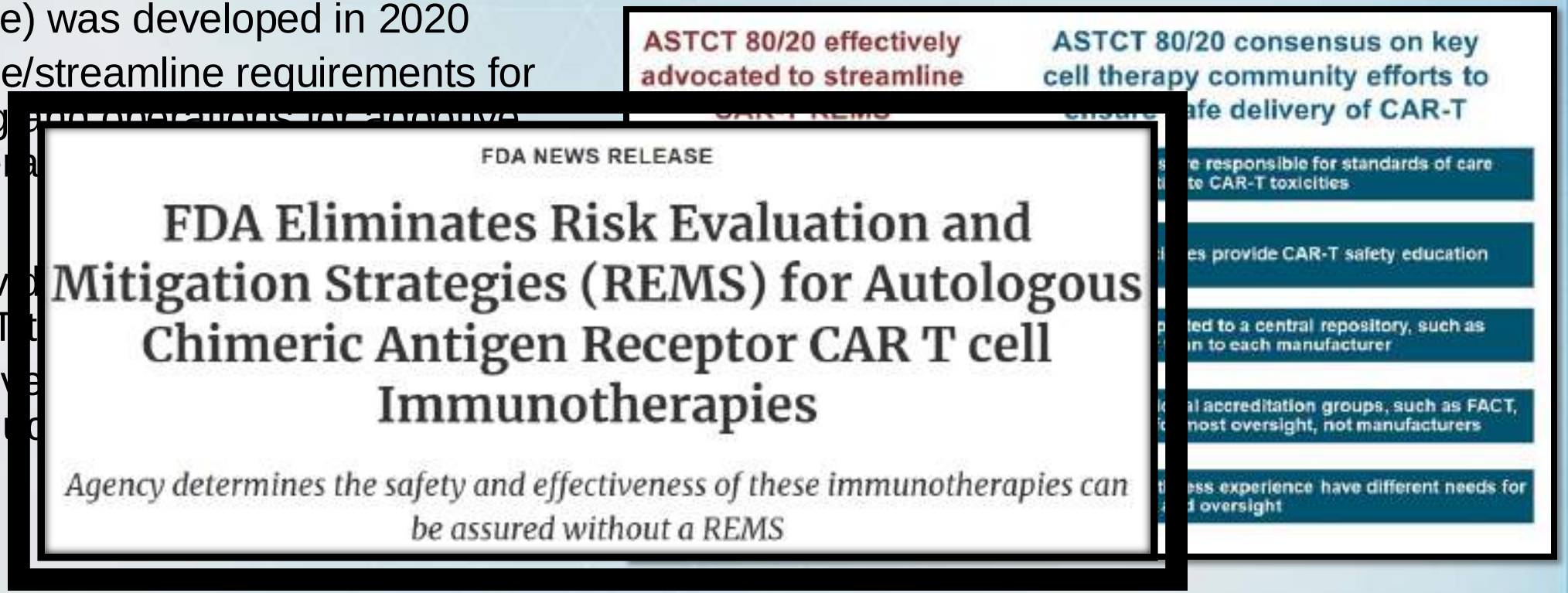
Perceived CAR-T Barriers Among US-based Large Academic and Community Practice

Barriers		Potential Solutions	
Reimbursement/ Financial burden	▪ **Health plan restrictions/denials for coverage of adoptive cell therapies** ▪ Slow approval process by payers ▪ Patient deterioration (in-eligible)	**Reimbursement /Financial burden**	▪ Streamline mechanisms for equitable reimbursement ▪ **Utilize manufacturer-provided resources for patient support, insurance coverage and benefit verification**

Atallah R, et al. *Transplant Cell Ther.* 2024;30(2S): S370S398., Gajra A, et al. *Immunotherapy*. 2020 Jul;12(10):725-732.

Advocacy for Safe and Equitable Access: Mission Accomplished June 26, 2025

- ASTCT 80/20 Taskforce (now subcommittee) was developed in 2020
  - o Standardize/streamline requirements for onboarding
    cellular ther
- Mission: provi
  use of CAR-T
  - o Collaborativ
    burden redu



Locke F, et al. *Transplant Cellular Ther*. 2025;31:349.e1 349.e12. Image available under creative commons CC BY-NC-ND license., FDA Eliminates Risk Evaluation and Mitigation Strategies (REMS) for Autologous Chimeric Antigen Receptor CAR T cell Immunotherapies. Accessed August 16, 2025, from: https://www.fda.gov/news-events/press-announcements/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor.

Financial Considerations for OP CAR-T: Creating a Sustainable and Patient-centric Approach

Reimbursement varies based upon public vs. private insurance and administration location

- High cost of CAR-T can be exacerbated by reimbursement restrictions
  - o Ensure single case/contractual agreements include IP and OP sites of care
  - o OP reimbursement*: average $ for CAR-T + ~ 6%
    - ➢ Medicare uses OP prospective payor system (OPPS):
      - PPS-non-exempt: 99% of other centers (fixed rate per patient) vs. PPS-exempt: 11 Cancer Centers (“reasonable cost payment”)
  - o IP reimbursement MS-DRG base payment
  - o Medicare copays capped
  - o Medicaid coverage varies (product/state-specific)

Ensure thorough EMR documents for labeling criteria

*Product price increase may occur and need to be vigilantly monitored for updates
MS-DRG: Medicare Severity Diagnosis-Related Group

Jagannath S, et al. *Oncol Ther*. 2023 Jun;11(2):263-275., American Society for Transplantation and Cellular Therapy. ASTCT CAR-T therapy coding and billing guide. Updated January 2025. Accessed August 15, 2025. https://www.astct.org/Portals/0/ASTCT_1492250-25_BillingandCoding_Q1_FINAL.pdf., Alsina M, et al. *Future Oncol*. 2025;21(10):1137-1144.

Financial Considerations for OP CAR-T: Creating a Sustainable and Patient-centric Approach

Even with insurance there is significant financial burden

- Medical costs, lost wages (patient/caregiver) and lodging/transportation
- Ensure access to general financial support for these out-of-pocket expenses
  - ➢ Local lodging programs or grants

Shifting CAR-T to the OP setting may improve patient experience, optimize HCRU, and decrease costs:

- Decreased hospital bed usage
- Shorter hospital stays
- Lower costs (patent and institution)
- Improved patients QoL

Jagannath S, et al. *Oncol Ther.* 2023 Jun;11(2):263-275., American Society for Transplantation and Cellular Therapy. ASTCT CAR-T therapy coding and billing guide. Updated January 2025. Accessed August 15, 2025. https://www.astct.org/Portals/0/ASTCT_1492250-25_BillingandCoding_Q1_FINAL.pdf., Alsina M, et al. *Future Oncol.* 2025;21(10):1137-1144.

HCRU: Healthcare resource utilization , QoL: quality of life, EMR: electronic medical record

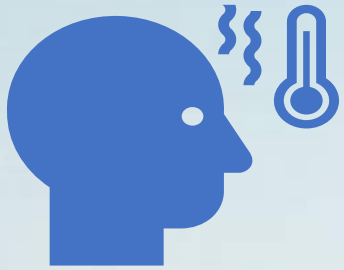
OP Administration Can Reduce Healthcare and Patient Costs While Maintaining Suitable Benefit-Risk Profile

Jagannath S, et al. Cilta-cel Component Cost of CAR-T: Average Total Costs Per Patient Based on 3 Phases$^{\psi}$

ψPopulation based on CARTITUDE-1: Exploring 3 Phases of Cost Components: pre-infusion, peri-infusion, post-infusion

Palomba ML, et al. Liso-cel Cost of Care: IP vs. OP

Retrospective review of TRANSCEND 001 and OUTREACH trials
(N = 303)



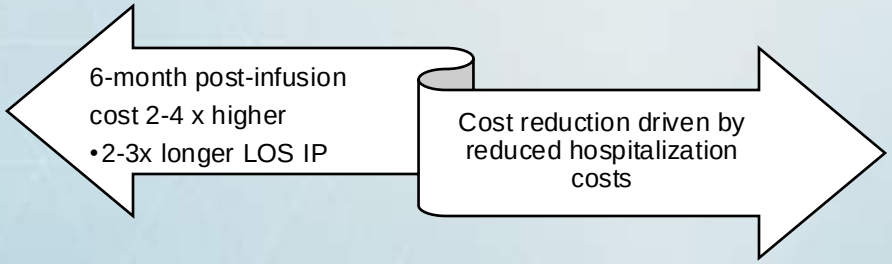
62% infused OP required admission
- 21% within 72 hours

Admission LOS, median (range)
- 15 (0-88) IP vs. 4 (0-77) OP

38% of OP never required admit within 6-months

Estimated 6-month post-CAR-T HCRU savings
- $89,535 IP vs. $36,702 OP

Hansen, et al. Direct Costs of pooled TRANSCEND 001, OUTREACH, TRANSFORM and PILOT (liso-cel) Clinical Trials with OP and IP data



Jagannath S, et al. *Oncol Ther.* 2023 Jun;11(2):263-275.,, Palomba ML, et al. *Leukemia Lymphoma.* 2021;9:2169-76., Hansen DK, et al. *Cancers (Basel).* 2023. Dec 7;15(24):5746.

Considerations for Successful Implementation of Outpatient CAR-T

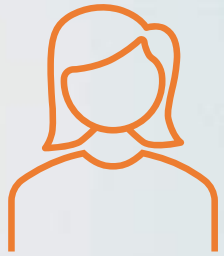
QUESTION 1

You are currently planning on developing outpatient CAR-T at your institution. During a strategic planning meeting you were asked what components of CAR-T can be administered in outpatient care setting?

a. Lymphodepleting chemotherapy (Day -5 to Day -3)
b. Cells infusion (D0)
c. Close monitoring post-cell infusion for certain eligible products
d. All of the above

Suitability Criteria for OP Administration of CAR-T

Key: Purposeful Selection



Patient

- Limited comorbidities with good PS
- Reliable 24-hour caregiver support
- Relatively stable disease burden, low risk of severe CRS/ICANS

Product

- Predictable timeline of toxicities
- Gradual onset of potentially severe toxicities

Myers GD, et al. *J Immunother Cancer*. 2021;9:e002056., Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142.

PS: performance status

Overall Patient/Product Considerations for CAR-T Eligibility*

- Indications and limitations
  - Consider antigen loss (e.g., CD19 for CD19-directed CAR-T)
  - Insurance coverage/preference of product
- How time sensitive/urgent is treatment?
- Is the patient at high risk of toxicity?
  - High tumor burden/need for bridging therapy
  - Multiple comorbidities

- Life expectancy > 6 weeks
- Adequate organ function
- ECOG PS: 0-2
- Ability to tolerate LD chemo
- Ability to tolerate CAR-T cell–related toxicities
- No active/ uncontrolled infections
- Caregiver support pre, during, and post CAR-T
- Housing/financial support

*Criteria for eligibility may differ from site by site

ECOG PS: Eastern Cooperative Oncology Group performance score

Abramson JS et al. *Am Soc Clin Oncol Educ Book*. 2019;39:446-453; Yakoub-Agha I et al. *Haematologica*. 2020;105(2):297-316.

Do’s and Don’ts of Patient Selection for OP Administration

Ideal

- No bulky disease or large tumor burden (risk of severe CRS/ICANS)
- No organ dysfunction/significant comorbidities
- Good health literacy and compliance/adherence
- Reliable caregiver and transportation

Not-ideal

- Dialysis-dependent
- Progressive disease symptoms (new onset AKI, TLS, etc.)
- Poor performance status or mobility (preventing tolerability of CRS)
- High psychosocial risk

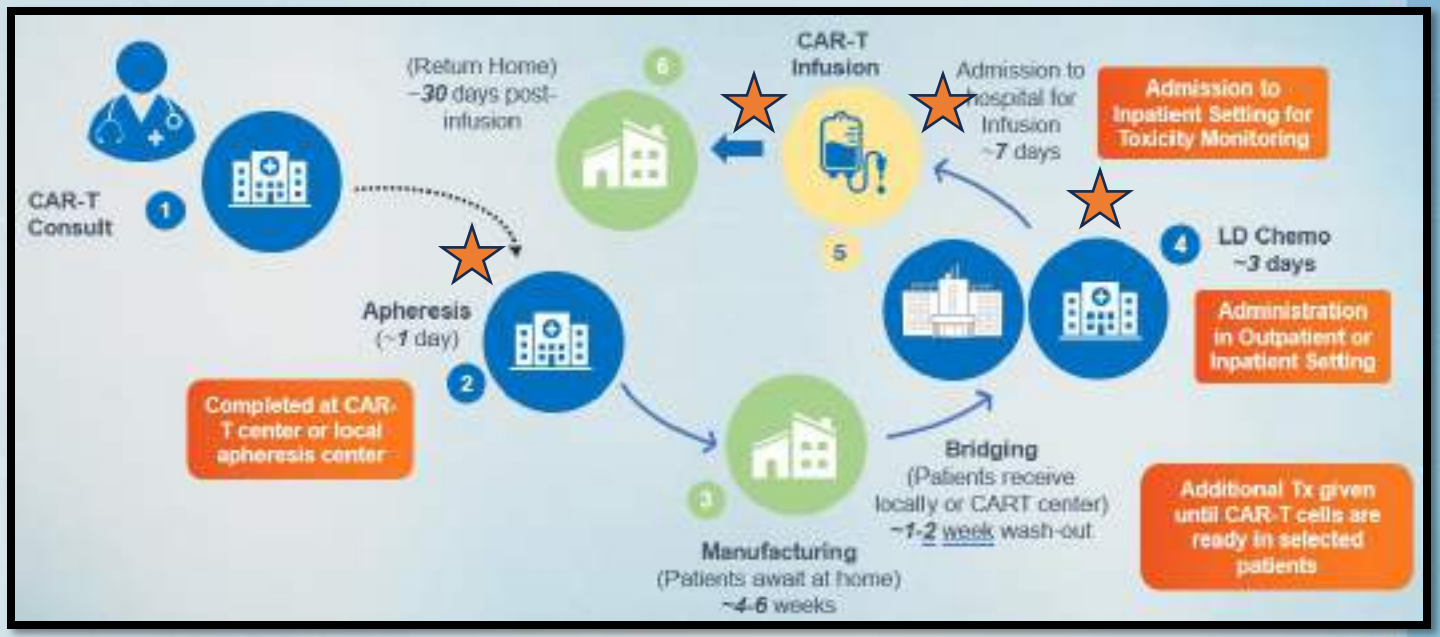
OP CAR-T should be planned & discussed with patient by primary provider and CAR-T team at re-evaluation and outlined in EMR

TLS: tumor lysis syndrome, AKI: acute kidney injury

Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142., Alsina M, et al. *Future Oncol.* 2025;21(10):1137-1144.

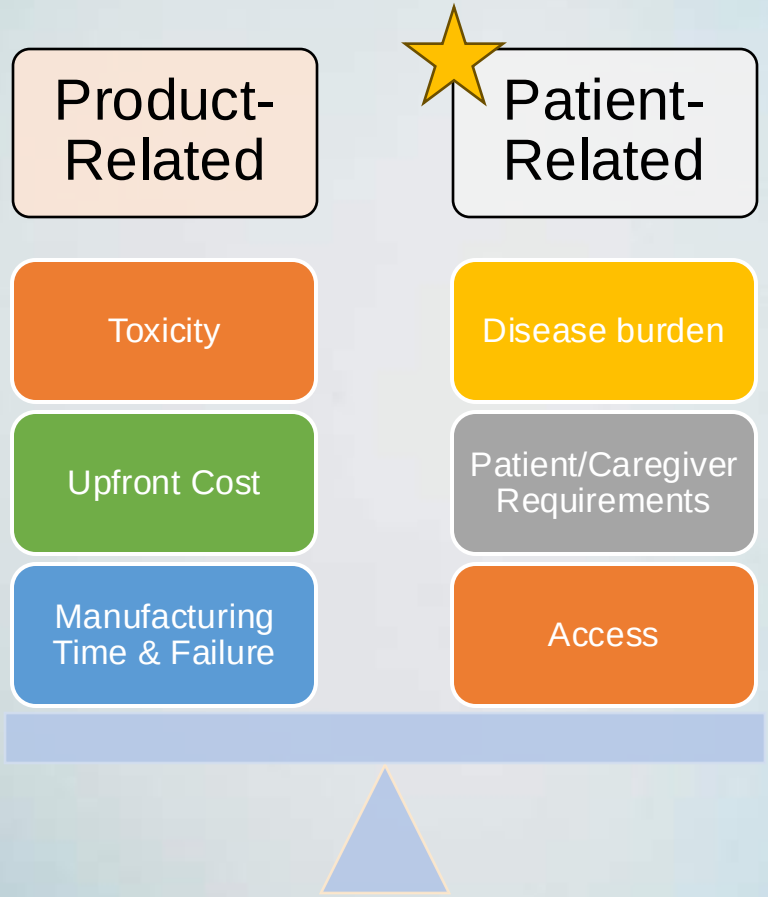
Critical Caregiver Factors Essential for OP CAR-T Administration

- Reliable transportation to/from facility
  - o Apheresis/line placement until return to home
- Local lodging to center post-infusion
  - o Within designated distance (~30-60 minutes)
- Access to a committed 24/7 caregiver
  - o As early as LD therapy
  - o Understanding of roles/responsibility to track symptoms and manage medications



Alsina M, et al. *Future Oncol.* 2025;21(10):1137-1144., Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142., Hansen DKD, et al. Front Immunol. 2024. Feb 21–24;15:1405452..

CAR-T Limitations: Rebalancing the Scale with OP Administration



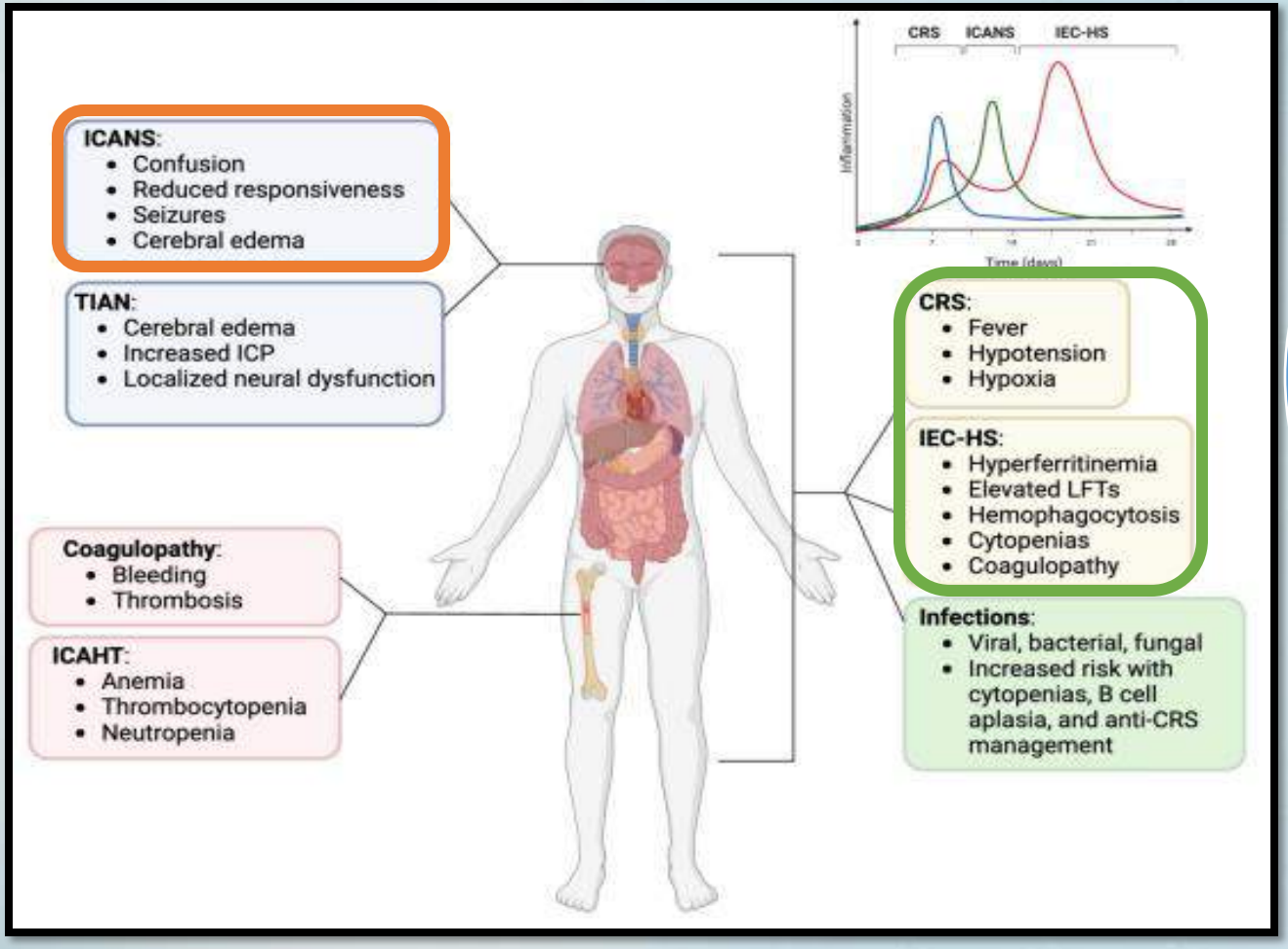
- Historically, CAR-T was administrated in IP setting driven by serious AE's (CRS, ICANS, etc.) and need for close monitoring
  - o Better understanding and predictability of the clinical course increased OP interest
    - Most experience is with 4-1BB products given toxicity profile
      - CD28 products possible with additional support and vigilance

- With appropriate infrastructure planning OP is feasible leading to several patient and institutional advantages:
  - o More cost favorable without compromise in clinical outcomes
  - o Associated with shorter hospitalization duration
  - o Increase access and reduced patient/caregiver burden

AE's: Adverse events

Alexander M, et al. *Transplant Cell Ther*. 2021;27:558, Gatwood KS, et al. *EJHaem*. 2021;3(Suppl 1):54-6 0., Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142.

Systemic Spectrum of CAR-T Associated Toxicities



Clinical Symptoms/Findings

Neurologic/Muscular Skeletal	• Headache • Non-ICANS neurotoxicity • Myalgia/Arthralgias
Pulmonary	• Dyspnea • Tachypnea • Hypoxia
General (flu-like)	• Fatigue • Nausea/Vomiting • Fevers/Rigors

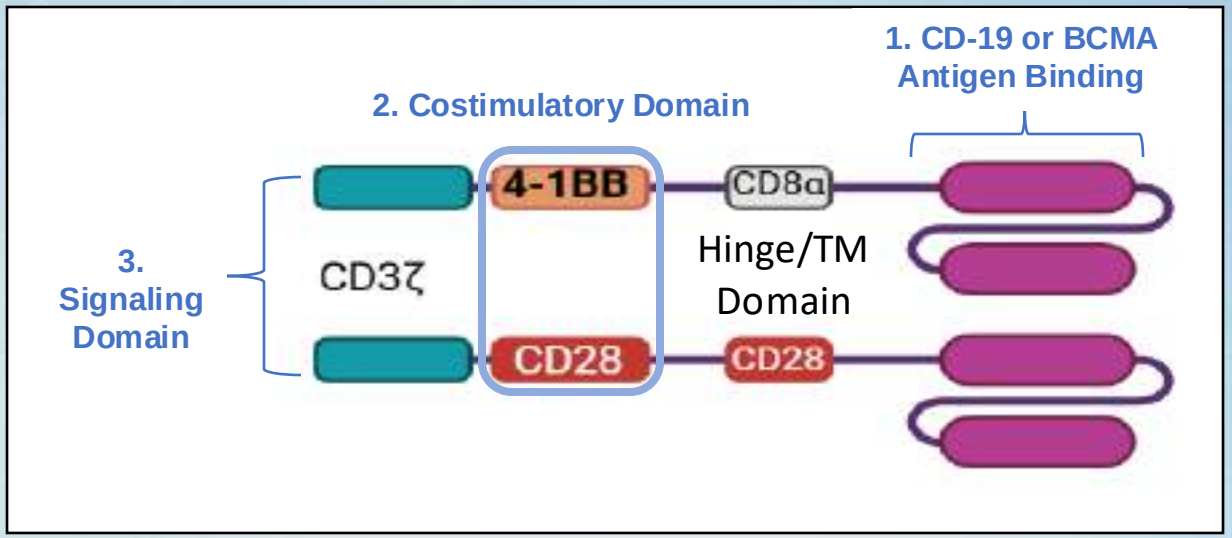
TIAN: tumor inflammatory-associated neurotoxicity, ICP: intracranial pressure, IEC-HS: Immune effector cell associated hemophagocytic lymphohistiocytosis-like syndrome, LFT: liver function test, ICAHT: Immune Effector Cell-Associated Hematotoxicity

Rankin, A.W., et al. *Cancer Metastasis Rev.* 2025;44, 17. Image available by http://creativecommons.org/licenses/by/4.0/., Hines MR, et al. *Transplant Cell Ther.* 2023. 29;438.e1-438.e16, Jain T, et al. *Blood.* 2023;141(20):2460-2469., Graham CE, et al. *Lancet Oncol* 2025; 26: e203–13. Maus MV, et al. *J Immunother Cancer.* 2020 Dec;8(2):e001511., Santomasso BD, et al. *J Clin Oncol*. 2021 Dec 10;39(35):3978-3992., Rejeski K, et al. *Blood.* 2023;142(10):865-877., Graham CE, et al. Lancet Oncol. 2025; 26:e203-13., Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625.

CAR Construct Directly Associated with Onset/Severity of AE's

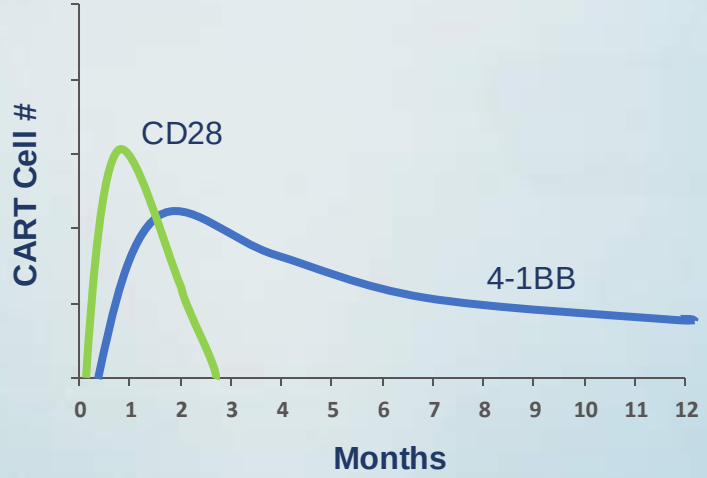
Domain Role Call:

1. Antigen Binding Domain: Recognizes CD19 or BCMA antigen on B-cells
2. Costimulatory Domain: Increase T-cell activation and enhances cytolytic function of T-cells
3. CD3-zeta chain signaling domain: Induces T-cell activation



CD28	4-1BB
Member of the immunoglobulin (Ig) family	Member of the TNF receptor superfamily
• Expands **preferentially effector-like T-cells** rapidly (limited CAR persistence)	• **Expands memory-like T-cells** (slow activation but enhanced persistence)

ScFV: short-chain variable fragment, TM: transmembrane



Cappell, K.M., et al. *Nat Rev Clin Oncol*. 2023; 20, 359–371. Figures recreated using biorender., Maus MV, et al. J *Immunother Cancer*. 2020 Dec;8(2):e001511.

Baseline Risk Factors for CAR-associated Toxicity

Toxicity Spectrum	Patient	Disease	Product/Tx Related	Additional Considerations
CRS*	Comorbidities +/- age, infections, **elevated inflammatory markers,** thrombocytopenia	**Tumor burden**, CNS involvement	Higher dose of CART-cells, **Co-stimulatory Domain [CD28 > 41BB CARs**, Flu-containing/ intensity of LD	**Onset/Duration variable and product specific**
ICANS*	CRS, **elevated inflammatory markers**, younger age, pre-existing neuro conditions, thrombocytopenia	**Tumor burden**, +/- CNS Involvement		ICANS often preceded by CRS
ICAHT + hypogam.**	**Elevated inflammatory markers**, older age, high baseline BM blasts	Refractory, poorly controlled disease, **Tumor burden**	Multiple prior LOT, intensity of LD	Multifactorial: poor patient condition, tumor burden, pe-treatment LD ***Consider CAR-HEMATOTOX**
Infections**	Age/comorbidities, Hx of CRS, Existing cytopenia's, prior frequent infections, hypogam	Refractory, poorly controlled disease	High-dose & long-duration steroids, other immunosuppressive treatments	Prior infections, biological age vs. chronological age

*Modified EASIX score=(LDH×CRP)/Platelets is associated with severe CRS and ICANS
** CAR-HEMATOTOX score: Score ≥2 pts are at risk for severe prolonged neutropenia and infections

BM: bone marrow, Hx: history, LOT: lines of therapy, Hypogam: hypogammaglobulinemia, CNS: central nervous system, CRP: c-reactive protein, LDH: lactate dehydrogenase

Rankin, A.W, et al. *Cancer Metastasis Rev*. 2025;44, 17., Frey N, et a.. *Biol Blood Marrow Transplant*. 2019;e123-e127., Garcia Borrega J, et al. *HemaSphere*;2019;3:2,. Brundo JN, Kochenderfer JN. *Blood Reviews*. 2019;45-55., Maus MV, et al. *J Immunother Cancer*. 2020 Dec;8(2):e001511.

Trustworthy Terrain: Navigating Product Choices with Predictable Safety

Best product selection for OP administration is dependent on main 2 factors:

1. Attributes of **toxicity onset** and **incidence of severe CRS/ICANS** events
   - o Delayed onset of toxicities is ideal
     - Potential for OP administration from LD to onset of toxicity warranting IP stay
     - Hospitalization only for toxicity management
   - o Low incidences of severe Gr. 2+ CRS/ICANS
     - Management of Gr. 1 CRS in OP setting feasible

2. Products with rapid onset of toxicities may be feasible for early discharge options

Example OP CAR-T RWE Studies

Disease State	Product	OP Infusion	Time to Admit (days)	Admit LOS Median (days)
MM, ALL, LBCL	Ide-cel, Tisa-cel, Liso-cel	80% (n=32/40)	2 (pre-emptive D0 approach, n=21)	8-14 vs. 19 IP only
LBCL	Tisa-cel	59% (n=93/157)	2.5 (45%OP required admit)	5 vs.13 IP only
ALL, LBCL	Axi-cel, Tisa-cel, Brexu-cel	96% (n=47/52)	2-4 (82% OP required admit)	7-10
MM	Cilta-cel	62.8% (n=27/43)	NR (92.6% OP required admit)	4 vs. 11 IP only

Gr: grade, LOS: length of stay RWE: real world experiences, NR: not reported

Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142., Hansen DKD, et al. *Front Immunol*. 2024. Feb 21–24;15:1405452., McGann M, et al. *Transplant Cell Ther.* 2022 Sep;28(9):583-585, Ahmed N, et al. *Transpl Cell Ther.* 2023. Jul;29(7):.e449.1–.e449.7. , Ly A, et al. *Br J Haematol.* 2023;203(4):688-692., Waqar, Syed Hamza Bin, et al. *Transpl Cell Ther.* 2024. 30(2):S388.

CRS and ICANS: Incidence, Onset and Duration of FDA Approved CAR T-Cell Products

LBCL Products

	Axi-cel DLBCL ZUMA-1	Axi-cel FL ZUMA-5	Brexu-cel MCL ZUMA-2	Tisa-cel DLBCL JULIET	Liso-Cel DLBCL TRANSCEND	Liso-Cel FL TRANSCEND FL
Gr. 3+ CRS	13%	**8%**	15%	22%	**2%**	**1%**
Median onset/ duration CRS	**2 days**/ 8 days	**4 days**/ 6 days	2 days/ 11 days	3 days/ 7 days	**5 days/** 5 days	**6 days/** 3 days
Gr. 3+ ICANS	28%	21%	31%	12%	10%	2%
Median onset/ duration ICANS	5 days/17 days	**6 days**/ 16 days	7 days/ 12 days	6 days/ 14 days	**9 days**/ 11 days	**8.5 days**/ 3.5 days

Delayed Onset (~ Day 4+) or **low Gr. 3+ events**: Potential for OP administration and IP for toxicity management

Early Onset (~ Days 1-3): Potential for early discharge from IP post-toxicity

ALL Products

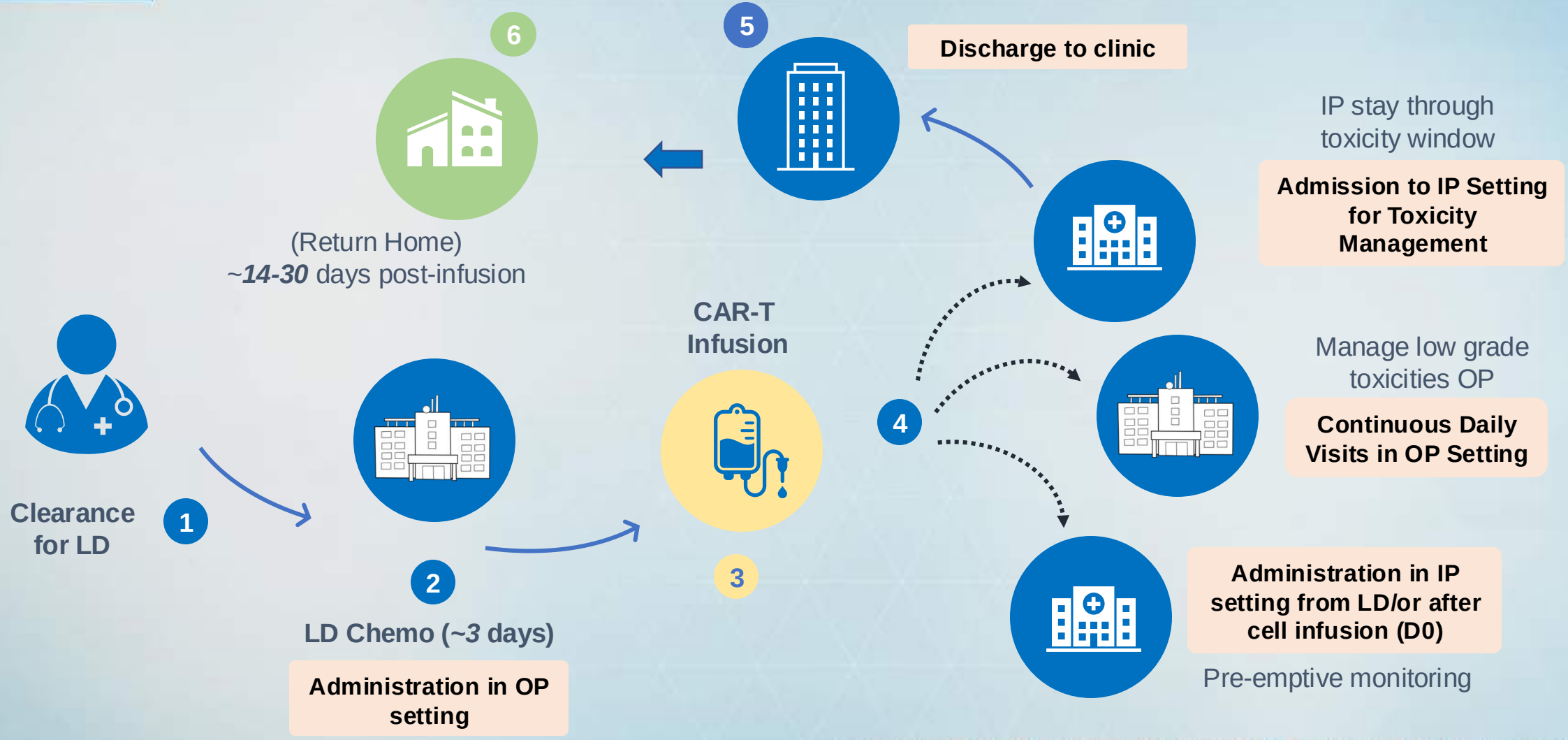
	Brexu-cel B-ALL ZUMA-3	Tisa-cel B-ALL ELIANA	Obe-cel B-ALL FELIX
Gr. 3+ CRS	24%	46%	3%
Median onset/ duration CRS	5 days/ 7.5 days	3 days/ 8 days	**8 days/** 5 days
Gr. 3+ ICANS	25%	13%	7%
Median onset/ Duration ICANS	9 days/ 7 days	<8 weeks/ 10 days	**12 days/** 8 days

MM Products

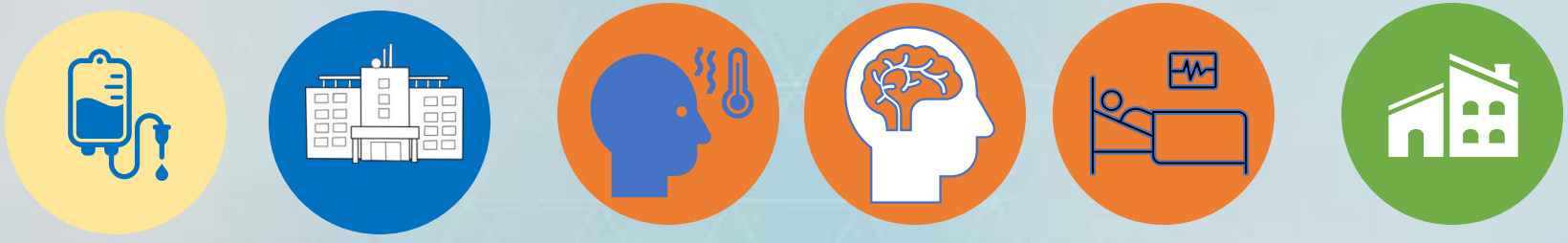
Ide-cel MM KarMMa	Cilta-Cel MM CARTITUDE-1
5%	4%
1 day/ 5 days	**7 days/** 4 days
3%	2%
2 days/ 3 days	**8 days/** 4 days

Neelapu SS, et al. *N Engl J Med*. 2017;377(26):2531-2544., Maude SL, et al. *N Engl J Med*. 2018;378:439-448., Shah BD, et al. *Lancet*. 2021; 398: 491-502., Roddie C, et al. *N Engl J Med*. 2024.12;391(23):2219-2230., Jacobson CA, et al. *Lancet Oncol*. 2022;23(1), Fowler NH, et al. *Nat Med.* 2022;28(2)., Abramson JS, et al. *Lancet*. 2020;396(10254):839-852., Kamdar M, et al. *Lancet.* 2022;399(10343)., Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716., Wang M, et al. *N Engl J Med.* 2020;382(14):1331-1342., Berdeja JG, et al. *Lancet*. 2021;398(10297)., Rodriguez-Otero P, et al. *N Engl J Med*. 2023;388(11):1002-1014., San-Miguel J, et al. *N Engl J Med*. 2023;389(4)., Bal S, et al. *Blood.* 2024;144(suppl 1):922,

Institutional Infrastructure Needs for OP Administration: Dedicated Space or Bed Availability

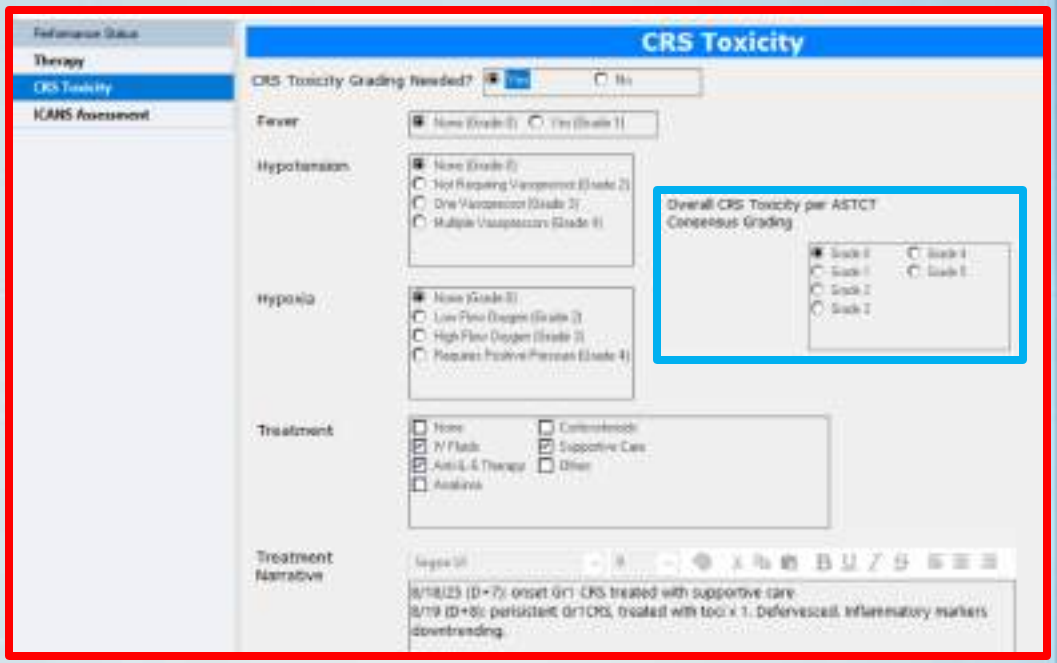


Toxicity Strategies for Outpatient CAR-T Administration



Considerations for CAR-T Toxicity Monitoring in OP Setting

- Utilize consult services at baseline to identify existing concerns
  - o Infectious disease, social work, neurology, etc.
- Create standardized EMR form for daily assessment (CRS/ICANS)
  - o Documentation is vital for effective and timely interventions
- Develop institutional criteria/monitoring protocols that are product/disease specific
  - o Eligibility for OP CAR-T vs. early transition to OP
  - o Create transition of care email group with all stakeholders
- Standardize monitoring requirements during OP CAR-T visits and at home



Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142.

Protocol Considerations for Prompt Escalation of Care

Determine institutional guidance of expected AE's that can be managed in OP setting

- Low-grade CRS, cytopenia's, neutropenic fever, etc.

Develop required IP treatment/monitoring Criteria

- Any Gr. 2 or higher CRS or any ICANS should trigger admission (obs status)

Streamline intake process for IP admission when needed

- Transparency of clinical status: EMR handoff tools, sign-outs, etc.
- Electronic notification tools including all stakeholders
  - o Chat/email groups for timely notification

Obs: observation

Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142.

ASTCT Consensus CRS Grading and Manifestations

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	**Temp ≥ 38 °C (100.4 °F)**			
With either:				
Hypotension	None	Not requiring vasopressors	One vasopressor +/- vasopressin	Multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Low-flow nasal cannula or blow-by	High-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Positive pressure (CPAP, BiPAP, intubation, and mechanical ventilation)

*Fever defined as temperature 38°C not attributable to any other cause.

- CRS patients who receive antipyretic or anti-cytokine therapy (tocilizumab, steroids, others) *fever is no longer required* to grade subsequent CRS severity
  - CRS grading driven by hypotension and/or hypoxia.

Other: Hepatic, renal, cardiovascular, pulmonary, GI, musculoskeletal, neurologic, hematologic
Note: Organ toxicities associated with CRS can be graded per CTCAE v.5 but doesn't influence CRS grading

Can progress to life-threatening vasodilatory shock, capillary leak, hypoxia and multiorgan failure

Low-flow nasal cannula: oxygen delivered at ≤6 L/minute
High-flow nasal cannula: oxygen delivered at >6 L/minute

Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-38

ASTCT Consensus ICANS Grading and Manifestations

ICE Score	
Task	**Points**
Orientation: orientation to year, month, city, hospital:	4
Naming: ability to name 3 objects	3
Following commands: ability to follow simple commands (e.g., show me the TV remote)	1
Writing: ability to write a standard sentence	1
Attention: ability to count backwards from 100 by 10	1

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)
Level of consciousness%	Awakens spontaneously	Awakens to voice	Awakens tactile stimulus only	Unarousable or requires vigorous or repetitive stimuli to arouse; Stupor or coma
Seizure	N/A		Any clinical seizure 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
Motor findings	N/A			Deep focal motor weakness (hemiparesis or paraparesis)
Elevated ICP/cerebral edema	N/A		Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; or cranial nerve palsy; or papilledema; or Cushing's triad

*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but patient with an ICE of 0 may be classified as grade 4 ICANS if unarousable
%Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication)

ICE score: Immune Effector Cell-Associated Encephalopathy
ICP: intracranial pressure, ICE: Immune effector cell associated Encephalopathy

Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-38

Principles of Toxicity Management: No Universal Guideline for Toxicity Management

Protocols vary by institution

- Rates of CRS/ICANS vary among products, disease, and patient characteristics
- Appropriate screening per institutional standards
- Baseline labs: CRP, ferritin, CBC/CMP, coagulopathy, and TLS labs

CRS:

Immune activation correlates with CAR expansion and elevations inflammatory markers and cytokines

- Symptomatic management of mild CRS is universal and relies on supportive care measures
- **Tocilizumab: 1st line treatment for CRS**
- Steroids typically reserved for tocilizumab-refractory CRS
- Alternative anti-cytokine therapy may be needed in refractory setting

ICANS

- Tocilizumab not effective
  - Does not penetrate CSF
  - May increase IL-6 levels and worsen ICANS
- **Corticosteroids: 1st line treatment**

CBC: complete blood count, CMP: comprehensive metabolic panel, CSF: cerebrospinal fluid, IL: interleukin

Santomasso BD, et al. *Cancer Discov*. 2018 Aug;8(8):958-971., Hay KA, et al. *Blood*. 2017;23;130(21):2295-2306., Maus MV, et al. *J Immunother Cancer*. 2020;8(2):e001511.

Toxicity Algorithms and Interventions

CRS onset usually within 1st week after CAR T-cell therapy (peaks within 1-2 weeks)

- #1 is to rule out other etiologies: infections vs. comorbidity flare vs. drug induced

ICANS can be biphasic and occur during CRS and/or present as late or delayed events

- Patients with ICANS should receive AED (if not given prophylactically) + appropriate CNS imaging/EEG monitoring

Gr.	CRS	ICANS	CRS + ICANS
1	Scheduled APAP x 24hrs ± Toci*≠	Supportive care (± dex)*	Supportive care (± Toci)*
2	Toci ± Dex	Steroids (dex)	Toci + dex
3	Toci + steroid +/- ICU transfer¥	Steroids (dex or MP); Consider ICU transfer	Toci + dex or MP
4	Toci + steroid¥ + ICU transfer	High-dose MP until Gr 1; ICU/critical care∞	Toci + High-dose MP; ICU/critical care∞

Steroid dosing: dexamethasone (10-20mg), HD steroids: MP (500-1000mg)

Special Considerations:

- * Toci for frail/elderly and those with persistent fever > 72hrs
- ≠ Toci (+/- dex) for high-risk for progression to severe toxicities (dz. Burden, CD28 product, age/comorbidities)
- ¥ Consider refractory (MP IV with rapid taper) +/- other anti-cytokine therapy (e.g. anakinra or emapalumab)
- ∞ If life threatening, consider use of anakinra, emapalumab, cyclophosphamide or IT chemo

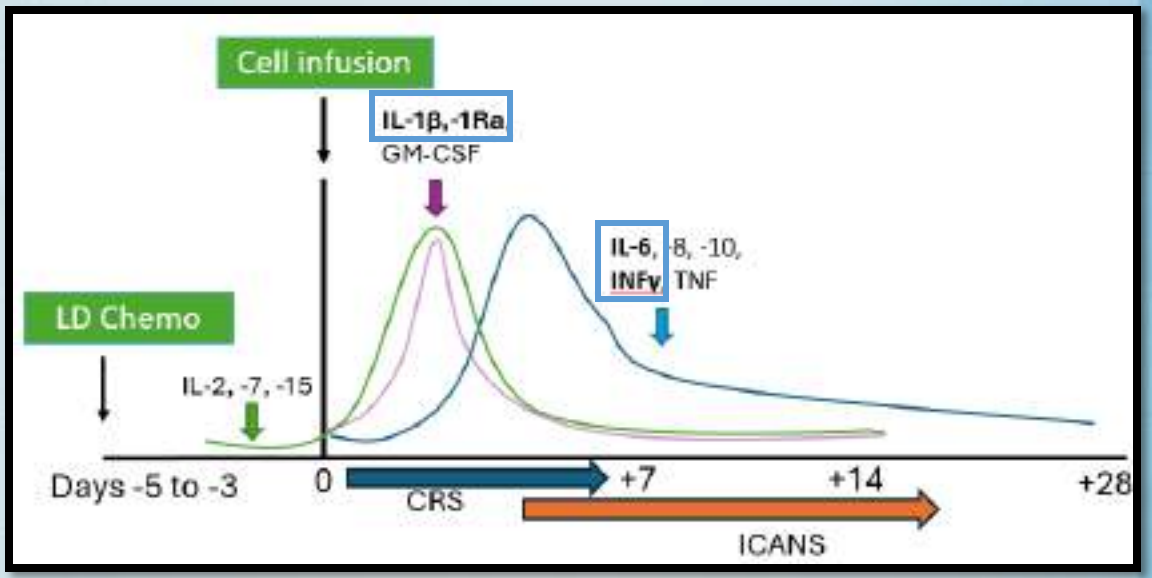
AED: antiepileptic drug, EEG: electroencephalogram, toci: tocilizumab, HD: high-dose, MP: methylprednisolone

Lee DW, et al. *Blood.* 2014;124:188-95., Lee DW, et al. *Biol Blood Marrow Transplant.* 2019 Apr;25(4):625-638, Neelapu S, et al. *Nat Rev Clin Oncol*. 2018;15:47-62., Maus MV, et al. *J Immunother Cancer*. 2020 Dec;8(2):e001511.,Santomasso BD, et al. *J Clin Oncol*. 2021 Dec 10;39(35):3978-3992., Dholaria BR, et al. *BioDrugs*.2019;33(1):45-60.

Using Anti-cytokine Therapies Wisely

	Tocilizumab	Siltuximab	Anakinra	Emapalumab
Description	**Anti-IL-6 receptor** mAb	**Anti-IL-6** mAb	**IL-1 receptor antagonist** (IL-1Ra)	**Anti-IFNγ** mAb
MOA	Inhibits IL-6 mediated signaling by **binding to IL-6R**	**Binds to soluble IL-6** inhibits both soluble & membrane bound IL-6R	Inhibits **binding of IL-1** to its receptor	**Binds free/ receptor-bound IFNγ**, preventing JAK/STAT pathways signaling
Dose	< 30kg: 12 mg/kg vs. ≥30kg: 8mg/kg 800mg (max) q8hr, 4 doses total	11mg/kg (max 1 dose/21 days)	**Highly variable dosing** ~100-200mg IV q6hr (IV q6= SQ q8) Consider max 7 days, (dosing up to 12 mg/kg/day)	1mg/kg (1-dose) Note: use extrapolated from primary HLH indication
Admin	IV over 1hr	IV over 1hr	SQ or IV push over 1-3 minutes	IV over 1hr

Timescale for CRS/ICANS Onset and Relative Cytokine levels in Peripheral Blood



MOA: mechanism of action, mAb: monoclonal antibody, r: receptor, IV: intravenous, SQ: subcutaneous, hr: hour, JAK/STAT: Janus kinase/signal transducer and activator of transcription, IL-1Ra: IL-1 receptor agonist (IL-1Ra), GCSF: granulocyte–macrophage colony-stimulating factor, IFNγ: interferon-γ, TNF: tumor necrosis factor, Admin: administration

Neelapu S, et al. *Nat Rev Clin Oncol*. 2018;15:47-62., Jain MD, et al. *Blood*. 2023 ;18;141(20):2430-2442., Rainone M, et al. *Blood Adv* 2023; 7 (4): 533–536., Rainone M, et al. *Blood Adv.* 2023. 7:533–6., ACTEMRA® [package insert]. San Francisco, CA; Genentech, Inc.; August 2017., Sylvant ® [package insert]. Bridgewater, NJ: Recordati Rare Diseases Inc; June 2024., Kineret ® [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; September 2024., Gamifant [package insert]. Waltham, MA: Sobi Inc; July 2024., Manghisi, et al. *Front. Immunol* 2025;16:1563736., Image adapted/recreated from Morris EC, et al. *Nat Rev Immunol* 2022. 22, 85–96.

Risk Adaptive Approaches To Mitigating Severe Toxicities

Risk-Adapted dosing: dosing based on disease burden and/or splitting cell doses

Obe-cel (CAT19-CD19) CAR-T

Holding of infusion if CRS/ICANS

- Real-time dose modifications

Adjusting affinity of binding domain for controlled antigen stimulation

Obe-cel CAT19 scFv

Future Directions:

- Controlled T-cell proliferation 4th and 5th generation CARs
- Logic-gating techniques

Prophylactic/Pre-emptive steroids or anti-cytokine therapy

- Dexamethasone (corticosteroid)
- Tocilizumab (IL-6R antagonist)
- Siltuximab (IL-6 antagonist)
- Anakinra (IL-1R antagonist)
- Emapalumab (INFy inhibitor)
- Infliximab (TNFα inhibitor)

Bui TA, et al. eBioMedicine. 2024;106: 105266., Rankin AW, et al. *Cancer Metastasis Rev*. 2024 Dec 15;44(1):17.

What prophylactic strategies can be used for high-risk CAR-T patients?

a. Tocilizumab + dexamethasone given Day -2
b. Dexamethasone given on Day 0, +1 and +2
c. There are no prophylaxis strategies at this time as it may impact CAR-T efficacy
d. Ibrutinib given on Day 0, +1 and +2

Early Intervention or Prophylactic Strategies to Mitigate CRS Toxicities without Compromising Efficacy

Prophylaxis
• Tocilizumab (Day 0 or Day +2)
• Dexamethasone 10 mg (Days 0, +1 and +2)
• Anakinra given on (Days 0, +1 and +2) or extend up to Day +7
• Anakinra given at 1st fever (or Day +2) up to minimum of 10 days

Pre-emptive Intervention (as early as Gr. 1)
• Dexamethasone
• Tocilizumab
• Anakinra
• Combination of Toci + Dex

Concurrent TKI in LBCL
Ibrutinib (BTK Inhibitor)
Itacitinib (JAK 1 Inhibitor)
Pirtobrutinib (BTK Inhibitor)**

***NCT06553872 in MCL treated with brexu-cel*

Oluwee OO, et al. *Br J haemtol*. 2021;194:690-700., Park JH, et al. *Nat Me*d. 2023;29:1710-1717., Jain M. *Blood.* 2023; *141*(20), 2430-2442., Strati. *Blood Adv*. 2023;7 (21): 6785–6789., Gardner RA, et al. *Blo*od. 2019;134(24):2149-2158, Kadauke S, et al. *J Clin Oncol*. 2021 Mar 10;39(8):920-930., Caimi PF, et al. *Front Immunol*. 2021;12:745320., Kadauke S, et al. *J Clin Oncol*. 2021;39(8):920-930., Topp MS, et al. *Br J Haematol*. 2021;195(3):388-398., Zurko JC, et al. *JAMA Oncol*. 2022;8(5):773-775., Gauthier J, et al. *Blood.* 2020;135(19):1650-1660., Pratta M, et al. *Blood.* 2022;140(Suppl 1):10350-10351., Frigault, MJ, et al. *Blood.* 2025; 46(4):422–436., Miklos DB, et al. *Target Oncol.* 2025 Mar;20(2):217-234., Wierda WG, et al. *Blood.*2024;144 (Supplement 1):887.

Role of **CAR-HAEMATOTOX (HT) score** and Opportunity for Early Intervention/Supportive Care

Clinical utility of CAR-HT as a validated predictive tool

- Baseline patient characteristics used to evaluate for risk of CRS/ICANS + other complications
  - Risk stratification for severe infections, neutropenia and disease progression
  - The ALL HT omits ferritin for disease burden
- Online calculator for CAR-HT: https://www.european-mcl.net/home/scores-car-hematotox-286.html

Anticipate patient needs/allocating resource and guiding toxicity management

- Potential role in guiding escalation of anti-infective prophylaxis (+/- use early G-CSF use and stem cell boost)
- Role for prophylactic strategies (day 0-2) in high-risk patients
- Plan for early intervention strategies

CAR-HT Scoring			
Baseline features	**0 points**	**1 point**	**2 points**
Platelet count	>175K	75-175K	<75K
ANC	≥1200	<1200	-
Hemoglobin	≥9.0	<9.0	-
CRP	<3.0	≥3.0	-
Ferritin	<650	650-2000	>2000
Low risk (HT^{low}): 0-1 high risk		**(HT^{high}): ≥2 (maximum 7)**	

ALL-HT Scoring			
Baseline features	**0 points**	**1 point**	**2 points**
Platelet count	> 175k	75-175k	< 75k
ANC	> 1200	< 1200	
Hgb	> 9	< 9	
CRP	< 3	> 3	
BM blasts	**< 5%**	**5-25%**	**> 25%**
Low risk: 0-3 points		**High risk: ≥ 4 points**	

k: thousand, G-CSF: Granulocyte Colony-Stimulating Factor

Rejeski K, et al. *Blood*. 2021;138(24):2499-513., Rajeski K, et al. *J Immunother Cancer*. 2022; 10(5): e004475., Rejeski K, et al. *Blood*. 2023;142(10):865-877.

General Monitoring Strategies for Acute Toxicity

Monitoring for CRS: onset usually within 1st week

- Close hemodynamic monitoring
- Monitor labs for organ dysfunction and inflammatory markers (ferritin/CRP)
- Initiate a full infectious workup and rapid implementation of anti-infective agents upon first signs of fever

Monitoring for ICANS: Manifestations can vary by product and occur up to Day +30

- Waxing and waning of symptoms
- ICE assessments at least twice daily (~14 days)

Tools to increase touchpoints

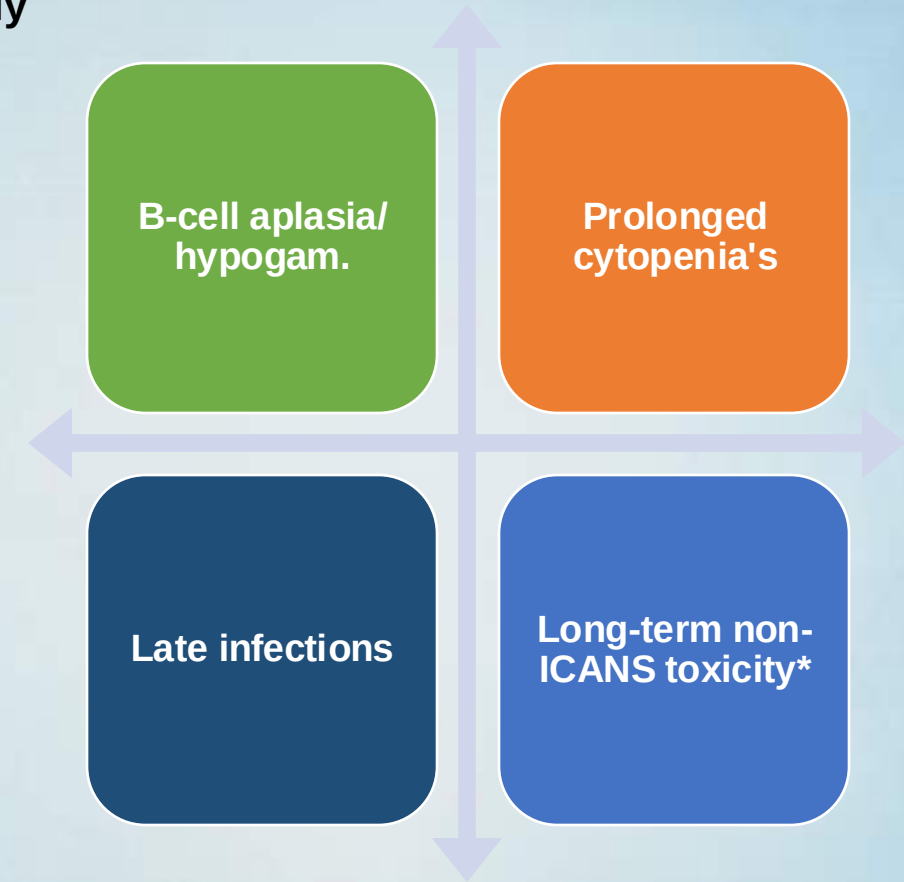
- Telehealth visits
- Post-visit phone calls
- Remote patient monitoring devices
  - Capacity to continually monitor temperature, pulse, respiratory rate and O_2 saturation
  - Can be utilized to decrease caregiver burden

SOC: standard of care, O: oxygen

Frey N, Porter D. *Biol Blood Marrow Transplant*. 2019;25(4):e123-e127., Raveeje S, et al. *Blood*.2023; 142 (Supplement 1): 1007, Lee. *Biol Blood Marrow Transplant*. 2019;25:625., Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15:47-62. Santomasso BD, et al. *Cancer Discov*. 2018;8:958–71., Oluwole OO, et al. *Transplant Cellular Ther*. 2024. Feb;30(2):131–142

General Monitoring/Supportive Care Strategies for Delayed Toxicity

- **Late onset toxicities are typically managed by treating facility or locally**
  - Supportive care strategies can be instrumental to reduce morbidity/mortality
- **B-Cell Aplasia/Hypogammaglobulinemia**
  - Check IgG levels monthly, then Q3-6mo
  - Administer IVIG if IgG levels < 400 mg/dL or < 600 mg/dL + recurrent infections
- **Hematologic toxicity with prolonged cytopenia's (ICAHT)**
  - Etiology multifactorial; Categorized as mild (Gr. 1), moderate (Gr. 2), severe (Gr. 3) and life-threatening (Gr. 4) categories
  - Managed with growth factor + other therapies
- **Late infections**
  - Ensure empiric antimicrobial are prescribed during neutropenia
    - As early as clearance day



ICAHT: Immune Effector Cell-Associated Hematotoxicity
*Product specific risk most associated with BCMA-directed CAR-T

Rejeski K, et al. *Blood.* 2023;142(10):865-877., Jain, et al. *Blood. 2023;*141.20: 2430-2442., Hill JA, et al. *Blood.* 2020; 20;136(8):925-935., Chakraborty R, et al. *Transplant Cell Ther.* 2021 Mar;27(3):222-22

Supportive Care Medications: Infection and Other Prophylaxis

TLS/Seizure	Antibacterial	Antiviral	Antifungal	
Allopurinol in high-risk patients • Higher BM burden, WBC and/or LDH (≥ 2000 U/L), etc. **Seizure prophy** Designated day pre-cells (e.g., D -1) • At time of neurologic toxicity	Recommended for patients with high risk of infections • Prophy may be considered once ANC is <500/µL	**VZV prophy in all patients** • LD up to 6+ months post-CAR-T and/or until CD4+ count is >0.2 × 10^9/L	**PJP prophy recommended** • LD or D+30 up to 6+ months post-CART and/or until CD4+ count is >0.2 × 10^9/L	**Antifungal prophy recommended** • Fluconazole/micafungin once ANC is <500/µL • Mold-active azole: high risk of IFI • High CAR-HT score, history of IFI, prolonged neutropenia, use of anti-cytokine therapy +/- steroids)

Prophy: prophylaxis, Infxn: infection, VZV, varicella virus, PJP: pneumocystis *jiroveci* pneumonia, IFI: invasive fungal infection

Jain T., et al. *Blood*. 2023; 141(2): 2460-68, Haidar G, et al. *Curr Opin Infect Dis*. 2020;33(6):449-457., Maus MV, et al. *J Immunother Cancer*. 2020 Dec;8(2):e001511., Shahid Z, et al. *Transplant and Cell Ther*. 2024;30 (10):955-969., Einarsdottir S, et al. *Blood Cancer Journal*. 2025; 15:114.

Summary of Strategies to Improve Toxicities in OP Setting

Risk-adapted Toxicity Management Protocols: Development of SOP's for early detection and intervention of CRS/ICANS

Patient/Product Specific Approach: Assess individualized risk of severe complications + predictability of toxicities to promote delivery of CAR-T in OP setting while preserving patient-centric care

Optimize Resource Utilization: Minimize cost burden by favoring OP CAR-T delivery and accelerated discharge pathways while limiting IP stays to manage severe toxicities where possible

It Takes a Village

- Nursing
- Data Manager
- Financial Counselor/Case Manager
- Pharmacy Team
- ED/Urgent Care Team
- Apheresis/ CAR-T Lab Personnel
- Social worker
- Consult Services
- Physician/APPs
- Cell Therapy Coordinator

Multidisciplinary Team

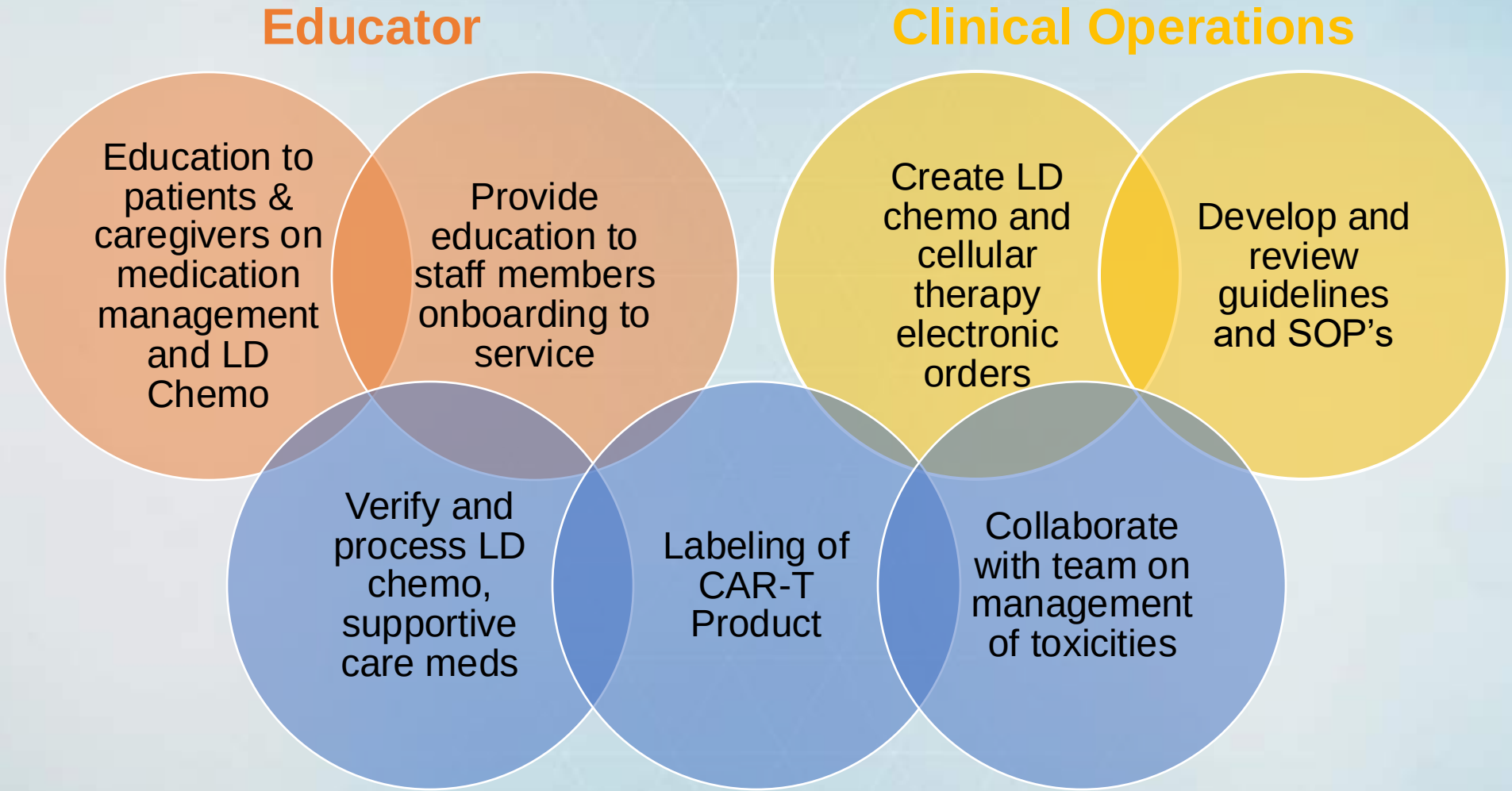
Alexander M, et al. *Transplant Cell Ther*. 2021;27:558-570., Gatwood K, et al. *Clin Hematol Int*. 2024;6(2): 1-20.

Key Roles of OP Multidisciplinary Team

Specialty	Key Roles/Responsibilities in OP Setting
Nursing	• Provide day to day clinical monitoring and supportive care services • Recognize early CAR-T associated toxicities • Effectively communicate all aspects of CAR T-cell therapy to patients and families, and answer patient questions
APPs/ Providers	• Recognize the unique needs of patients receiving CAR T-cell therapy • Follow CRS/ICANS management algorithms, and administer interventions early • Communicate timely and efficiently with all CAR-T team members and consultative services
Case Managers	• Ensure support for high-cost medications • Assist with transitions of care from OP to IP when needed • Arrange supportive services including home health, PT/OT, etc.
Social workers	• Arrange lodging, transportation, and reimbursement assistance • Provide emotional support to patients and caregivers

PT: physical therapy, OT: occupational therapy

Clinical Pharmacists: The Swiss Army Toolkit of OP CAR-T



Clinical and Operational Considerations

Patient

- Limited comorbidities, PS >90, ECOG 0-1
- Reliable caregiver
- Transportation to and from center

Product/ disease burden

- Stable disease without concern for severe CRS/NT
- Predictability of toxicity timeline

Institutional

- OP bed/chair availability
- Access to 24/7 on-call care team for in-person or telemed evaluation
- Multidisciplinary trained staff

Protocols/ SOPs

- Dedicated cellular therapy coordinators /logistics team
- Seamless transition of care from OP to IP setting

Myers GD et al. *J Immunother Cancer*. 2021;9(4):e002056; Mikhael J, et al. *JCO Oncol Pract*. 2022.Dec;18(12):800–807., Hansen, et al. *Front Immunol.* 2024 Feb 21–24;15:1405452., Perez A, et al. *Front Immunol.* 2024;15:1412002. Gatwood K, et al. *Clin Hematol Int.* 2024;6(2): 1-20.

QUESTION 3

Which of the following components is MOST critical to ensuring patient safety in an outpatient CAR-T program?

a. Clearly defined roles for each member of the multidisciplinary team
b. Standardized workflow for patient monitoring and escalation
c. Established protocols for managing cytokine release syndrome and neurotoxicity
d. All of the above

Best Practices for Institutional Operational Considerations

Regular Meetings	Education of Support Service	Development of SOP's and Workflows	Staff Education	Quality Control/Metrics
• Include clinical and ancillary members • Cost/benefit review • Workflow re-eval	• Emergency Department • Urgent Care • ICU	• Patient selection • Monitoring frequency • Admission procedure • Toxicity Management	• Clinical Standards • Grand rounds • Lecture series • Onboarding boot camp for new hires	• EMR/SOP variances • Safety/efficacy Analysis • Drug-use evaluations • CIBMTR Reporting • FACT compliance

Eval: evaluation, ICU: intensive care unit, FACT: Foundation for the Accreditation of Cellular Therapy

Alsina M, et al. *Future Oncol*. 2025;21(10):1137-1144., Alexander M, et al. *Transplant Cell Ther.* 2021;27:558-570., Gatwood K, et al. *Clin Hematol Int*. 2024;6(2): 1-20.

Multidisciplinary Standard Operating Procedures and Guideline Development

Devise comprehensive procedures + product-specific guidelines for OP

Leverage shared digital platforms for easy access to latest protocol

Complete detailed education for all staff on recognition of CAR-T toxicities and AE management

Review procedures of care escalation

Create process to recognize and intervene with prophy measures

Provide refresher training (new hires and cross covering staff)

Attend multidisciplinary meetings and educational sessions to assist with knowledge gaps and skills

Tumor boards

SOP development

Lecture series/ Conferences

Participate in QI initiatives

Continually optimize protocols in response to quarterly (or event-driven) protocol-review meetings with key stakeholders

Establish a formal document-control system

Hansen DKD, et al. *Front Immunol*. 2024. Feb 21–24;15:1405452, Perez A, et al. *Front Immunol*. 2024;15:1412002.

QI : quality improvement

Moffitt Cancer Center CAR-T Structure

Designated 8 bed outpatient infusion center for CAR-T plus 24 bed/chairs in BMT infusion clinic (shared with CAR-T) – Open everyday (~7AM-7PM)

Attending CAR-T Provider On Call

2 Nocturnist APPs (shared BMT/CAR-T)

Monitored Triage Line 24/7

Designated 2-3 APPs for OP CAR-T Management

Designated OP CAR-T Clinical Pharmacist

CAR-T clinics (Mon-Fri)

Direct admit process

Cell Therapy Facility (1-2) – available everyday

Patient/ caregiver monitoring kits

18 dedicated CAR-T RNs

Day in the Life of an Example OP CAR-T Service Line

- Education by provider, nurse coordinator and/pharmacist
- **Clearance by social work, financial and/or consult services** (ID, neuro, cards)

Pre-LD: Completion of VOT's +/-bridging

- Baseline labs, imaging and treatment course review, line placement
- Review of home medications
- **Prescribing of CAR-T related supportive care medications**

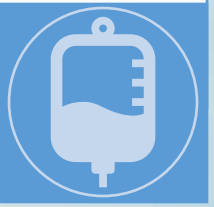
Day -6: Clearance day completed by provider, APP and clinical pharmacist

- **Daily labs +/- APP visit**
- Clinical pharmacist to review ongoing LD toxicity

Day -5 through -3: Lymphodepleting chemotherapy

- Collaboration between RN, cell therapy and clinical pharmacist for release of pre-medications and product labeling
- Clearance by provider
- **If needed: initiation of prophylactic measures (dex, anakinra, other)**

Day 0: Cell infusion



Coordination of Care for OP Monitoring: Standardized but Individualized

Create designated follow-up protocols for frequency of visits conducted by RN, APP +/- Provider in OP setting

- On clearance day [D-6] and cell infusion [D0] (Provider and Clinical Pharmacist Required)
- Structured expectations for daily OP monitoring (labs/VS at minimum)
  - Nursing assessment (Q4hr VS with ICE assessments during acute window)
    - Reinforcing responsibilities of care to patient/caregiver
  - Visit by APP +/- Provider

Frequency/duration based off CRS/ICANS timeframe

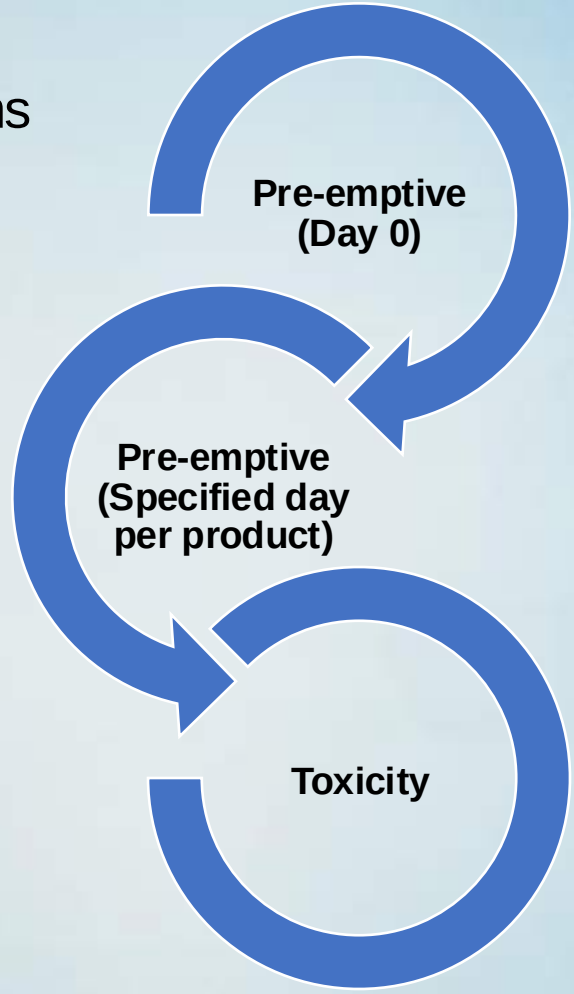
- Designate number of daily visits (~7-14 days) for appropriate chair/bed scheduling
  - e.g. cilta-cel: daily monitoring D0 through D+10 vs. obe-cel or brexu-cel for ALL patient: D0 through D+14
- Early transition discharges to OP setting
  - Email communication to key members (RN, APP leadership or designee) to accept candidate
    - Ensure OP capacity, staffing and medical suitability

VS: vital signs

Institution Infrastructure: Triaging and Admissions

Given approximately 30-50% of all OP treated patients may need an admission for CAR-associated toxicities and/or infection complications

- **Ensure adequate staffing for continuity of care**
  - ✓ Dedicated triage line to report after-hours medical issues
  - ✓ Dedicated/knowledge providers on call 24/7
    - ✓ Fellows, residents, hospitalists, APP's
- **Hospital bed access for escalation of care**
  - ✓ Direct admit from OP
  - ✓ Transfer from ED or Urgent Care



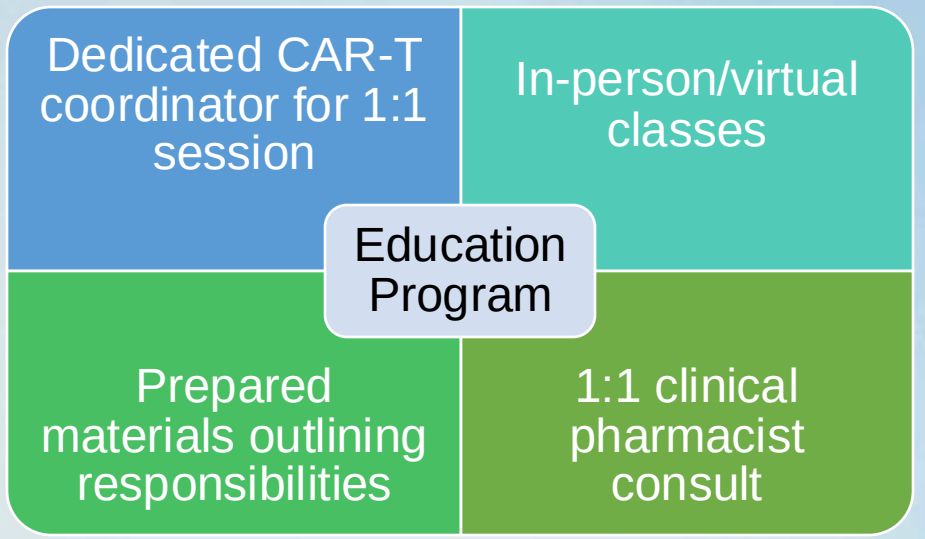
ED: emergency department

McGann M, et al. *Transplant Cell Ther*. 2022;28(9):583-585 ,Gatwood K, et al. *Clin Hematol Int*. 2024;6(2): 1-20.

Patient and Caregiver Education Enhances Safety and Boosts Adherence to Clinical Protocols

- **Step 1:** Effective communication and understanding of caregiver responsibility for close patient monitoring
  - ✓ Need for 24-hour care and proximity to center for at least 2 weeks after treatment
  - ✓ Have a plan to ensure there are no gaps in caregiver availability

- **Step 2:** Patients/caregivers educated about the common AEs of CAR-T and when to seek care or treatment
  - ✓ Both trained in use of thermometer/blood pressure cuff
  - ✓ Provide checklists, wallet cards, etc. in case of transfer from outside facility



What to do in the event of an adverse event

Taylor L, et al. *Clin J Oncol Nurs*. 2019;23(2):20-26, Alsina M, et al. *Future Oncol*. 2025;21(10):1137-1144., Hansen DKD, et al. *Front Immunol*. 2024. Feb 21–24;15:1405452.

New Changes to REMS Mandate for CAR-T Products: **Reducing Barriers to Access and Regulatory Burden**

Pros	Cons	Potential Solutions
Removes requirement to maintain **special certification** and on-site, **immediate access to Toci**	Shifts responsibility for CRS/ICANS management onto institution's standard protocols (variable practices)	• Development of SOP's based upon current best practice GL • Robust toxicity surveillance and rapid-response infrastructure
Streamlines product labeling: safety information through BBW/med guides vs. separate REMS program	Without REMS-driven central oversight, data on rare or late toxicities may decline	• Standardize documentation & feedback to improve/support data capture • Ongoing QI metrics

BBW: black box warning, GL: guidelines

FDA Eliminates Risk Evaluation and Mitigation Strategies (REMS) for Autologous Chimeric Antigen Receptor CAR T cell Immunotherapies. Accessed August 16, 2025, from: https://www.fda.gov/news-events/press-announcements/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor., Abid MB, et al. *Transplant Cell Ther*. 2025:S2666-6367(25)01326-0.

New Changes to REMS Mandate for CAR-T Products: **Reducing Barriers to Access and Regulatory Burden**

Pros	Cons	Potential Solutions
Reduces administrative burden and $, potential increase in community referrals and **improvement in access**	Complacency over time, with less frequent refresher training on CAR-T toxicities and mitigation strategies	• Use ongoing educational sessions to highlight recognition of CRS and ICANS grading, symptoms and intervention
Shortens patient monitoring windows in updated labels • Driving restrictions 8→ 2 weeks • Proximity requirement 4→ 2 weeks	Removes a formal safety "check" that previously ensured meeting uniform standards	• Implement routine virtual check-ins from day 0–14 if not seen in person

FDA Eliminates Risk Evaluation and Mitigation Strategies (REMS) for Autologous Chimeric Antigen Receptor CAR T cell Immunotherapies. Accessed August 16, 2025, from: https://www.fda.gov/news-events/press-announcements/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor., Abid MB, et al. *Transplant Cell Ther*. 2025:S2666-6367(25)01326-0.

Summary: One Step Closer in De-centralizing Access to CAR-T

- OP CAR-T broadens care access, eases burden, and boosts satisfaction
- Enhanced toxicity detection, risk assessment, and early management makes OP delivery feasible
- Eligibility for OP administration hinges on patient and product safety criteria so choose wisely
- Successful implementation requires several components including knowledgeable personnel and clinical space
- Elimination of the REMS requirement is a shift in easing patient/caregiver burden, reducing delivery costs and enhances access equity

Reimagining CAR-T: The Outpatient Evolution

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