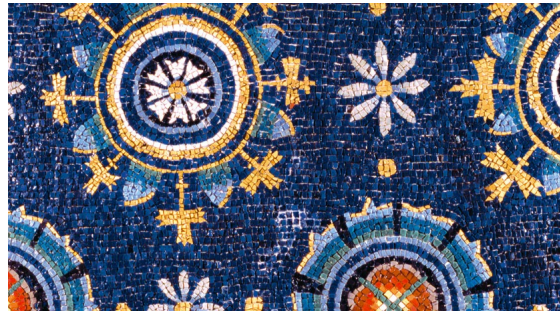


Eventi avversi a lungo termine dopo terapia CAR T

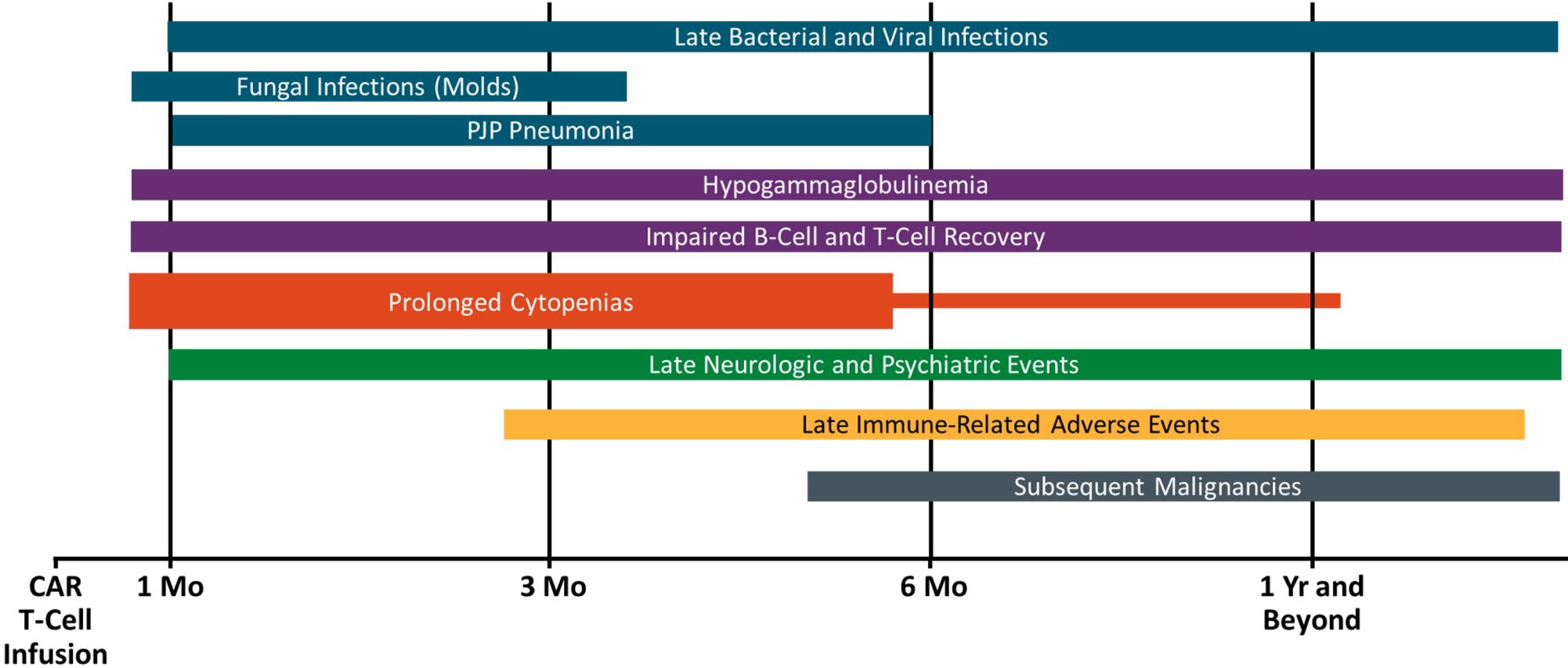


28-11-2025

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Timeline for Delayed Toxicities With CAR T-Cells



Definition of long term toxicities: adverse events occurring beyond day 90

CAR-T long term adverse events: first warning signs from registrative studies

Study (year of publication)	CAR name and patient population (n)	Median follow-up (range)	Prevalence of persistent B cell/IgG depletion in patients with a CR ^a	Prevalence of late severe cytopenias ^b	Incidence of late infections	Incidence of second malignancy
Chong et al. (2021) ³¹	Tisagenlecleucel; adults with B cell lymphomas (38)	61 months	B cell: 4/12 (33%); IgG: 2/11 (18%)	1/38 (3%), ongoing at 57 months	NR	6/38 (16%)
Zhao et al. (2022) ⁵⁹	LCAR-B38M ^c ; adults with multiple myeloma (74)	48 months (0.4–61 months)	NR	NR	NR	4/74 (5%)
Cappell et al. (2020) ¹⁶	FMC63-28Z ^d ; adults with B cell lymphoma or CLL (43)	42 months (1–123 months)	B cell: 9/24 (38%); IgG: 5/24 (21%)	NR	4/43 (9%) developed an infection requiring hospitalization ≥6 months after CAR T cell infusion	7/43 (16%)
Cordeiro et al. (2020) ⁸⁹	Lisocabtagene maraleucel; adults with ALL, NHL or CLL (86)	28 months (13–63 months)	B cell: NR; IgG: 14/19 (74%)	3/19 (16%) of patients in CR	33/54 (61%) developed an infection and 80% of these were non-severe infections (mostly URIs); 20% of infections required hospitalization at ≥3 months after infusion	13/86 (15%)
Locke et al. (2019) ⁶⁷	Axicabtagene ciloleucel; adults with B cell lymphomas (108)	27 months (IQR 26–29 months)	B cell: 8/32 (25%); IgG: NR	18/108 (17%) of all patients	2 grade 3 infections occurred ≥12 months in patients in ongoing remission	1 case of MDS
Locke et al. (2022) ^{23,e}	Axicabtagene ciloleucel; adults with B cell lymphomas (170)	25 months	B cell: 55/160 (34%) of all patients; IgG: NR	NR	NR	NR

Cytopenias, infections, second malignancies represent the most common long-term adverse events

Clinical case 1

62-year-old female

Feb 2023: Diagnosis of **GCB-type DLBCL, stage IVB-S**, with mediastinal mass and extensive hepatic, splenic and bone marrow involvement.

1st line (2023): 6 CHOP + 8 rituximab → **complete remission**.

Jan 2024: **CNS relapse** (occipito-parietal lesion) → craniotomy and histologic confirmation.

2nd line (2024): MATRix ×4 → poor stem cell mobilization (total $1,8 \times 10^6$)
→ radiologic CR (MRI 24 Apr 2024)

Aug 2024: **CNS progression** → **radiotherapy** (Oct–Dec 2024, 25 fractions).
MRIs Jan–Feb 2025: CR, post-RT cavity

CAR-T infusion: 9 Jul 2025, total 2×10^6 CD19 CAR-T cells.
ICANS prophylaxis: levetiracetam + anakinra (day 0 - 10)

Clinical case 1

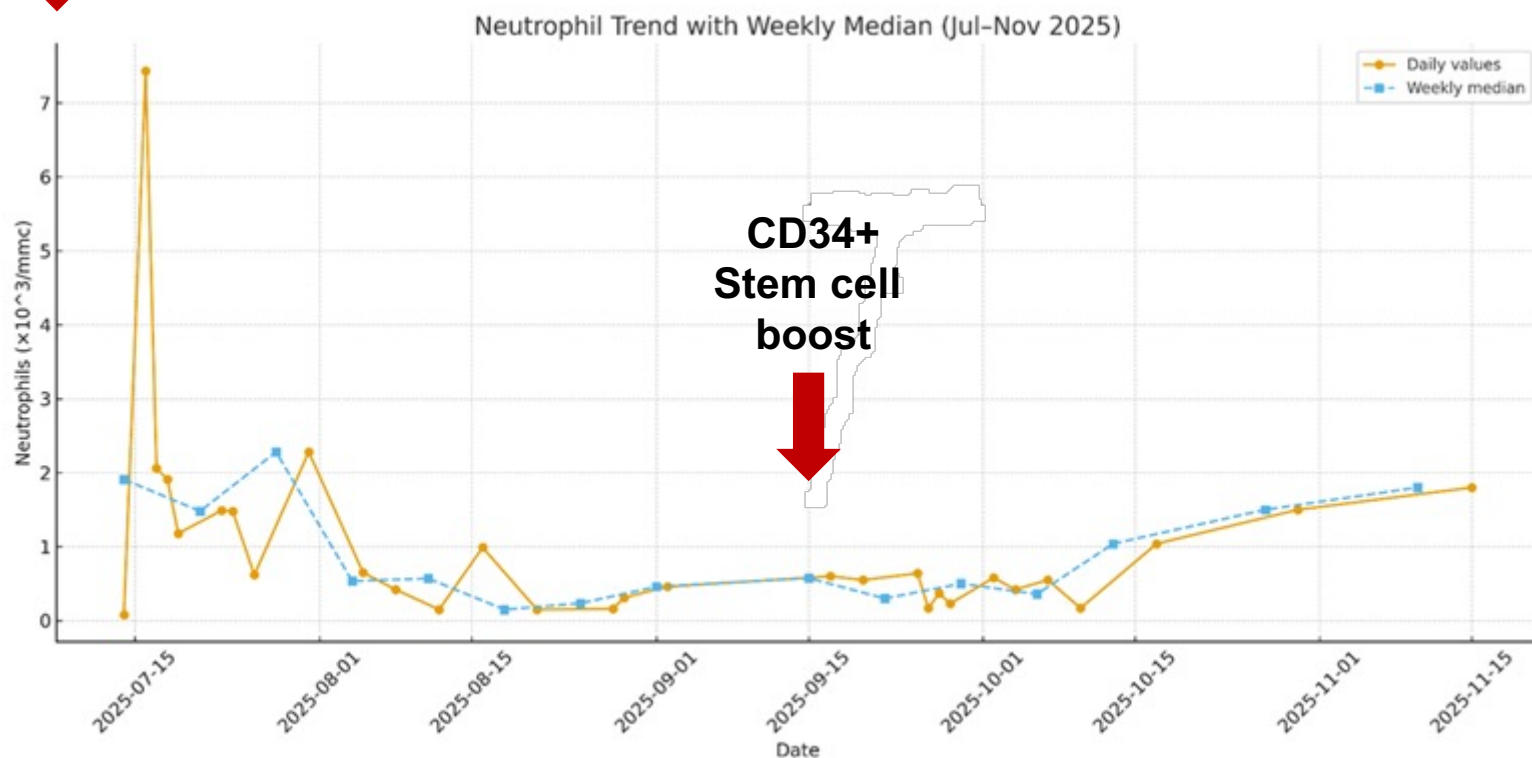
Early Toxicities (0–30 Days)

- Neck local CRS (day +6): fever, bilateral neck swelling, muffled voice; laryngoscopy → severe perilaryngeal edema.
- Management: dexamethasone 10 mg, protective intubation, broad-spectrum antibiotics. Extubated 18 Jul, stable thereafter.

Long-Term Course (Aug–Nov 2025)

- Persistent **pancytopenia**
- Bone marrow aspirate showed hypocellular BM
- Received **autologous stem cell boost on 15 Sep 2025** (1.8×10^6 CD34+/kg) without complications.
- Last follow up: Clinically well (Nov 2025): ECOG 1, improving fatigue, normal daily activities, no infections.
- WBC/PMN 2500/1200, Hb 10, PLT 38000

**CAR-T
infusion**



CAR-T long term adverse events: immune effector cell–associated hematotoxicity (ICAHT)

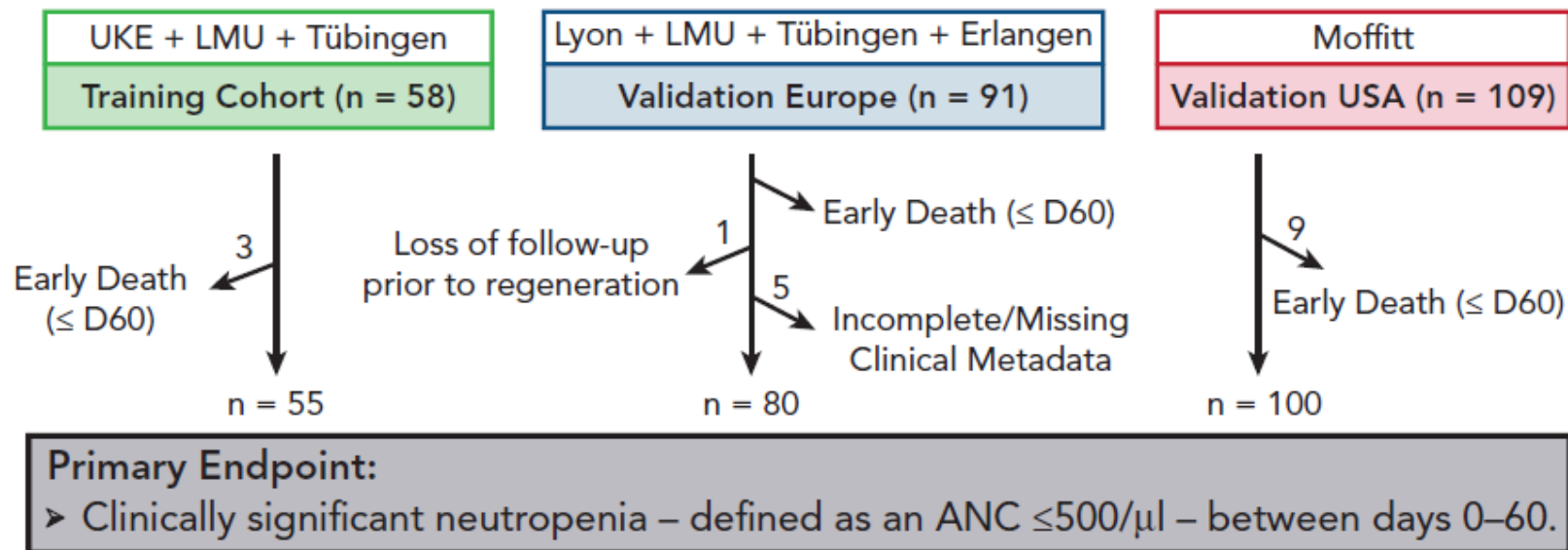
Multicenter (3 cohorts) real-world retrospective study; axi-cel or tisa-cel in relapsed/refractory LBCL

Primary endpoint: duration of severe neutropenia (ANC $<500/\mu\text{L}$) within the first 60 days

258 patients included. DLBCL, transformed FL, PMBCL; median prior therapies = 3; 27% had prior auto-HCT

Baseline variables assessed before lymphodepletion: ANC, hemoglobin, platelets, CRP, ferritin

Aim to develop a score predictive of ICAHT (training cohort and 2 independent validation cohorts)



CAR-T long term adverse events: immune effector cell–associated hematotoxicity (ICAHT)

Incidence of hematotoxicity (ICAHT):

- Severe neutropenia: 91%; Prolonged >21 days: 64%; Profound (ANC <100/ μ L): 72%
- Severe thrombocytopenia: 62%
- Severe anemia: 69%

Predictors of prolonged neutropenia:

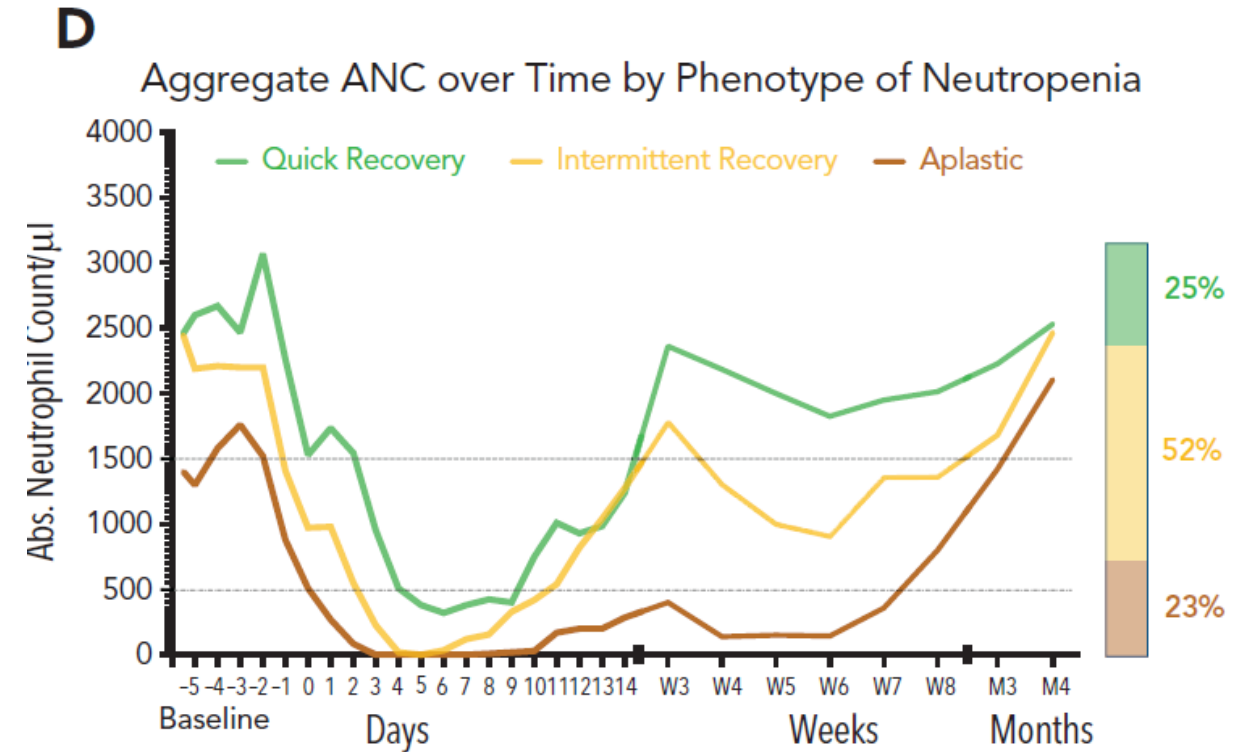
- Baseline cytopenias (especially platelets; $r = -0.43$)
- Elevated CRP and ferritin (strongest predictor: $r = 0.54$)
- Bone marrow involvement

No association with CRS or ICANS severity, nor with peak IL-6.

3 different patterns of ANC dynamics

Most common pattern is biphasic with a second dip around month 2

Hematological toxicity is the most common adverse event after CAR T-cell therapy



Immune effector cell–associated hematotoxicity (ICAHT): CAR-HEMATOTOX score

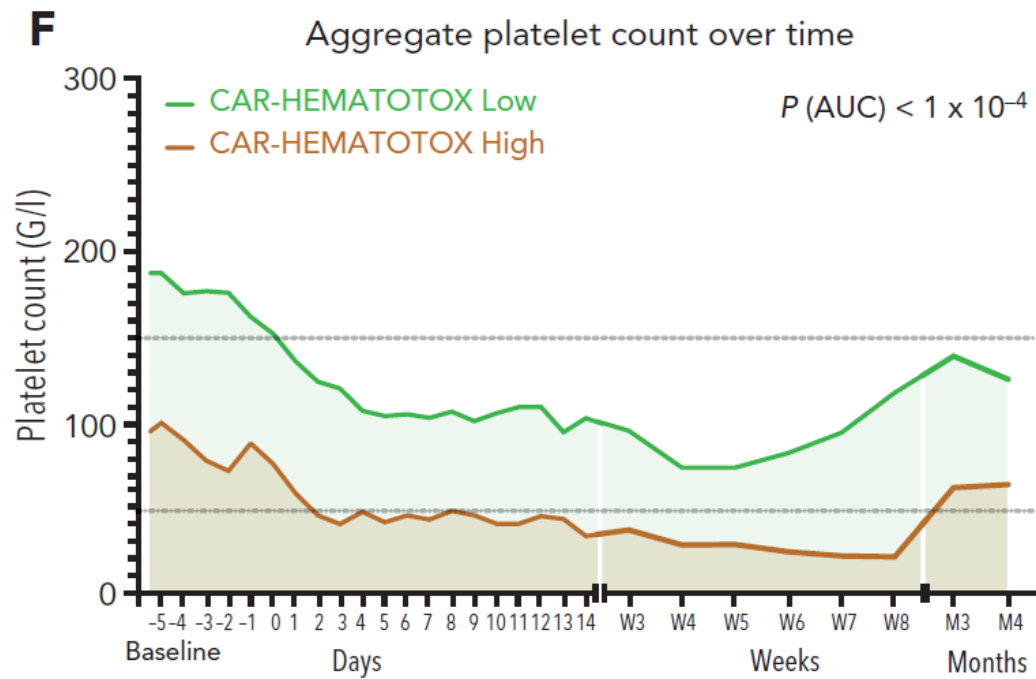
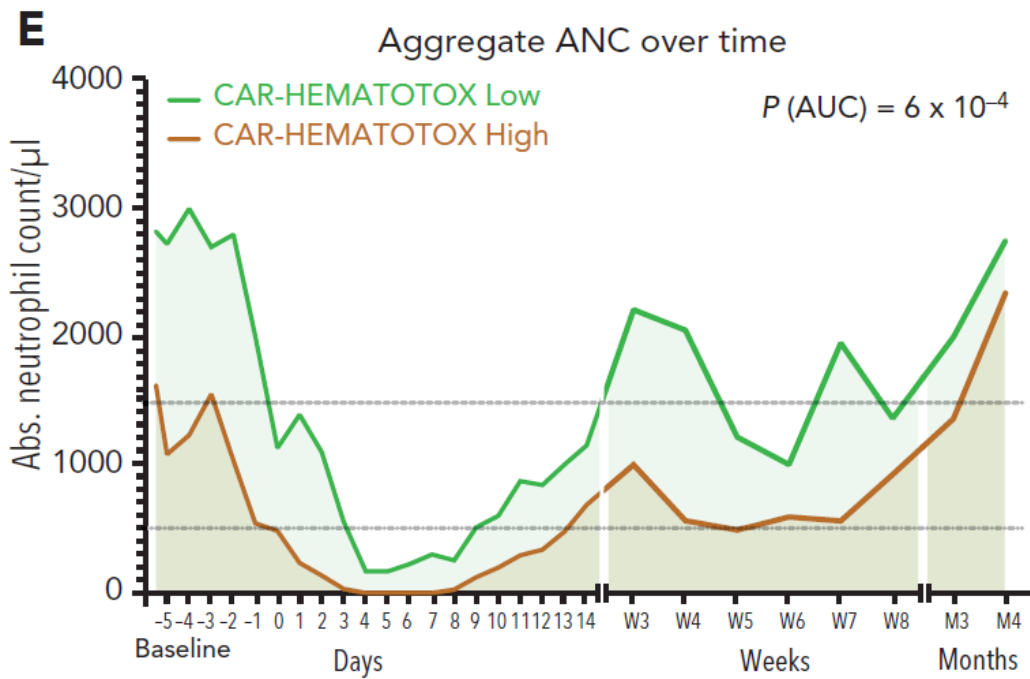
Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/ μ l	75,000 – 175,000/ μ l	< 75,000/ μ l
Absolute Neutrophil Count (ANC)	> 1200/ μ l	< 1200/ μ l	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1 High: ≥ 2			

CAR-HEMATOTOX score

Pre-lymphodepletion risk model integrating PLT + ANC + Hb + CRP + ferritin

2 Biological domains captured by the score:

- Systemic inflammatory state (CRP, ferritin)
- Bone marrow reserve / treatment burden (PLT, ANC, Hb)



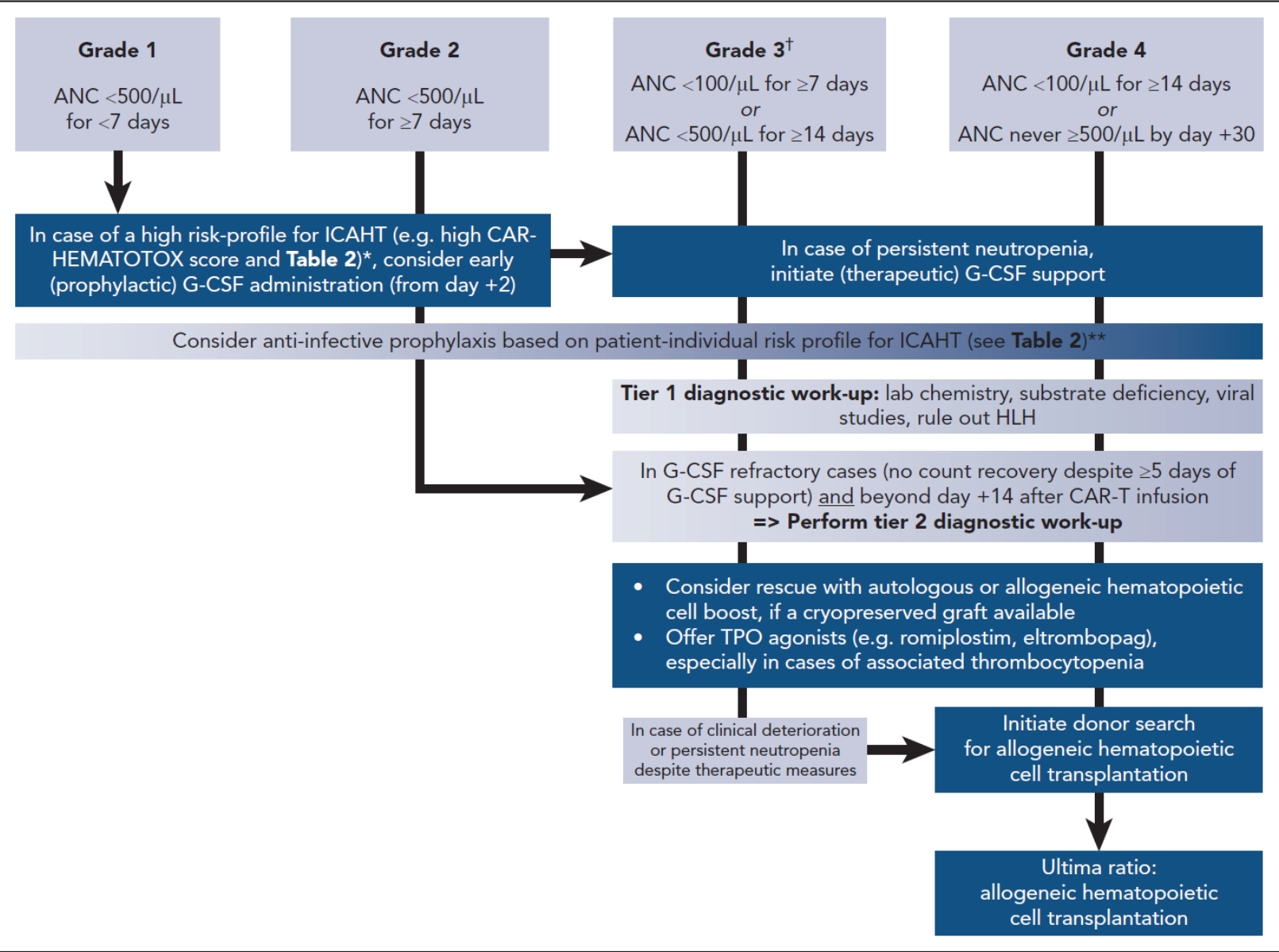
High-risk patients show deeper, longer neutropenia and persistent thrombocytopenia

Risk factors associated with increased risk of ICAHT

Category	Risk factors	Comments
Disease-related features	.Underlying disease (BCP-ALL > B-NHL) .Disease burden prior to CAR T-cell infusion (progressive disease, high LDH)	Evidence concerning the rate of cytopenias in patients with MM still emerging Especially BM disease burden
Prior therapies	.Number of prior therapy lines Prior hematopoietic stem cell transplantation .Bridging therapy	Associated with baseline hematopoietic function
Baseline marrow status	.BM infiltration .Preexisting cytopenias .Clonal hematopoiesis of indeterminate potential (CHiP)?	Particularly preexisting thrombocytopenia Has been linked to increased inflammation, potential emerging risk factor
Baseline inflammatory status	Increased serum CRP Increased serum ferritin	
CAR T-cell product and postinfusion risk factors	.Costimulatory molecule (CD28 > 4-1BB) Type of construct (tandem > single target) Severe CRS Sustained increased inflammatory markers Oligoclonal T-cell expansion .Active infection CRS/MAS or IEC-HS	.May also reflect differences in lymphodepletion dosing (cyclophosphamide dosing) In select patients: the success of autologous stem cell boost argues against this as a general mechanism Mainly viral or in case of concomitant sepsis Cytopenia as overlapping symptomatology

Rejeski, blood 2023; Roddie C. Blood Adv. 2023; Brudno JN, Leukemia & Lymphoma 2022; Jain T. Blood Adv 2020; Rejeski K, Blood 2022; Gagelmann N, Blood Adv. 2023.

EBMT/EHA consensus: ICAHT treatment algorithm



- Prophylactic G-CSF
- Bone marrow aspiration to rule out MDS
- Autologous stem cell boost
- Initiate donor search in persistent neutropenia

Clinical case 2

69-year-old male

Jan 2019: diagnosis of **Double-hit DLBCL (MYC/BCL2), stage IVB**

1st line: R-CHOP ×3 → PR.

2nd line: R-DHAP ×3 → ASCT with FEAM (Aug 2019) → CR at 1 year.

May 2022: Systemic and marrow **relapse**. Referred to CAR-T program.

Bridging therapy: Polatuzumab–Bendamustine–Rituximab × 2. Pre–CAR-T PET (Aug 2022): metabolic CR.

CAR-T Therapy (Axi-cel). Infusion: 30 Aug 2022.

CRS: Grade 2→3 on day 1 → tocilizumab + steroids.

ICANS: Grade 2 on day 5 (ICE 5): aphasia, dysphagia, cognitive slowing → dexamethasone with full resolution by day 10.

Disease Status After CAR-T: Persistent **metabolic CR** on all PET scans

Clinical case 2

Long term Complications

Severe cachexia: 10–15 kg weight loss since early 2023; severe sarcopenia; anorexia; dehydration.

Chronic diarrhea (Mar–Oct 2023): extensive workup negative (colonoscopy & biopsies, stool cultures, *C. difficile*, parasites, elastase, calprotectin normal).

Pulmonary nodules:

- Nov 2023 CT: 1 cm cavitary spiculated RUL lesion + small nodules; no adenopathy. Negative BAL
- PET 21 Dec 2023: CR systemically; lung lesion non-hypermetabolic.

Admission 21 Jan 2024: Presented with **dyspnea**

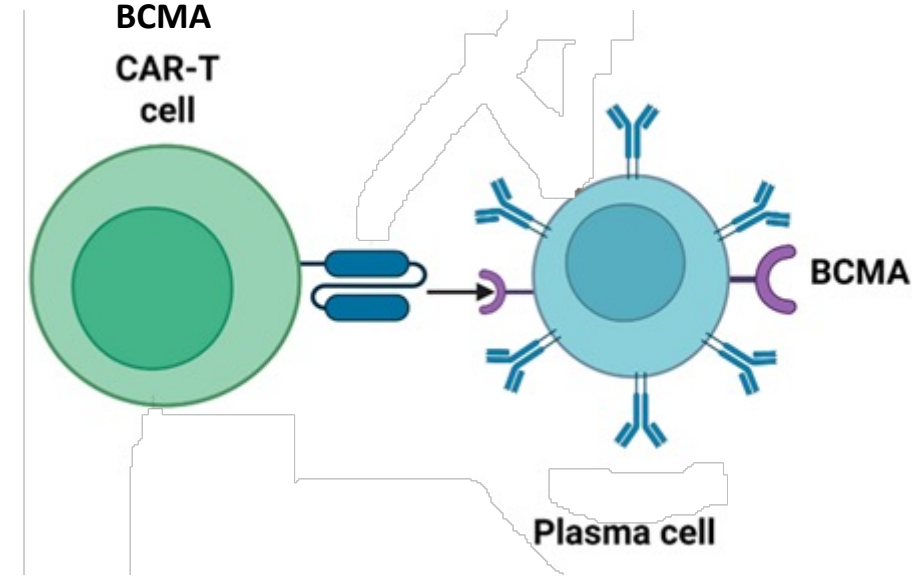
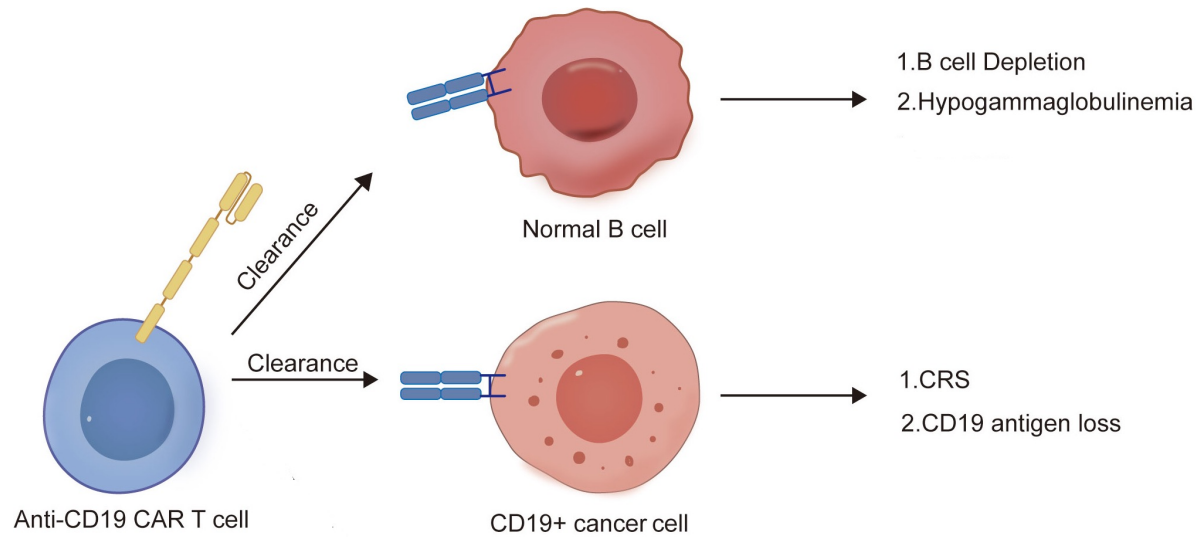
→ **BAL: nocardiosis**

Treated with TMP-SMX + meropenem

Developed ARDS and died on february 2024



Infectious complications: on target, off tumor effect



On-target, off-tumor effects drive infection risk

- **CD19 CAR-T** → prolonged **B-cell aplasia** → hypogammaglobulinemia.
- **BCMA CAR-T** → **plasma-cell depletion** → marked loss of antibody diversity.

These are on-target but off-tumor effects leading to profound humoral immunodeficiency
Result: increased infection risk even in the absence of neutropenia

Late-onset infectious complications after CD19 CAR T-cell therapy

Prospective, observational, multicenter study across 6 Spanish centers

DLBCL patients treated with commercial CD19 CAR-T (axi-cel or tisa-cel)

79% of patients experienced at least one late adverse event

Infections were the most frequent late AE, with the highest incidence of any event category: 5.6 per 100 person-months

Late infectious complications

87% of infectious episodes started after the 3-month landmark

Median onset: 271 days post infusion (range 98–751)

Types of infections

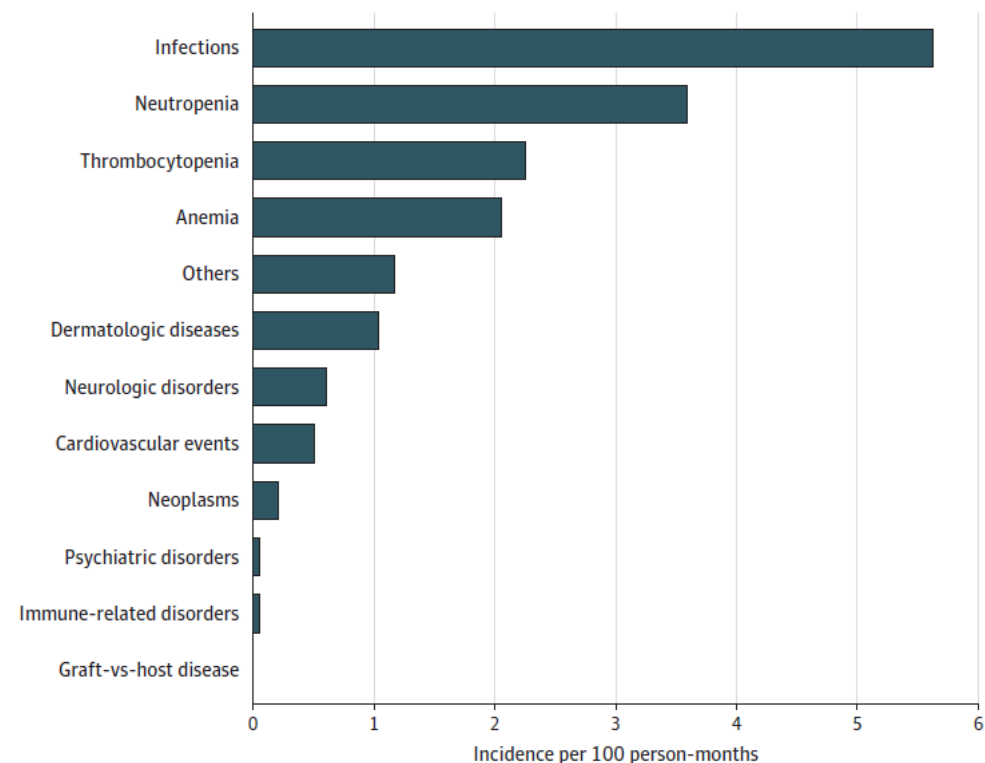
COVID-19 was the most common infection:

- 44 patients (25.6%), 45 episodes.
- Median onset 307 days; median duration 37 days.

Other frequent infections: Clostridioides difficile, Pseudomonas aeruginosa, Campylobacter, Herpes zoster, Influenza virus, RSV

All 7 cases of non-relapse mortality (4%) were due to infections

Figure. Long-Term Adverse Event Incidence Per 100 Person-Months



Infectious complications represent the most frequent and deadly long term adverse events

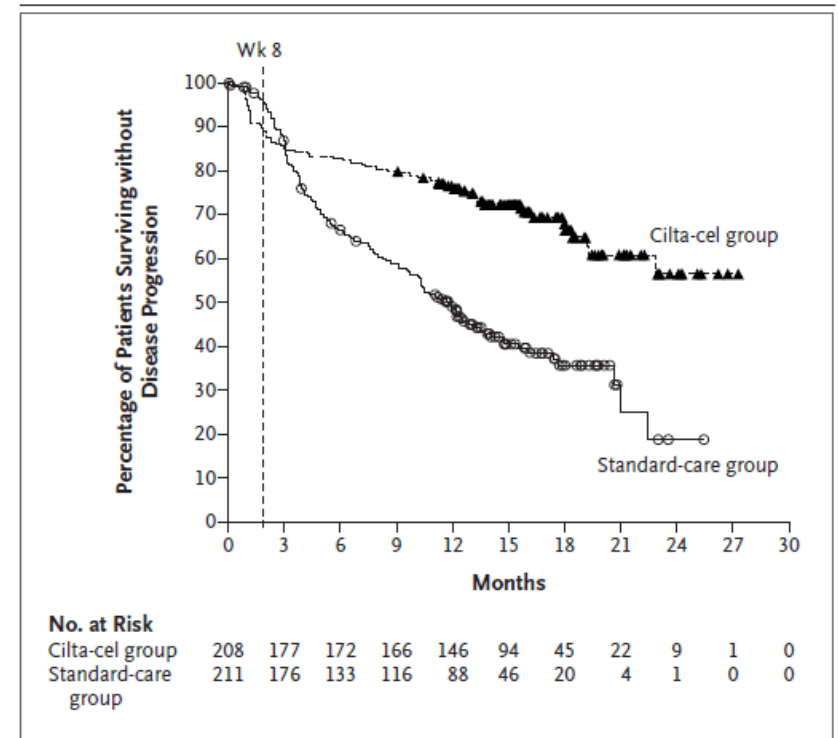
Late-onset infectious complications after BCMA-directed CAR T-cell therapy

Product	Total infections (%)	Grade 3-4 infections (%)
Cilta-cel (CARTITUDE-4)	58	30
Ide-cel (KarMMa-3)	50	25

COVID-19 infection main issue in those studies (especially CARTITUDE-4), omicron variant.

Neutropenia is more frequent and deeper in CAR-T vs standard of care, however infection rate not higher

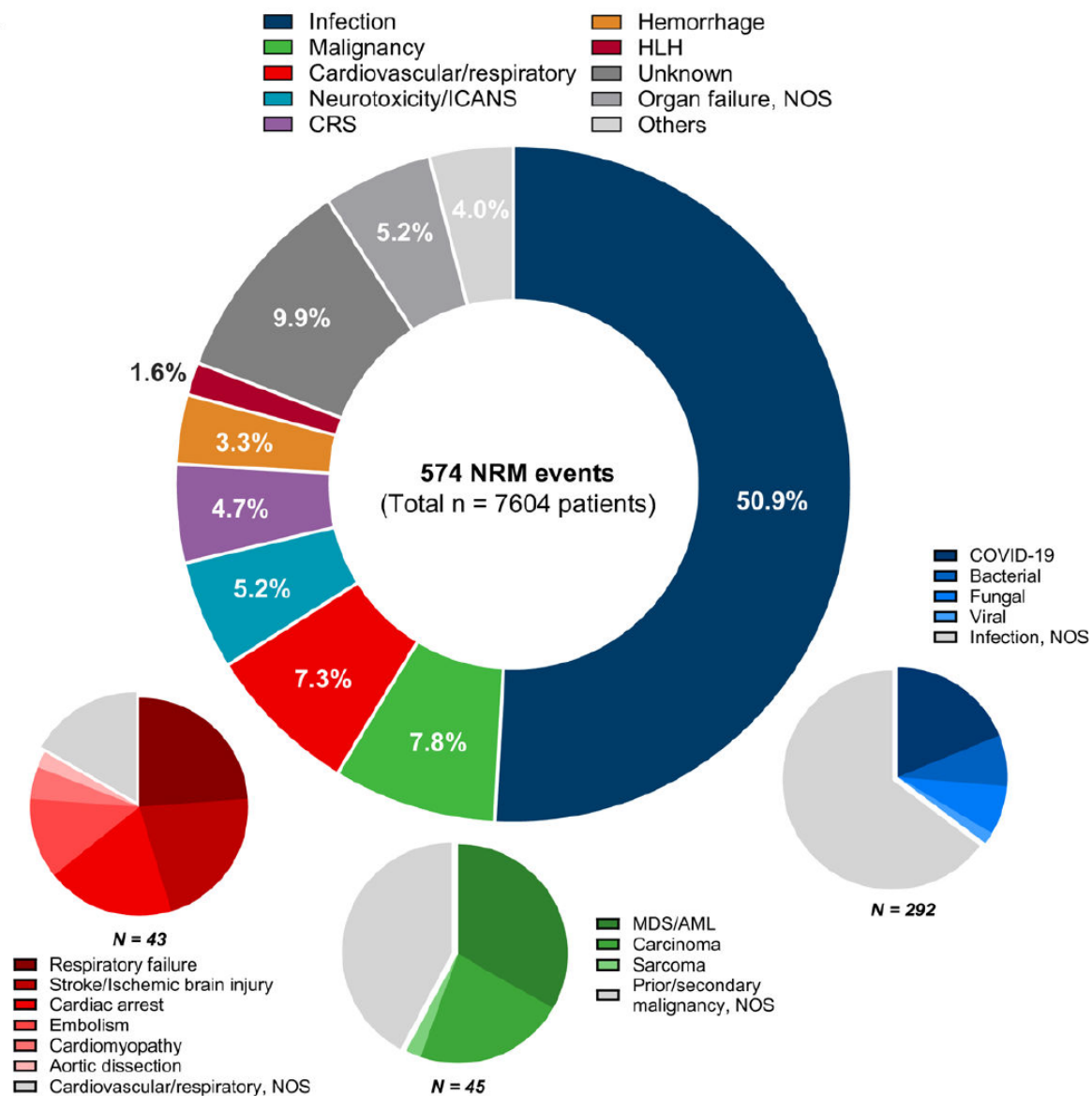
Hypogammaglobulinemia >90% of patients (vs 70% standard of care).
2/3 of patients received IVIG



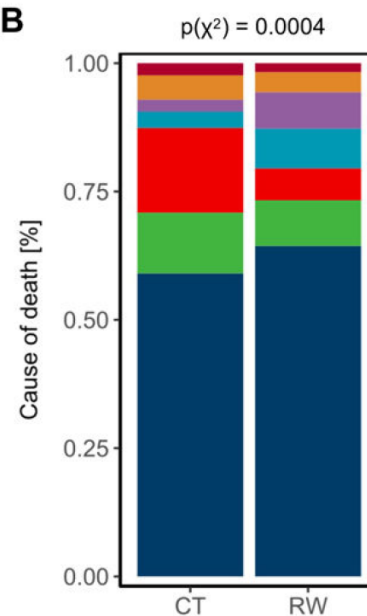
Multiple studies show hypogammaglobulinemia correlates with increased infection risk, especially late respiratory infections

Non relapse mortality after CAR-T cell therapy: meta-analysis of 46 studies

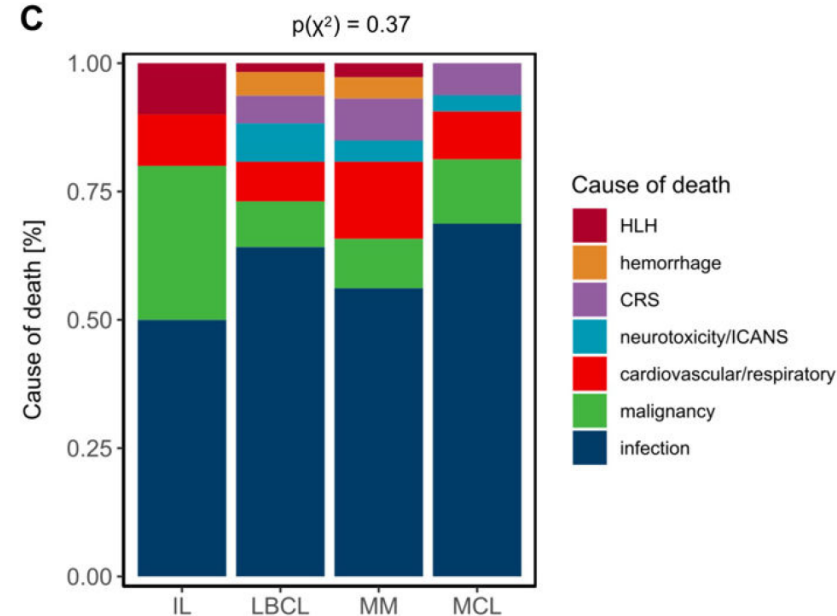
A



B



C



median NRM 7%

Infection is the leading cause of non-relapse mortality

How to prevent long term infections? EBMT/EHA consensus on antimicrobial prophylaxis

	When	How	Precautions	Comments
Antibacterial prophylaxis	In patients with a low risk for ICAHT, not recommended In patients with a high-risk profile for ICAHT, prophylaxis may be considered once ANC is $<500/\mu\text{L}$	As per institutional standards (eg, levofloxacin or ciprofloxacin)	Warning in case of colonization by MDR pathogens	Look at local bacterial epidemiology. High local prevalence of MDR GNB might prevent the use of antibacterial prophylaxis.
Antiviral	All patients	Start from LD conditioning until 1 y after CAR T-cell infusion AND/OR until CD4^+ count is $>0.2 \times 10^9/\text{L}$ Valaciclovir 500 mg twice a day or acyclovir 800 mg twice a day		
Antipneumocystis	All patients	Start from LD conditioning until 1 y after CAR T-cell infusion AND/OR until CD4^+ count is $>0.2 \times 10^9/\text{L}$ Co-trimoxazole 480 mg once daily or 960 mg 3 times each week	In case of co-trimoxazole allergy, pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered	Can be started later depending on center guidelines
Systemic primary antifungal prophylaxis	Prophylaxis may be considered in case of severe neutropenia ($\text{ANC} < 500/\mu\text{L}$) and a high-risk profile for ICAHT (eg, CAR-HEMATOTOX score and risk profile per Table 2) and/or prolonged neutropenia	Mold-active prophylaxis for 1-3 mo (depending on the duration of neutropenia and use of steroids): posaconazole (300 mg/d) or micafungin (50 mg per day, IV)		In patients with prior allo-HCT, prior invasive aspergillosis, and those receiving corticosteroids (long-term >72 h, or high-dose), prophylaxis is recommended

Antibacterial (?)
Antiviral
+ anti PJ
+ mold-active prophylaxis
in high risk patients

Vaccination recommendations for adult patients receiving CAR T-cell therapy

Vaccine	Timing	Comments
Killed/inactivated vaccines	• ≥ 6 months after CAR T-cell infusion and ≥2 months since last immunoglobulin replacement therapy	• Contraindicated: ◦ Actively receiving immunosuppressive agents ◦ ≤6 months from receiving anti-CD19 or anti-BCMA therapy other than CAR-T cells ◦ Actively receiving chemotherapy
Live and nonlive adjuvant vaccines	• ≥12 months after CAR T-cell infusion and ≥8 months since last immunoglobulin replacement therapy	• Contraindicated: ◦ ≤12 months from receiving immunosuppressive agents ◦ ≤12 months from receiving anti-CD19 or anti-BCMA therapy other than CAR-T cells ◦ ≤12 months from receiving autologous HSCT ◦ ≤24 months from receiving allogeneic HSCT ◦ Actively receiving chemotherapy ◦ CD4+ count ≤200 cells/mL
Influenza virus	• ≥3 months after CAR-T cell infusion	• Although high likelihood of lower vaccine response, the majority opinion is that vaccinations may still provide some protection
SARS-CoV-2	• ≥3 months after CAR T-cell infusion	• Although antibody responses are poor, there is evidence that T-cell responses may be achieved

The post–CAR-T vaccination schedule is derived from allo-HSCT practice but adapted to a different pattern of immune recovery

Earlier vaccination with inactivated influenza and SARS-CoV-2 (from ~3 months) is encouraged due to high respiratory infection risk

Secondary malignancies post CAR-T – 2023 FDA boxed warning

FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

November 28, 2023

Summary of the Issue

The Food and Drug Administration (FDA) has received reports of T-cell malignancies, including chimeric antigen receptor CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T cell immunotherapies. Reports were received from clinical trials and/or postmarketing adverse event (AE) data sources.

FDA has determined that the risk of T-cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies. T-cell malignancies have occurred in patients treated with several products in the class. Currently approved products in this class (listed alphabetically by trade name) include the following:

PERSPECTIVE



Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy

Authors: Nicole Verdun, M.D., and Peter Marks, M.D., Ph.D. [Author Info & Affiliations](#)

As of Dec 31, 2023, 22 cases of secondary T-cell malignancies had been notified across all products and indications

These events remain rare, with incidence estimates <1%, but triggered a class-wide boxed warning.

Potential Genotoxicity:

In several cases, vector sequences (retroviral or lentiviral) were detected in malignant T cells → raising the possibility of clonal expansion driven by insertional mutagenesis

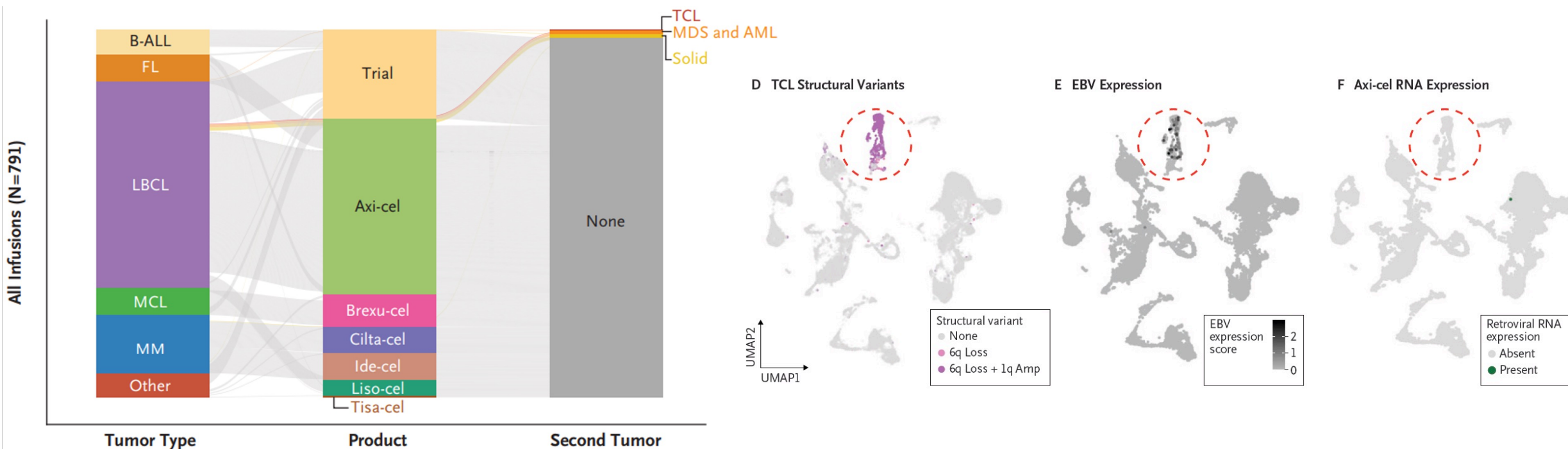
Secondary malignancies post CAR-T: Stanford retrospective study

724 patients treated with CAR-T between 2016–2024. Median follow-up: 15 months

25 second cancers identified (excluding non-melanoma skin cancers)

- 14 hematologic (13 MDS/AML; 1 T-cell lymphoma).
- 11 solid tumors (melanoma, prostate, breast, lung, endometrial, mesothelioma).

Cumulative incidence of hematologic second tumors at 3 years: 6.5%

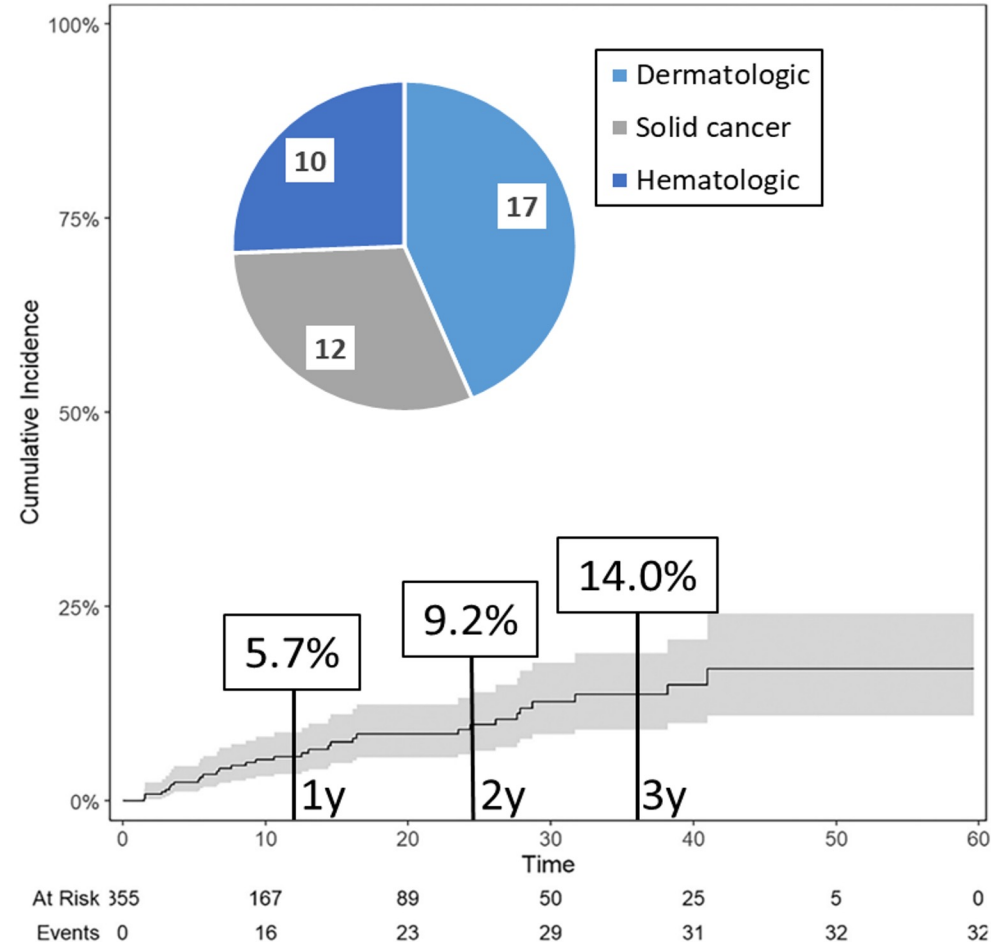


Both lymphomas developed in the context of CHIP (DNMT3A, TET2).

T-cell lymphoma after CAR-T is extremely rare (1 case) and not arising from CAR-T

Suggests interplay of pre-existing clonal hematopoiesis, EBV infection, and post-therapy immune dysfunction

Secondary malignancies post CAR-T: retrospective MSKCC (NY) + Hackensack (NJ) data



Retrospective study, two US centers (MSKCC + Hackensack)
355 patients treated 2016–2022
CAR-T products: Axi-cel (53%), Tisa-cel (21%), Liso-cel (21%), Brexu-cel (5%).
Median follow-up: 19.3 months

Subsequent malignancies after CD19 CAR-T occur in ~10–14% at 3 years—similar to rates seen with prior chemotherapy and autologous HCT;

MDS/AML represent the most clinically significant events; onset can be early and aggressive;

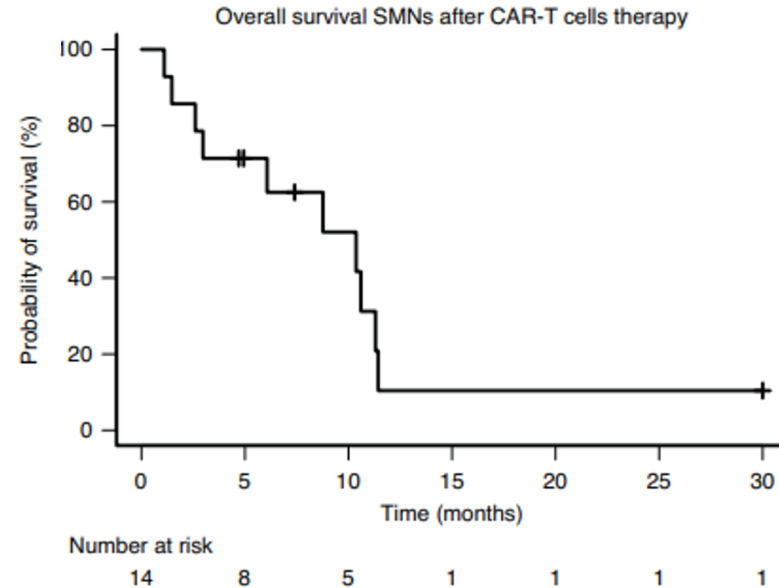
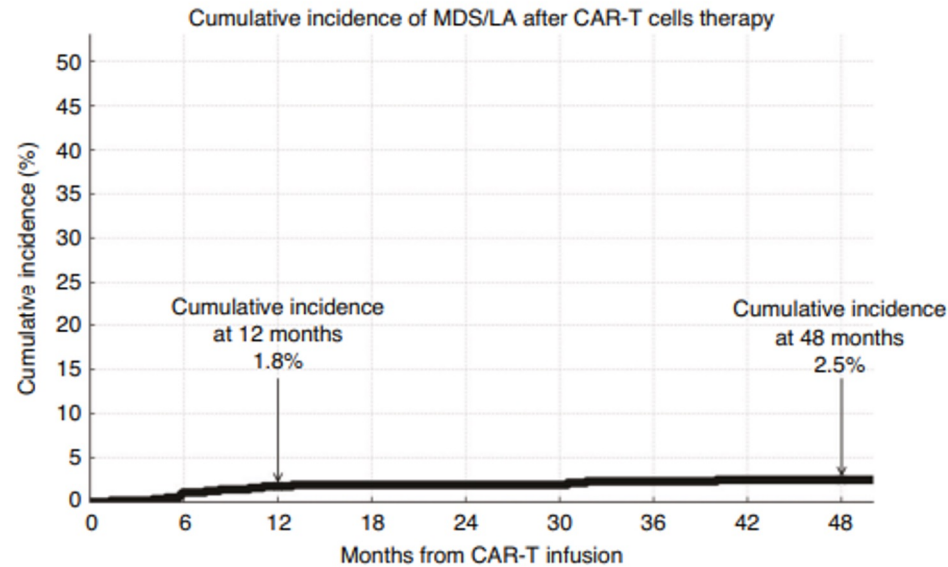
No cases of T-cell lymphoma were identified, contrasting with FDA concerns regarding T-cell malignancies;

Persistent or late-onset cytopenias after CAR-T should prompt bone marrow evaluation to rule out MDS.

Secondary malignancies post CAR-T: GITMO data

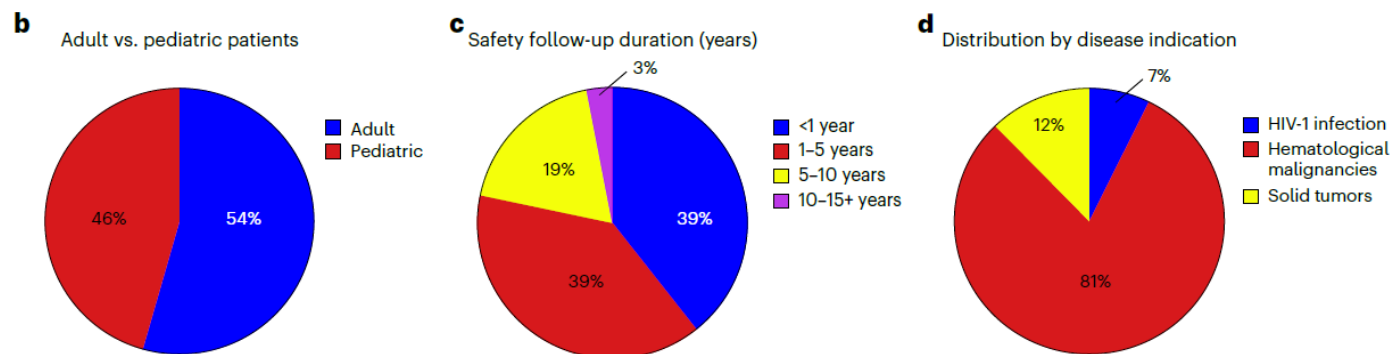
Multicenter real-world Italian study (16 centers).
Included 555 patients treated with commercial CD19 CAR-T
(axi-cel, tisa-cel, brexu-cel).
Median f-up 29m.

Incidence and Timing:
14 SMNs (2.5%) detected: 13 MDS, 1 AML
Median onset: 7.9 months from infusion; 71% occurred within 1 year.



Secondary malignancies post CAR-T: Penn “safety audit”

783 patients treated across 38 clinical trials with genetically modified autologous T-cell therapies using integrating viral vectors (lentiviral or gammaretroviral)



Incidence of Second Primary Malignancies (SPMs): 18 patients (2.3%). 5-year cumulative risk: ~4%

Latency: Median time to SPM: 1.9 years after infusion

Mostly hematologic neoplasms:

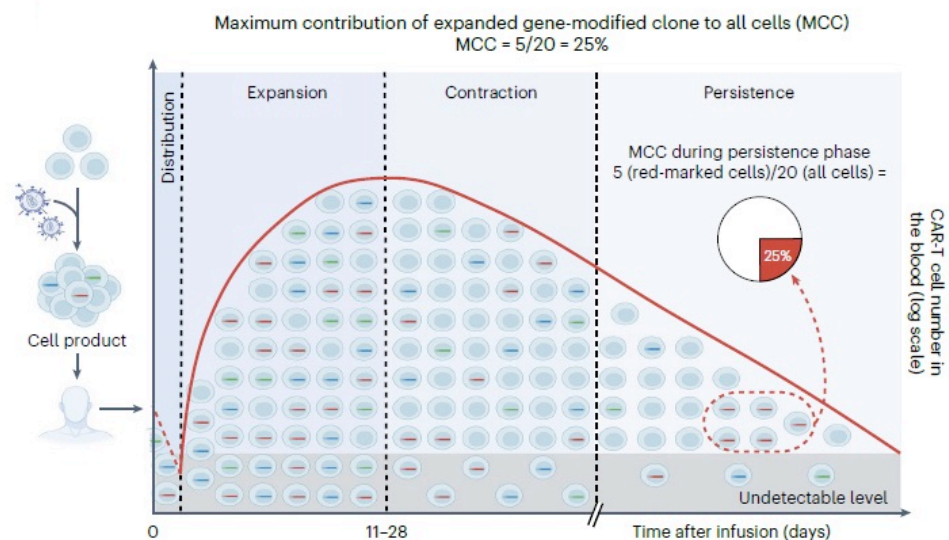
- therapy-related MDS/AML
- other myeloid or lymphoid neoplasms

Several solid tumors (lung, prostate, melanoma, others)

Only one T-cell lymphoma, which did not contain vector sequences, definitively excluding vector-driven transformation.

The observed rate of SPMs is consistent with what is expected in patients with multiple prior cytotoxic regimens, autologous or allogeneic transplants, radiotherapy, advanced hematologic malignancies

No excess incidence attributable to the gene-modified T-cell therapies themselves



Long term adverse events: delayed neurotoxicities

Late neurologic events described after BCMA CAR-T (ide-cel, cilta-cel)

Incidence: rare but clinically significant (~3–5% overall); highest with cilta-cel (5-6%)

Time of onset: typically 2–8 weeks post-CAR-T; range 3–90 days; some neuropathies occur months later.

Clinical phenotypes:

- Movement/neurocognitive disorder (MNT) with parkinsonism (bradykinesia, hypomimia, gait disorder, cognitive decline).
- Cranial nerve palsies (VII, VI; usually G1–2, reversible).
- Peripheral neuropathies including CIDP/GBS-like demyelinating syndromes.
- Late ICANS/encephalopathy (rare).

Pathogenesis:

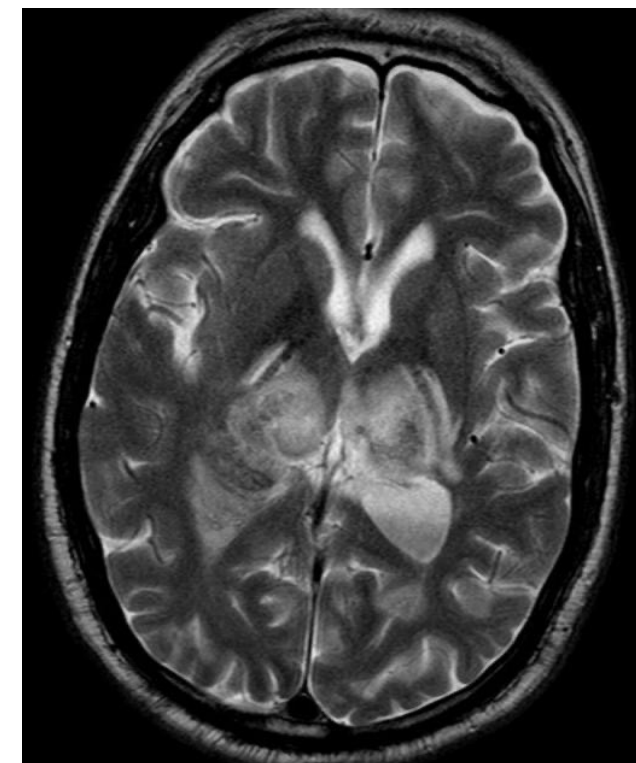
- On-target/off-tumor BCMA expression on neurons/astrocytes (basal ganglia).
- Exuberant CAR-T expansion/persistence, high tumor burden, prior CRS/ICANS → increased risk.
- Autoimmune neuroinflammatory mechanisms (neuropathies).

Management:

- MNT/parkinsonism: limited response to steroids; consider dopaminergic therapy, chemo debulking (HD-cyclophosphamide), IT chemo, ruxolitinib (case reports).
- Neuropathies → IVIG / steroids / PLEX.

Prognosis:

- Cranial palsies usually resolve; neuropathies often improve.
- MNT can be severe, sometimes progressive



Conclusions

- **CAR T-cell therapy creates a new population of long-term survivors**, in whom late toxicities (>90 days) become a major determinant of quality of life and non-relapse mortality.
- **Cytopenias remain the most frequent long-term complication**, often biphasic, sometimes profoundly prolonged. They are strongly associated with baseline inflammation, bone marrow reserve and high CAR-HEMATOTOX score → require structured monitoring and timely bone marrow evaluation.
- **Infections are the leading cause of non-relapse mortality**: driven not only by neutropenia but also by profound humoral immunodeficiency (B-cell aplasia for CD19 CAR-T; plasma-cell depletion for BCMA CAR-T) → Long-term prophylaxis, IVIG support, and vaccination strategies are essential.
- **Secondary malignancies occur but are largely explained by pre-existing risk factors** (prior chemotherapy/ASCT, clonal hematopoiesis, EBV) and not by vector-driven insertional oncogenesis → Most cases are therapy-related MDS/AML; T-cell lymphomas remain exceedingly rare and not linked to CAR-T integration
- **Delayed Neurotoxicity** is rare but significant after BCMA CAR-T (movement/neurocognitive syndromes).

Let's overcome successfully early CRS/ICANS and spare resources to take care of **long-term survivors** through shared follow-up (CAR-T center + referring hematologist).

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Mario Giacomelli – *Io non ho mani che mi accarezzino il volto*, 1963

Thank you!