Allogeneic Transplant and CAR T-cell: Contrasting Cell Therapies

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March 2026

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Research Support	**N/A**
Employee	**N/A**
Consultant	**N/A**
Major Stockholder	**N/A**
Speakers' Bureau	**N/A**
Scientific Advisory Board	**Medexus Pharmaceuticals**

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Research Support	**Gilead, J&J**
Employee	**N/A**
Consultant	**J&J, Gilead, BMS, Abbvie, Astra Zeneca, Lilly**
Major Stockholder	**N/A**
Speakers' Bureau	**N/A**
Scientific Advisory Board	**J&J, Gilead, BMS, Abbvie, Lilly**

Objectives: Contrast and highlight
(Not a debate!)

1. Contrast and compare mechanisms of action
2. Greatest clinical achievement to date
3. Biggest disappointment
4. Single most concerning toxicity and mitigation strategies
5. Top challenge when counseling patients
6. Most exciting innovation expected in the next year
7. Applicability beyond cancer

Mechanism of action

Allo HCT

Allo-HCT: sequential process relying on the combined power of conditioning therapy & donor's immune system

Intensive conditioning + donor immune control; GVL is central but inseparable from GVHD risk

CONDITIONING (high-dose chemo ± TBI) → **STEM CELL INFUSION (day 0)** → **IMMUNE RECONSTITUTION (months 1–12+)**

Key evidence for GVL effect

GVHD–relapse link	T-cell depletion	DLI efficacy	RIC efficacy	Immune escape
Lower relapse in patients with GVHD	Increased relapse with TCD grafts	DLI induces remission in relapsed CML, AML	Disease control despite non-ablative doses	HLA loss, checkpoint upregulation at relapse

- MAC vs RIC: higher conditioning intensity reduces relapse but increases NRM
- Donor T cells target leukemia via histocompatibility antigens and tumor neoantigens
- Post-transplant relapse: immune evasion (HLA downregulation, T-cell exhaustion)
- Mixed chimerism + pre-emptive DLI: potent GVL without severe GVHD in select patients

Giralt et al. Blood 1997; PMID: 9192777 | Horowitz et al. Blood 1990; PMID: 2297567 | Kolb et al. Blood 1990; PMID: 2265242 | Sweeney et al. Front Oncol. 2019; PMID: 31803612 | Vago et al. NEJM 2009; PMID: 19641204

Conditioning intensity: MAC vs RIC trade-off

BMT CTN 0901: MAC offers superior OS vs RIC in AML/MDS ≤65y (HR 1.54, p=0.03)

Myeloablative (MAC)

▲ Higher cytoreduction
▼ Lower relapse rates
▲ Higher NRM (15–30%)
Preferred: fit patients <60y, MRD+

Reduced Intensity (RIC)

▼ Lower NRM (10–20%)
▲ Higher relapse rates
▲ Relies more on GVL effect
Preferred: older/comorbid, MRD−

Key clinical findings

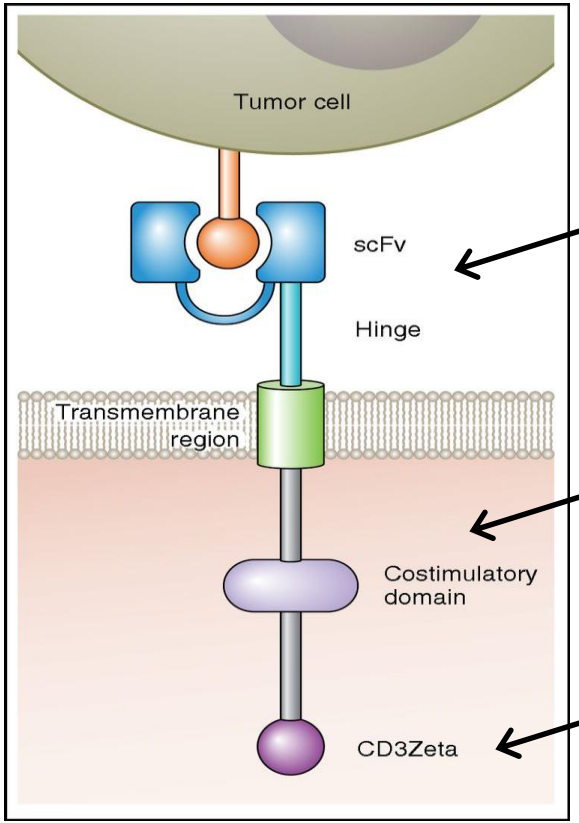
OS advantage
MAC superior OS in AML/MDS ≤65y

RIC role
Relies on donor immune control; may benefit from maintenance

Future direction
MRD-adapted conditioning intensity under investigation

Scott et al. J Clin Oncol 2017; PMID: 28380315 | Scott et al. Transplant Cell Ther 2021; PMID: 33775615

Chimeric Antigen Receptor (CAR)



Antigen-binding domain:
- scFv derived from a MoAb
- CD19, BCMA, many others

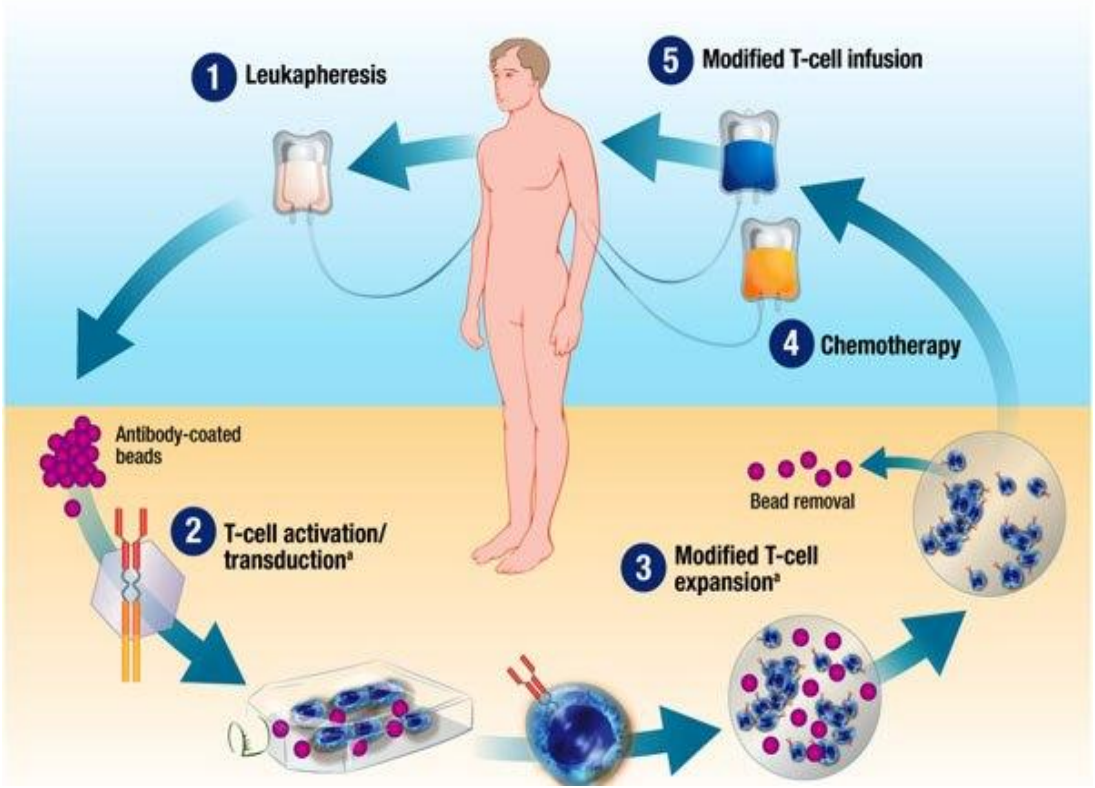
Costimulatory domains:
CD28, 4-1BB

T-cell activation domain: CD3zeta

A genetically manipulated "live" drug

Lekha Mikkilineni, and James N. Kochenderfer Blood 2017;130:2594-2602

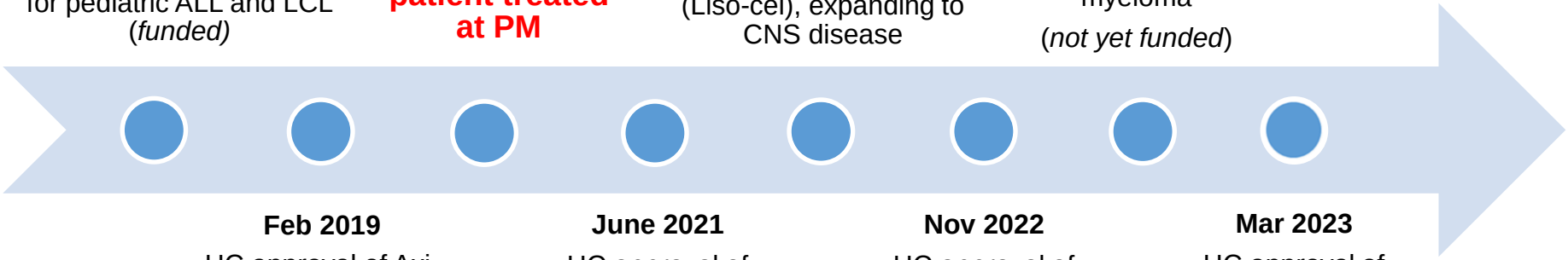
CAR T-Cell Therapy



- Complex, resource intensive pathway

- It takes a village:
  - Apheresis and cell processing lab staff
  - Specialists in handling, storage, infusion of cells
  - Expert clinicians
  - Data coordinators
  - Quality oversight
  - (External – manufacturers, couriers)

Rapid uptake of standard of care CAR T-cell therapy in Canada



September 2018
HC approval of Tisa-cel for pediatric ALL and LCL (*funded)*

Feb 2019
HC approval of Axi-cel for LCL (*funded*)

Feb 2020
First commercial CAR T-Cell patient treated at PM

June 2021
HC approval of Brexu-cel for mantle cell lymphoma (*funded*)

June 2022
HC approval for our 3rd CD19 CAR T for LCL (Liso-cel), expanding to CNS disease

Nov 2022
HC approval of Brexu-cel for adult B-ALL (*funded*)

Feb 2023
HC approval of Cilta-cel for myeloma (*not yet funded*)

Mar 2023
HC approval of second-line Axi-cel and Liso-cel for LCL (*funded*)

Currently at PM
>80 CAR T / year
Could double in next 1-2 years

UHN Princess Margaret Cancer Centre

HC = Health Canada; LCL = large cell lymphoma; FL = follicular lymphoma; ASCT = autologous stem cell transplant

What is the greatest clinical achievement to date?

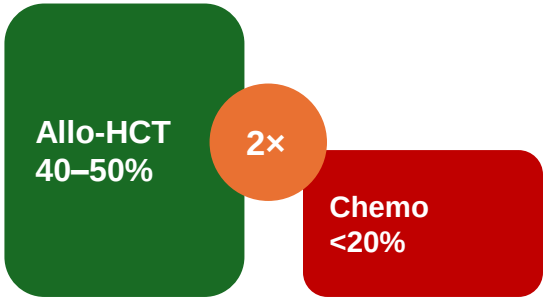
Allo HCT

Curative potential of allo-HCT in high-risk disease

Durable remission & potential cure in otherwise universally fatal disease; adverse-risk AML in CR1: ~2× OS benefit vs chemo alone

Disease	5-yr OS	Key risk features
High-risk AML	**35–55%**	Adverse cytogenetics, FLT3-ITD, TP53
High-risk ALL	**50–70%**	Ph+, Ph-like, t(4;11), MRD+
High-risk MDS	**20–40%**	IPSS-R high/very high, TP53+
Advanced MPN	**40–55%**	Myelofibrosis DIPSS≥2, accel. phase
BP-CML	**20–40%**	TKI-resistant, blast phase

Adverse-risk AML in CR1



Landmark survival

2-yr survivors: 76% AML, 81% ALL alive at 10 yrs

MRD is critical

MRD-negativity pre-HCT reduces relapse by >50%

NRM declining

2-yr NRM <20% with modern supportive care

Relapse challenge

30–50% at 5 yrs in adverse-risk; leading cause of failure

MAC preferred for fit patients <60y with active disease; RIC for older/comorbid; MRD status is the strongest predictor of post-HCT outcomes

Badar et al. Leukemia 2023; PMID: 36807649 | Bazarbachi et al. Hemasphere 2025; PMID: 40224161 | Bewersdorf et al. TCT 2021; PMID: 34052505 | Buckley et al. Haematologica 2017; PMID: 28126965 | Larue et al. Hemasphere 2024; PMID: 39440198 | Penack et al. Blood Adv 2020; PMID: 33351121 | Radujkovic et al. BBMT 2019; PMID: 31271884 | Scheid et al. BMT 2017; PMID: 28892084 | Stelljes et al. Haematologica 2011; PMID: 21459795 | Webster et al. Front Oncol 2021; PMID: 34976845

Expanding curative access: haploidentical HCT and older patients

PTCy-based haploidentical HCT and RIC regimens have expanded access to curative transplant

Haploidentical donors

- >90% of patients have HID
- PTCy-based GVHD prophylaxis
- Outcomes comparable to MUD
- Rapid donor availability

Older patients (age 60–75)

- RIC regimens enable transplant
- 2-year OS: 40–50% in selected pts
- HCT-CI remains key NRM predictor
- Expanding eligibility criteria

Cord blood (emerging)

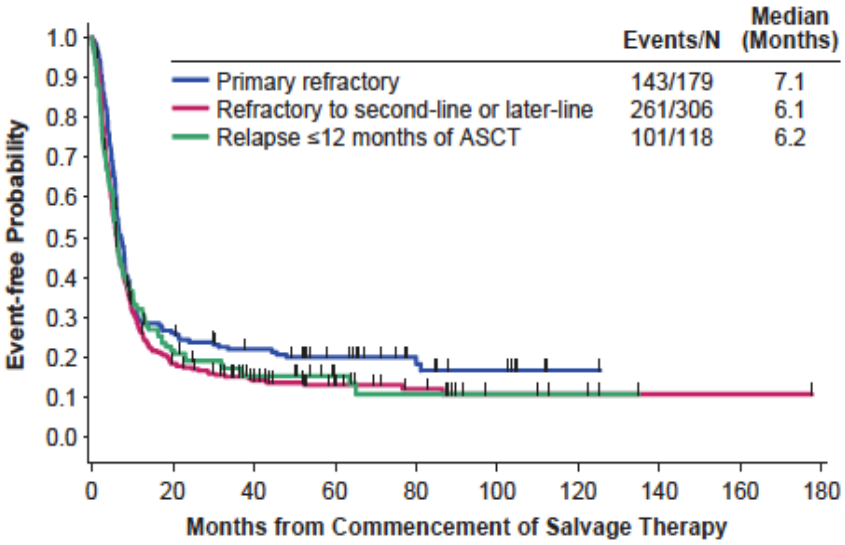
- One million units banked: rapid availability
- Lower cGVHD rates
- Improved engraftment strategies needed
- Bridge to definitive therapy

- PTCy: grade III–IV aGVHD <10%, moderate-severe cGVHD ~15%
- Age alone not contraindication: comorbidity burden (HCT-CI) more important than chronologic age
- “Transplant-eligible” definition expanding: more patients accessing curative therapy

Ciurea et al. Blood 2015; PMID: 26130705 | Di Majo et al. Bone Marrow Transplant 2025; PMID: 41023427 | Kanakry et al. J Clin Oncol 2014; PMID: 25267759 | Luznik et al. Biol Blood Marrow Transplant 2008; PMID: 18489989 | McCurdy et al. Blood 2019; PMID: 31751485 | Rocha et al. N Engl J Med 2000; PMID: 10861319 | Sorror et al. JAMA 2011; PMID: 22045765

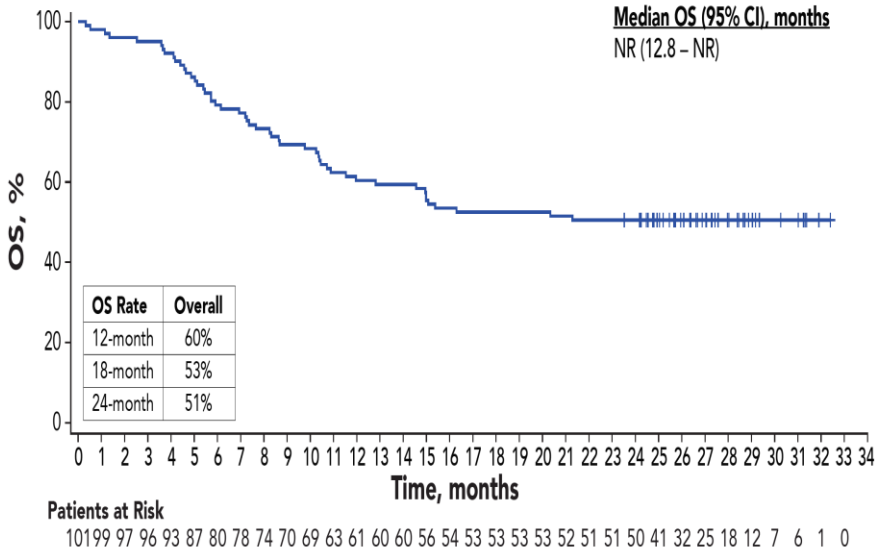
CAR T in Large B-cell Lymphoma

Overall survival: SCHOLAR-1



- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

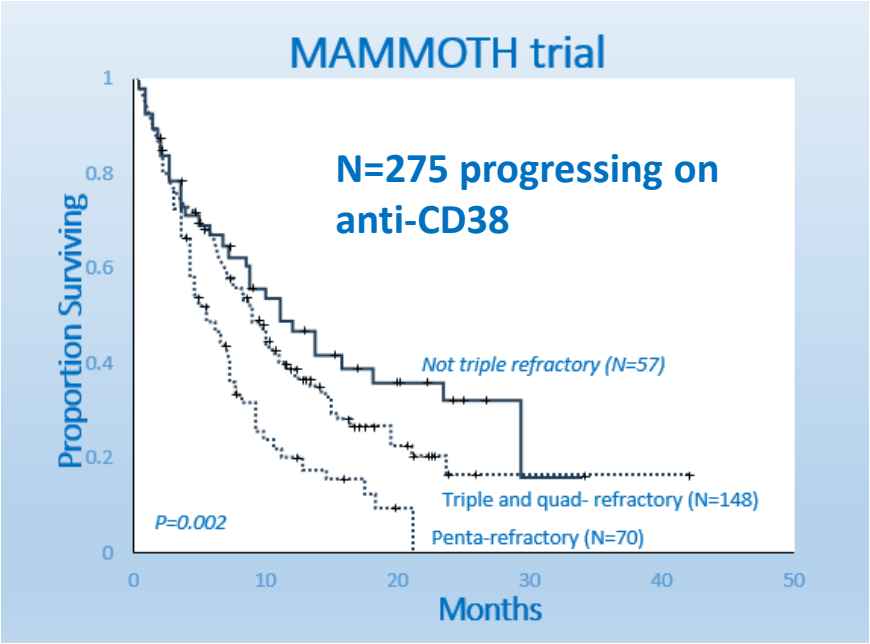
Overall survival: ZUMA-1



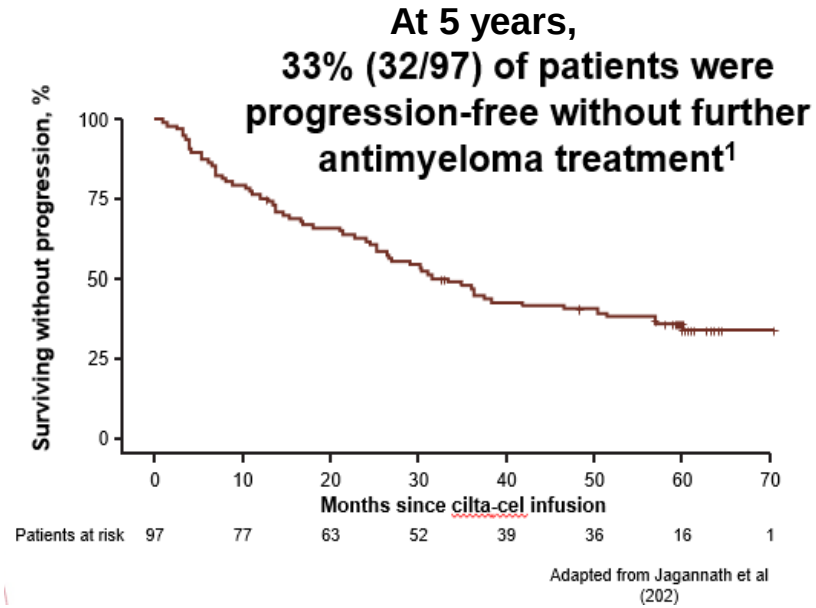
- N = 108
- ORR = 83%; CR rate = 58%
- Median OS = 25.8 months

Scholar-1 Crump et al. JCO 2016;34:7516; ZUMA-1 Neelapu et al. ASH 2017; ZUMA-1 vs SCHOLAR-1 Neelapu et al. ASH 2017

CAR T in Multiple Myeloma



Median PFS 3.4 mos, median OS 9.3 mos



Median OS 60.7 months!

Gandhi et al. Leukemia 2019;33:2266

What has been the biggest disappointment?

Post-HCT relapse: the central challenge & immune evasion

Allo HCT

Relapse accounts for 40–50% of deaths post-HCT; relapsed leukemia displays distinct immune escape features

RELAPSE 40–45%

NRM 20–25%

5-yr causes of failure

HLA loss

Somatic mutations
Transcriptional ↓
15–30% of relapses

Checkpoint ↑

PD-L1/L2, CTLA-4
TIM-3, LAG-3 ↑
Non-overlapping w/ HLA

T-cell exhaustion

Loss of functional CTL
High PD-1+ T cells
Early post-HCT predictor

↓ EVADES DONOR T-CELL RECOGNITION ↓

Relapse by risk

Adverse: 35–45%
MRD+: 40–50%
TP53+: 50–60%

Risk factors

Pre-HCT MRD+
Adverse genetics
RIC, T-cell depletion

Post-relapse OS

Median 3–6 months
Salvage DLI in select
HLA loss → DLI fails

Clinical implications

HLA alterations ↑ in haplo
CPI: GVHD risk 30–50%
Genomic Rx at relapse

Al-Ali et al. BMT 2026; PMID: 41286512 | Barnett et al. Expert Rev Hematol 2010; PMID: 21083034 | Bejanyan et al. BBMT 2015; PMID: 25460355 | Christopher et al. NEJM 2018; PMID: 30380364 | Christopher et al. BMT 2023; PMID: 37770590 | Crucitti et al. Leukemia 2015; PMID: 25371177 | Fernandez et al. Hematology ASH 2024; PMID: 39644031 | Horowitz et al. Blood 1990; PMID: 2297567 | Hourigan et al. JCO 2020; PMID: 31860405 | Kong et al. Blood Cancer J 2015; PMID: 26230954 | Magenau et al. Blood Adv 2025; PMID: 40198769 | Norde et al. Cancer Res 2011; PMID: 21659460 | Schmid et al. JCO 2007; PMID: 17909197 | Schmid et al. Blood 2012; PMID: 22167752 | Toffalori et al. Nat Med 2019; PMID: 30911134 | Vago et al. NEJM 2009; PMID: 19641204 | Zeiser & Vago. Blood 2019; PMID: 30578254

Allo HCT

Addressing relapse risk: prevention & early intervention

Pre-emptive MRD-guided approaches show promise; prophylactic maintenance has mixed results

Pre-emptive DLI	Azacitidine	FLT3 inhibitors	Checkpoint Inh.	Venetoclax+HMA
MRD/chimerism-guided Mixed chimerism, molecular relapse *Best at low tumor burden*	**Conflicting RCT data** High-risk MDS/AML (FLT3-neg) *No universal standard yet*	**Gilteritinib, sorafenib** FLT3-mutated AML *Strongest maintenance evidence*	**Promising but risky** Post-relapse salvage *GVHD risk 30–50%*	**Active investigation** MRD+, early relapse *Combination strategies*

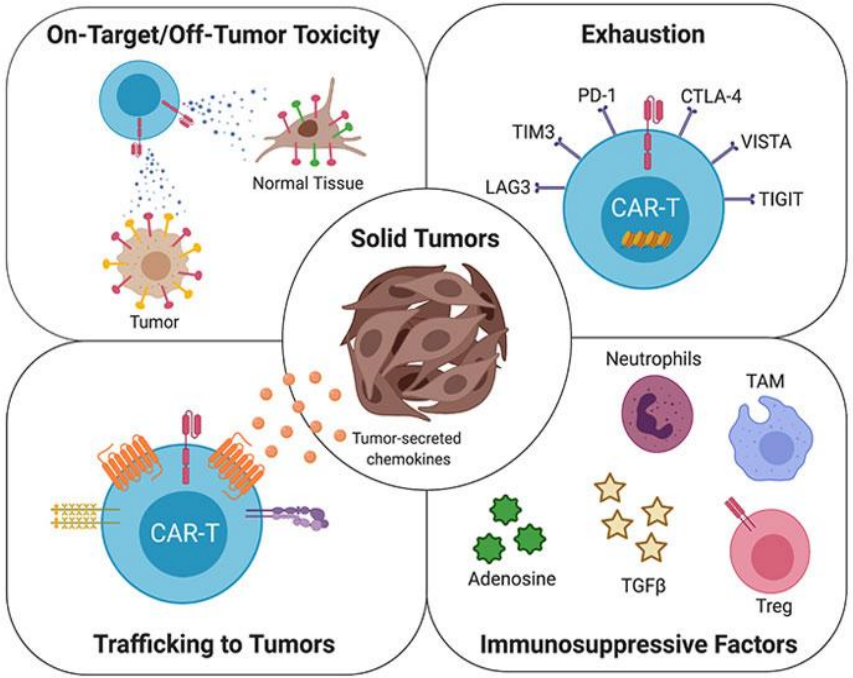
MRD monitoring	Maintenance Rx	Emerging agents
Flow cytometry, PCR, NGS enable risk-adapted intervention timing	Select patients benefit (adverse-risk, MRD+); no universal standard established	IDH inhibitors, menin inhibitors under active investigation post-HCT

Joshi et al. Blood Cancer J 2021; PMID: 33664234 | Levis et al. J Clin Oncol 2024; PMID: 38471061 | Magenau et al. Blood Adv 2025; PMID: 40198769 | Pasvolsky et al. Clin Lymphoma Myeloma Leuk 2024; PMID: 38403505 | Schmid et al. Bone Marrow Transplant 2022; PMID: 34750562

Suboptimal efficacy in CARs for solid tumor

Lack of tumor-specific antigens and antigenic heterogeneity

Lack of optimal signaling and physical barriers

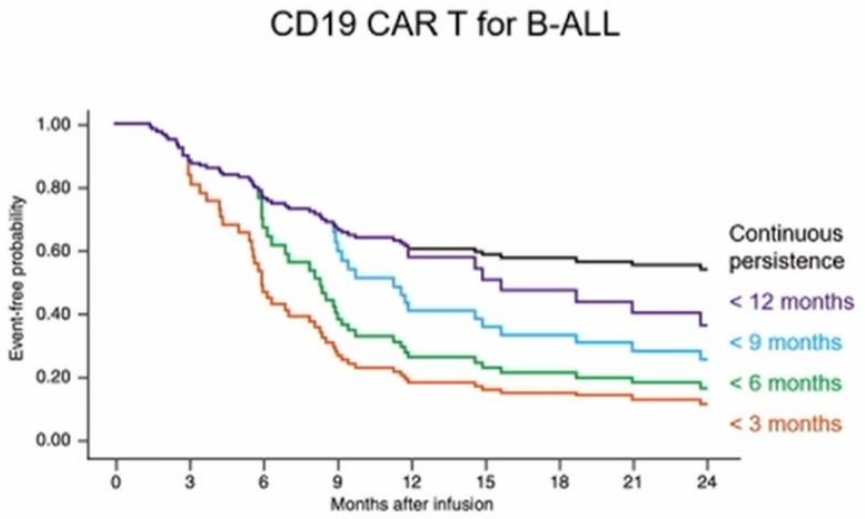


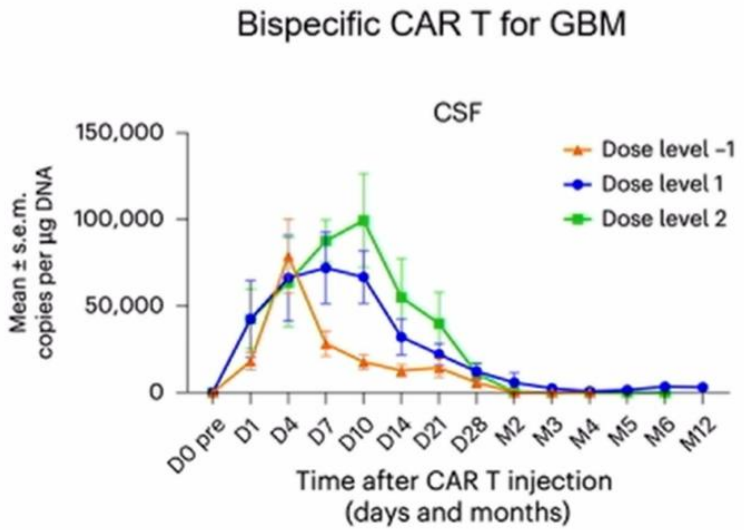
Poor substrate for autologous CAR T production

Hostile tumor microenvironment

Adapted from Srivastava and Riddell, Journal of Immunology. 2018;200(2):459-468.

CAR T cell persistence is short in solid tumor





Pulsipher et al. *Blood Cancer Discov* 2021
Bagley et al. *Nat Med* 2024

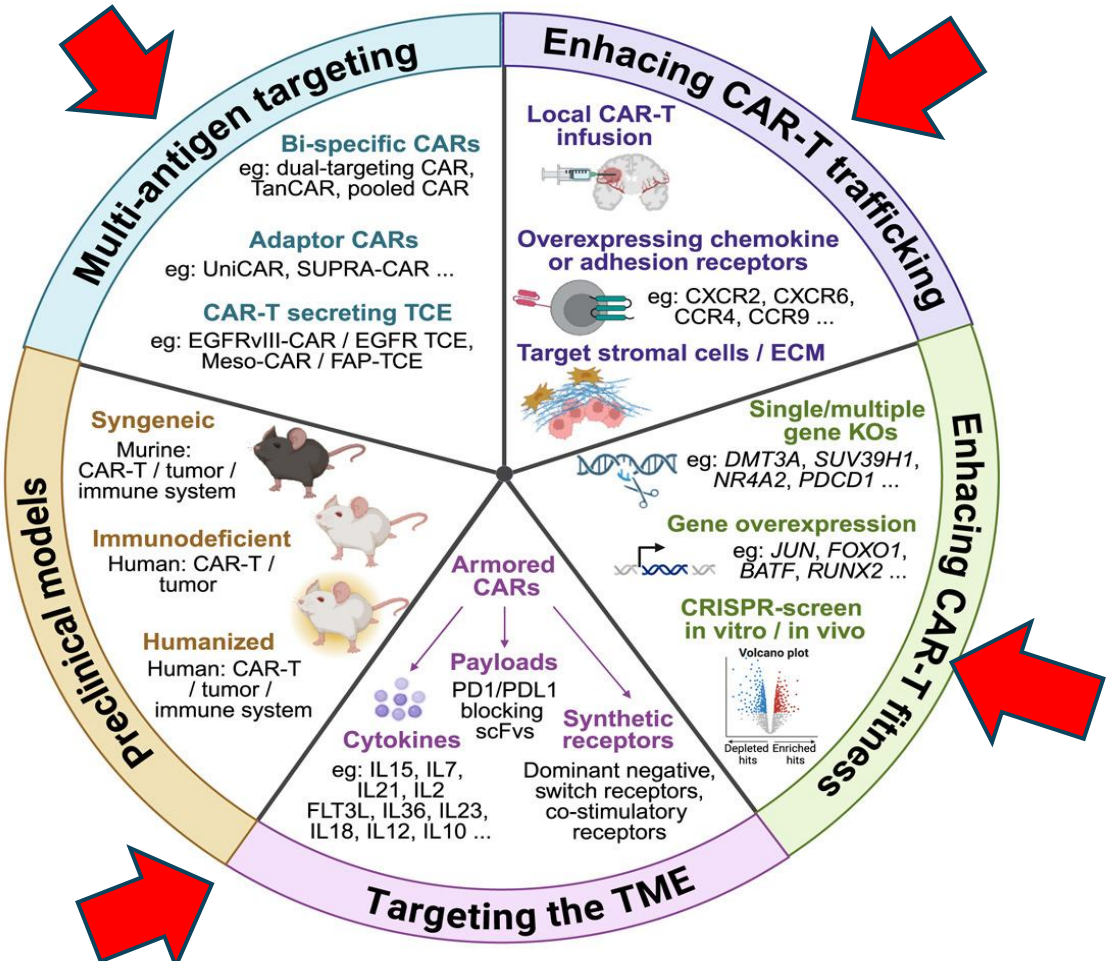
Overcoming barriers

CAR T infusions into CSF, pleura, tumor cavities

Gene editing of CAR T-cells with knockout epigenetic regulators

Multi-targeted antigens to prevent antigen escape

Armoring CAR T cells to secrete cytokines or therapeutic payloads



Escobar et al. Cell Reports Med 2025;6:102353

Single most concerning toxicity, and most impactful mitigation strategy learned?

Allo HCT

GVHD: central challenge & the PTCy breakthrough

Leading cause of non-relapse morbidity; PTCy now enables haploidentical transplant with matched-donor outcomes

ACUTE GVHD	CHRONIC GVHD
Within 100d; skin, gut, liver Gr II–IV: 30–50%; Gr III–IV: <10% Gr III–IV mortality: 30–50% Conditioning → cytokine storm → donor T-cell activation	After 100d; multisystem, autoimmune-like Moderate-severe: 10–15% of survivors B-cell dysregulation; tissue fibrosis 5-yr NRM: 22%; 12-yr NRM: 40%

PTCy-based	CNI + MTX	CNI + MMF	Ex vivo TCD
aGVHD III-IV **6–10%** cGVHD mod-sev **15–20%** NRM **10–20%**	aGVHD III-IV **15–25%** cGVHD mod-sev **30–50%** NRM **15–25%**	aGVHD III-IV **20–30%** cGVHD mod-sev **30–40%** NRM **15–25%**	aGVHD III-IV **<5%** cGVHD mod-sev **5–10%** NRM **10–15%**

GVL vs GVHD	PTCy breakthrough
Partially overlapping; same donor T cells mediate both	**Mechanism:** High-dose Cy (50 mg/kg ×2d) eliminates alloreactive T cells **BMT CTN 1703:** Longer IS-free survival, lower severe GVHD **Trade-off:** Delayed immune reconstitution; increased CMV/EBV reactivation

- Steroid-refractory GVHD: major therapeutic challenge — now FDA-approved agents available
- Chronic GVHD: leading cause of long-term morbidity, profoundly affects quality of life
- PTCy expanding to matched donors, replacing traditional CNI-based approaches

Bolaños-Meade et al. NEJM 2023; PMID: 37342922 | Chhabra et al. BBMT 2019; PMID: 30153491 | DeFilipp et al. Blood Adv 2021; PMID: 34521116 | El-Jawahri et al. BBMT 2016; PMID: 26748160 | Locatelli et al. Blood 2017; PMID: 28588018 | Ram et al. BMT 2009; PMID: 18997826

Approved agents for steroid-refractory GVHD

Three approved targeted therapies transformed management of steroid-refractory chronic GVHD

RUXOLITINIB (JAK1/2i)

- FDA: 2019 (aGVHD), 2021 (cGVHD)
- REACH2: ORR 50% vs 26% (p≤0.001)
- JAK-STAT inhibition
- AE: Cytopenias, infections

IBRUTINIB (BTKi)

- FDA: 2017 (SR-cGVHD)
- iNTEGRATE: ORR 67%
- B-cell signaling inhibition
- AE: Bleeding, atrial fibrillation

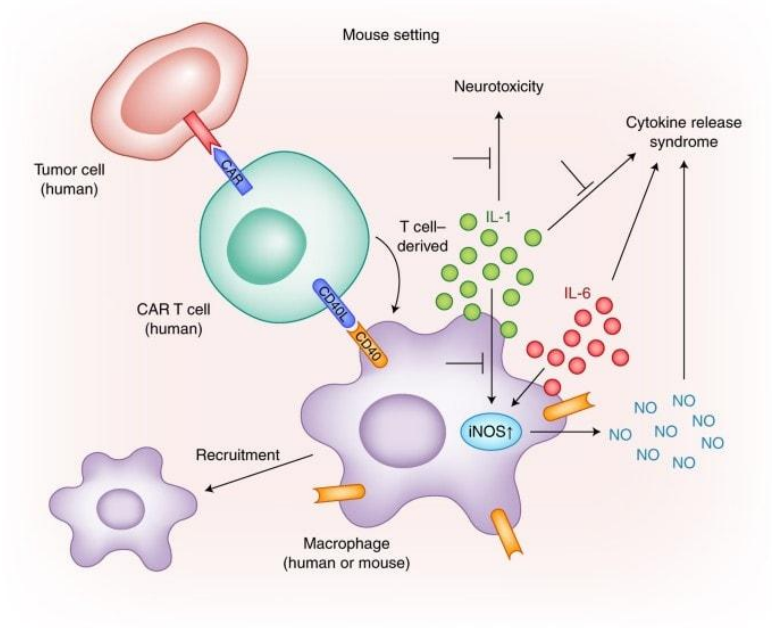
BELUMOSUDIL (ROCK2i)

- FDA: 2021 (SR-cGVHD)
- ROCKstar: ORR 75% after 2+ lines
- ROCK2 inhibition, Treg promotion
- AE: Generally well-tolerated

- Steroid-refractory: progression on prednisone 1 mg/kg × 7d OR no improvement after 14d
- Combination approaches: ruxolitinib + ibrutinib feasible in pediatric patients
- Prevention remains superior to treatment: no agent fully separates GVL from GVHD

Cutler et al. Blood 2021; PMID: 34265047 | Miklos et al. Blood 2017; PMID: 28924018 | Zeiser et al. N Engl J Med 2020; PMID: 32320566 | Zeiser et al. N Engl J Med 2021; PMID: 34260836

CAR T toxicity: Cytokine Release Syndrome (CRS)



- Constructs with improved safety profiles (41BB vs CD28)
- Decreasing risk – lowering tumor burden with effective bridging, low dose radiation to multiple sites, earlier use
- Learning curve with management – earlier and increasing use of tocilizumab, steroids, use of prophylactic steroids/anakinra

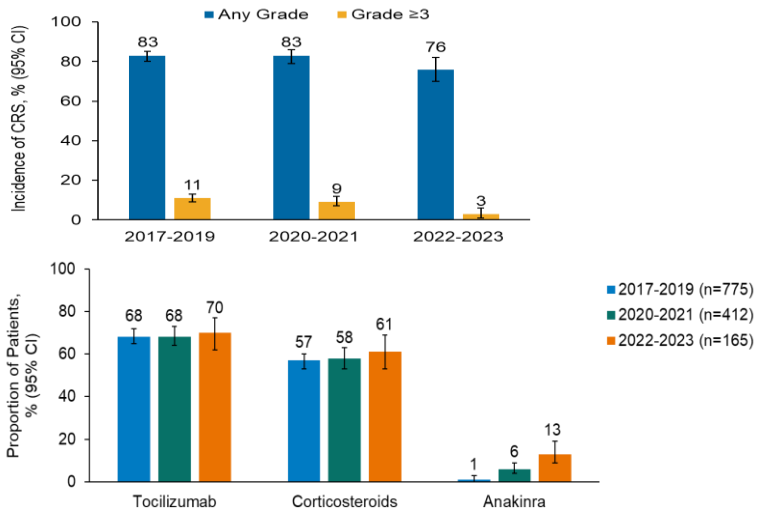


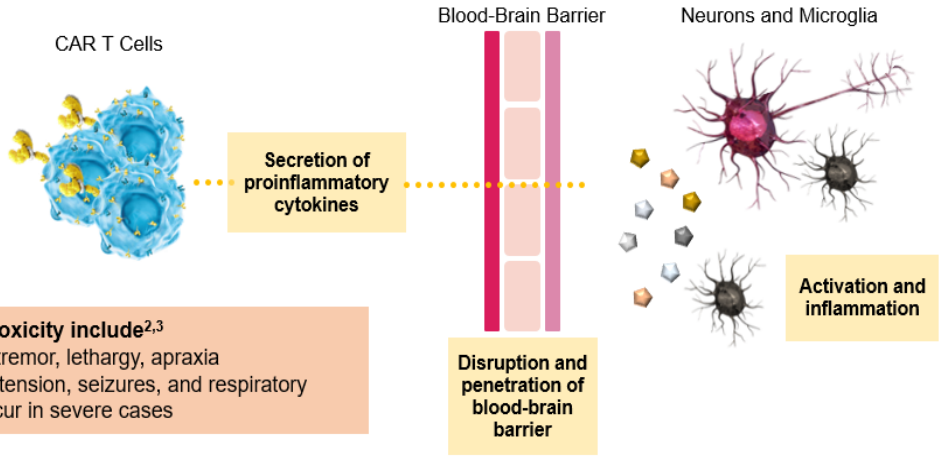
Image from Askhematologist.com

Wang et al. ASH 2024 CIBMTR

Neurotoxicity remains a major concern

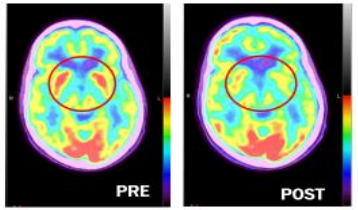
ICANS – IEC-Associated Neurotoxicity Syndrome

ICANS is believed to occur when cytokines cause an inflammatory state in the brain



Symptoms of neurotoxicity include[2,3]
- Aphasia, delirium, tremor, lethargy, apraxia
- Bradycardia, hypertension, seizures, and respiratory depression can occur in severe cases

NMT – Neurocognitive movement disorder



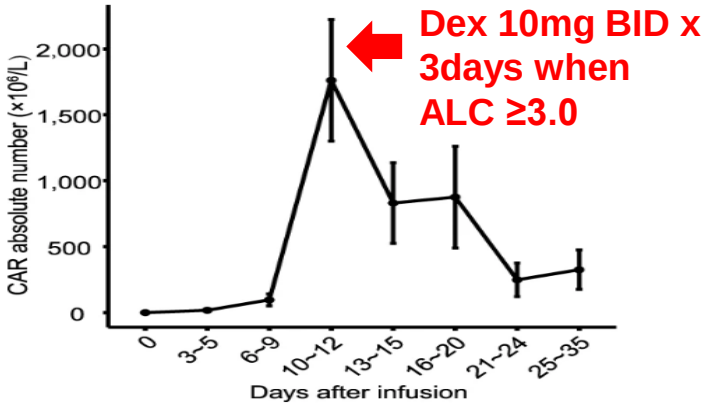
- Mask-like facies
- Mood and personality changes
- Rigidity and bradykinesia
- Cognitive dysfunction
- **Not consistently reversible**
- **Potentially fatal**

Yanez et al. *HemaSphere*. 2019; Lee et al. *Biol Blood Marrow Transplant.* 2019; Brudno et al. *Blood Rev*. 2019.

Van Oekelen Nature Med 2021

What have we learned?

- Parkinson's is associated with:
  - 1) High tumor burden → Give everyone bridging
  - 2) Lack of response to bridging therapy → Move CAR T earlier
  - 3) CAR T-cell expansion → Monitor lymphocyte count and intervene



IMWG registry of 15 institutions and 6 countries

N=52	Incidence CARTITUDE-1	Incidence CARTITUDE-4	Onset (range)
Parkinson's	6%	1%	27.0 (14–108)
Cranial nerve palsies	3%	9%	26 (15-87)
Peripheral neuropathy	7%	7%	31 (7-482)

Kumar et al. ASH 2024; Dingli et al. Leukemia 2025;**39:**1005; Saldariaga et al. Blood Adv 2024;8:3859

Top challenge when counselling patients and families

Allo HCT

Risk-benefit balance & patient stratification

Allo-HCT uniquely offers cure but carries significant risk — HCT-CI, age, and donor type enable personalized risk estimates

POTENTIAL BENEFITS	POTENTIAL HARMS
Cure (40–60% long-term survival) Disease control via GVL effect Best case: cure + excellent QOL	NRM 15–30% at 2 years Acute & chronic GVHD, infections Infertility, organ toxicity Worst case: treatment-related death

Excellent	Standard	Higher risk	Alternatives
<40, HCT-CI 0 2-yr NRM **8–12%** 2-yr OS **70–80%**	40–60, HCT-CI 1–2 2-yr NRM **15–20%** 2-yr OS **55–70%**	60–70, HCT-CI 3–4 2-yr NRM **25–35%** 2-yr OS **35–50%**	>70, HCT-CI ≥5 2-yr NRM **35–50%** 2-yr OS **20–35%**

Donor hierarchy	Disease status	Mortality context
MRD < MUD ≈ Haplo-PTCy < Mismatched/Cord blood; donor age >50 increases NRM	Transplant in CR1/2 far superior to active/refractory disease — status trumps all other factors	100-day mortality 5–15%; survivors >2 yr still 4–9× higher mortality than age-matched population for ≥30 yr

- HCT-CI components: cardiac, pulmonary, hepatic, renal, diabetes, prior malignancy (score 0–15+)
- Key counseling factors: age, comorbidities (HCT-CI), donor type, disease risk, performance status

Abid et al. Transplant Cell Ther 2023; PMID: 37406882 | Bhatia et al. Blood 2007; PMID: 17671231 | Gooley et al. N Engl J Med 2010; PMID: 21105791 | Gooptu et al. Blood 2021; PMID: 34292325 | Socié et al. N Engl J Med 1999; PMID: 10387937 | Sorror et al. Blood 2005; PMID: 15994282 | Sorror et al. J Clin Oncol 2014; PMID: 25154831 | Wingard et al. J Clin Oncol 2011; PMID: 21464398

Allo HCT

Practical counseling: balancing hope and realism

Transparent, personalized risk communication builds trust and enables informed shared decision-making

Opening frame	Discussing NRM	Discussing GVHD	Long-term perspective
"Transplant offers a chance for cure that no other therapy can provide, but it comes with significant risks including death from complications."	*"Based on your age, health, and disease, we estimate a [X]% chance of serious complications in the first 2 years."*	*"GVHD is both a challenge and potentially a benefit — the same immune response fighting your disease can also attack healthy organs."*	*"If you survive the first 2 years in remission, your chances of long-term survival are excellent — approximately 75–85% at 10 years."*

Risk calculators	Acknowledge uncertainty	QOL discussion
Use individualized tools: DRI (disease risk), EBMT risk score, HCT-CI (comorbidities)	Outcome prediction imperfect; patient autonomy is essential in shared decision-making	Late effects: cGVHD 30–40%, secondary malignancies, organ dysfunction, infertility

- NRM ranges: MRD/young/low HCT-CI (10–15%) → Mismatched/older/high HCT-CI (25–35%)
- 100-day mortality: 5–15% in modern era (infection, GVHD, organ failure)

Armand et al. Blood 2014; PMID: 24744269 | Bhatia et al. Blood 2007; PMID: 17671231 | Flowers et al. Blood 2015; PMID: 25398933 | Gooley et al. N Engl J Med 2010; PMID: 21105791 | Gratwohl. Bone Marrow Transplant 2012; PMID: 21643021 | Socié et al. N Engl J Med 1999; PMID: 10387937 | Sorror et al. Blood 2005; PMID: 15994282 | Wingard et al. J Clin Oncol 2011; PMID: 21464398

CAR T Attrition

Factors associated with failure to proceed with CAR T therapy

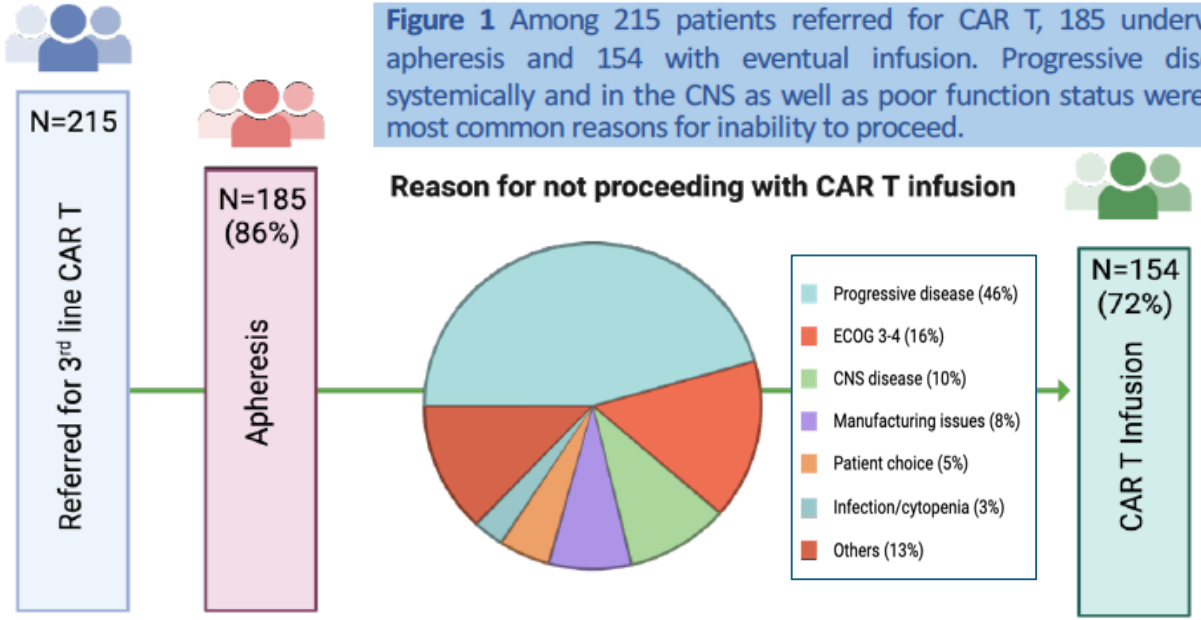


Figure 1 Among 215 patients referred for CAR T, 185 underwent apheresis and 154 with eventual infusion. Progressive disease systemically and in the CNS as well as poor function status were the most common reasons for inability to proceed.

Barriers contributing to attrition
Geography and capacity
Affordability
Lack of support
Eligibility and timing
Regulatory and reimbursement
Information and equity

Almost 1/3 of CAR T referrals did not get infused

Gong et al. ICML 2025

Challenge in patient counselling:
Getting off the CAR T train

Fortunately, we see dropping rates of attrition:

- CAR T in earlier line (secondline, even firstline)
- Awareness for early referral to CAR T centre
- More aggressive/uniform bridging therapy
- Improvements in manufacturing capacity, success, and turnaround
- Greater efficiency in workflows as CAR T centres gain experience

Most exciting innovation emerging in the next year

Innovation 1: toward immunosuppression-free transplantation

Ex vivo graft engineering removes alloreactive cells while preserving immunity

TCRαβ+/CD19+ depletion

- Remove: αβ T cells, B cells
- Preserve: γδ T cells, NK cells
- Gr II–IV aGVHD: 20–40%
- Severe cGVHD: 5–10%

CD45RA+ depletion

- Remove: Naïve T cells
- Preserve: Memory T cells (CD45RO+)
- Gr II–IV aGVHD: 30–50%
- Severe cGVHD: 15–25%

CD3/CD19 depletion + add-back

- Remove: All T/B cells
- Add-back: Tregs, Donor NK
- Gr II–IV aGVHD: <10%
- Infection risk higher

- αβ TCD: removes alloreactive T cells, preserves γδ T cells (anti-viral, anti-tumor)
- Early immune reconstitution: faster NK and γδ T-cell recovery vs conventional
- Trade-offs: higher relapse risk (less GVL), increased infection, requires monitoring
- GRFS: 40–50% vs 30–35% with conventional prophylaxis

Bleakley et al. J Clin Invest 2015; PMID: 26053664 | Bleakley et al. J Clin Oncol 2022; PMID: 35007144 | Di Ianni et al. Blood 2011; PMID: 21292771 | Locatelli et al. Blood 2017; PMID: 28588018 | Martelli et al. Blood 2014; PMID: 24923299

Innovation 2: antibody-based conditioning

CD117 and CD45-targeted antibodies enable marrow clearance without traditional conditioning toxicity

Approach	Mechanism	Toxicity	Stage	Key study
Traditional MAC	Chemo ± TBI	High: mucositis, organ damage	Standard of care	Multiple
CD117-ADC	Anti-c-kit ADC	Reduced: preserved fertility	Phase I/II	*Czechowicz et al. Nat Commun 2019; PMID: 30728354*
CD45-ADC	Anti-CD45 ADC	Intermediate myelosuppression	Phase I/II	*Saha et al. Blood 2022; PMID: 34986233*
CD47+CD117+JAKi	Antibody-based	Anemia (main), no chemo	Preclinical	*Persaud et al. Blood Adv 2024; PMID: 38968137*

- CD117-ADC: targets c-kit on HSCs, clears marrow space, preserves non-hematopoietic tissues
- CD45-ADC: broader clearance, combined with low-dose TBI in early trials
- Applications: older patients, comorbid patients, non-malignant diseases (SCD, SAA)
- Timeline: Phase I/II ongoing; likely 3–5 years to phase III data

Innovation 3: precision relapse prevention via MRD monitoring

Real-time MRD monitoring enables pre-emptive intervention before clinical relapse

PRE-EMPTIVE
Stop ISS • DLI • Targeted Rx

EARLY INTERVENTION
DLI • HMA+VEN • Chemo

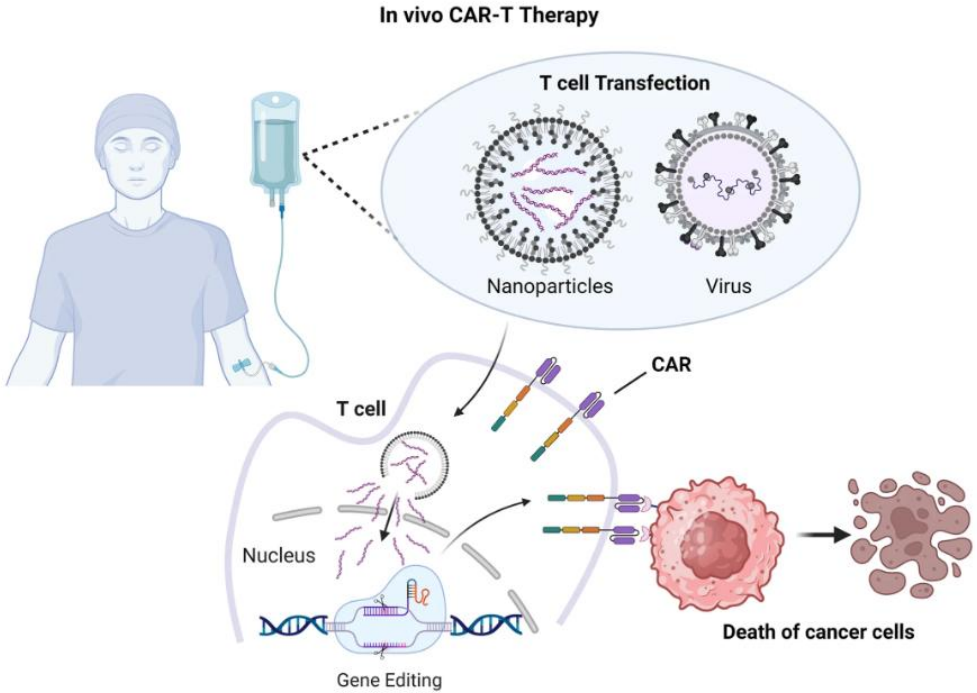
LATE / SALVAGE
Chemo • 2nd HCT

← Best outcomes **Worst outcomes →**

- MRD technologies: Flow cytometry (10^{-4}), PCR/NGS (10^{-5} to 10^{-6})
- Pre-emptive DLI: effective when MRD detected early, tumor burden low; 50–70% durable responses
- Post-HCT maintenance: targeted agents (FLT3i, IDH1/2i, menin inhibitors) under investigation
- Future: liquid biopsies, ctDNA, single-cell sequencing for ultra-sensitive monitoring

Burchert et al. J Clin Oncol 2020; PMID: 32673171 | Heuser et al. Blood 2021; PMID: 34724563 | Platzbecker et al. Lancet Oncol 2018; PMID: 30442503 | Schuurhuis et al. Blood 2018; PMID: 29330221 | Yan et al. Blood 2012; PMID: 22337715

In vivo CAR T-cell Therapy



Now approved in Europe: clinical trials for in vivo CAR T therapy. (Figure taken from Bui et al., in eBioMedicine 2024, CC BY NC ND 4.0, DOI: 10.1016/j.ebiom.2024.105266)

1. Fast (1-3 days for expansion)
2. No manufacturing resources (off the shelf)
3. Cheap(er)
4. Accessible
5. Scalable (1 formulation could treat thousands)
6. Safer (?) – no LD chemo, mRNA in nanoparticles are transient
7. More effective (?) - healthier T cells, can co-opt multiple immune cell types

Now in human clinical trials

Applicability beyond cancer

Beyond cancer: severe aplastic anemia – transplant as first-line

For young patients with SAA and matched sibling donor, allo-HCT offers 85–95% long-term survival

Age <40 + MSD	→ ALLO-HCT (first-line)	85–95% OS @ 5 yr
Age <40, No MSD / Age ≥40	→ IST (ATG/CsA)	70–80% response
IST failure/relapse	→ MUD Allo-HCT	70–85% OS

- MSD allo-HCT: bone marrow preferred over PBSC (lower chronic GVHD)
- IST: ATG + cyclosporine – 70–80% response but 30–40% relapse at 10 years
- MUD transplant: outcomes improving with PTCy-based GVHD prophylaxis
- Late effects: near-normal life expectancy if MSD HCT done in childhood

Bacigalupo et al. Haematologica 2012; PMID: 22315497 | DeZern et al. Blood 2023; PMID: 37084383 | Locasciulli et al. Haematologica 2007; PMID: 17229630 | Rosenfeld et al. Blood 1995; PMID: 7756640 | Young NS. N Engl J Med 2018; PMID: 30354958

Allo HCT

Sickle cell disease: allo-HCT offers cure with caveats

NMA allo-HCT achieves 80–90% DFS in adults with SCD, but graft failure remains a barrier

Pediatric MSD	Adult NMA	Haploidentical
Myeloablative | Matched sibling DFS **90–95%** Graft failure: <5% | GVHD: 10–20%	Non-myeloablative | MSD or MUD DFS **75–85%** Graft failure: 10–20% | GVHD: 10–15%	RIC + PTCy | Haploidentical DFS **70–80%** Graft failure: 15–25% | GVHD: 10–15%

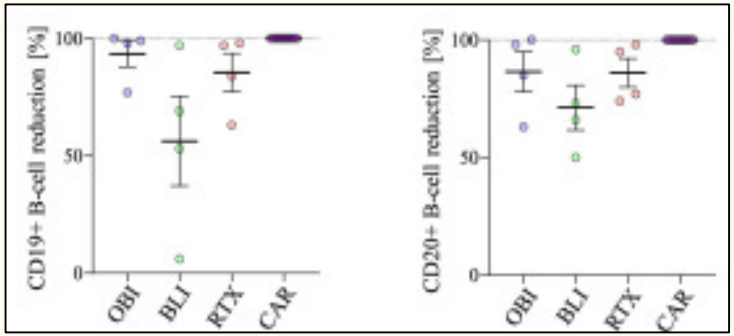
Curative outcomes	Graft failure barrier	Key toxicities	Gene therapy competition
~80% achieve normal Hb, resolution of vaso-occlusive crises	Major impediment (10–25%); driven by RBC alloimmunization, ABO incompatibility	GVHD 15–25% | Infertility 80–90% | Seizures 10–25%	Lentiviral, base editing emerging; avoids GVHD but durability TBD vs allo-HCT

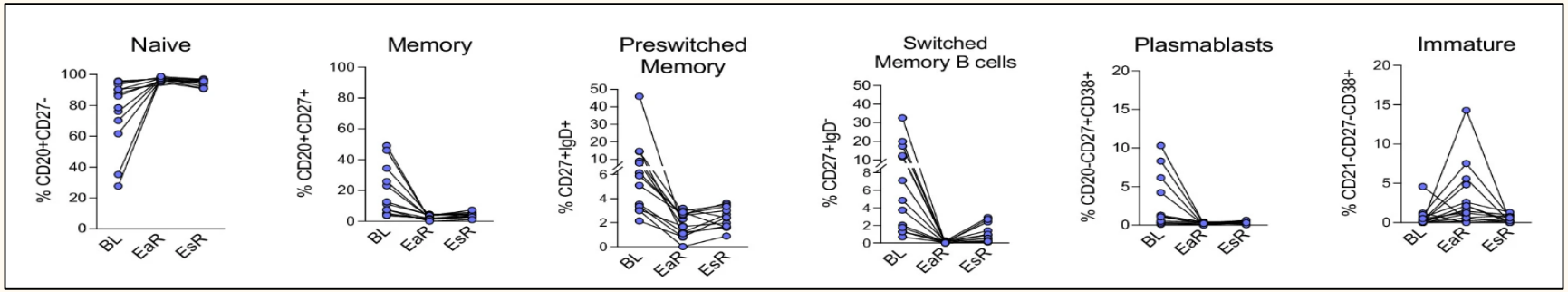
Bolaños-Meade et al. Blood 2012; PMID: 22955919 | Eapen et al. Lancet Haematol 2019; PMID: 31495699 | Gluckman et al. Blood 2017; PMID: 27965196 | Hsieh et al. JAMA 2014; PMID: 25058217 | Walters MC. Curr Opin Hematol 2015; PMID: 25767957

CAR T-cell therapy for autoimmune disease

- B cell depleting monoclonal antibodies can be effective, but have limited tissue penetration and require continuous administration to control disease

- CD19 CAR T leads to profound B cell depletion followed by reconstitution with naïve B cells (>90%) without memory B cell and plasmablast compartments
→ **“Immune Reset”**

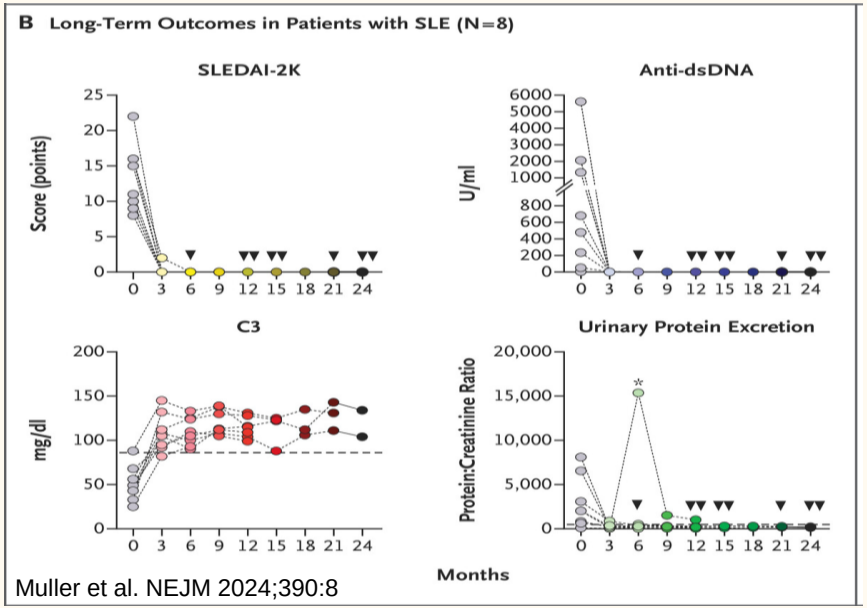




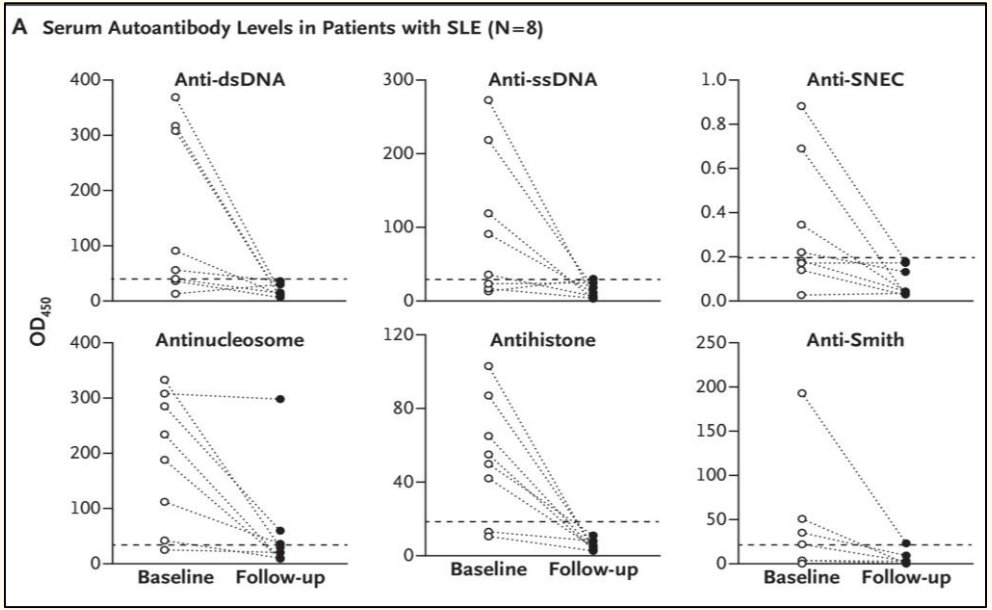
Schett et al. Nat Med Jan 2026 Castle study https://doi.org/10.1038/s41591-025-04185-6; Tur et al. Ann Rheum Ds 2025;84:2065

CD19 CAR T for autoimmune disease

- Case series of severe SLE (n=8), Idiopathic inflammatory myositis (n=3), and systemic sclerosis (n=4) – all with inadequate response to at least 2 prior therapies
- All stopped immunosuppressive therapy, with durable clinical remission



Muller et al. NEJM 2024;390:8



Many trials testing CD19 or BCMA CAR T in autoimmune disease in progress

Conclusions:
Allogeneic transplant and CAR T-cells

1. Both have critical roles in the management of hematologic cancer and beyond

2. Challenges include toxicity, expense, intensive use of resources, access

3. Exciting innovations on the horizon!

Questions or comments?