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Rischio di seconde neoplasie dopo CAR-T?

Angelica Barone, MD

Fondazione IRCCS Istituto Nazionale dei Tumori

Università degli Studi di Milano

angelica.barone@unimi.it



UNIVERSITÀ
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Corso di Formazione GITMO

Trapianto e terapie cellulari: cellule, donatori e condizionamenti

Udine, 8-9 Ottobre 2026

Aula Polifunzionale Ospedale di Udine

Disclosures of Angelica Barone

Nothing to disclose

From Genome Engineering to FDA 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:

- Abecma (idecabtagene vicleucel)
- Breyanzi (lisocabtagene maraleucel)

Patients and clinical trial participants receiving treatment with these products should be **monitored life-long for secondary malignancies**. In the event that a new malignancy occurs following treatment with these products, contact the manufacturer to report the event and obtain instructions on collection of patient samples for testing for the presence of the CAR transgene. To report suspected adverse events including T cell malignancies, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

2009–2017



Pioneering CD19 CAR-T trials (Penn, NCI): 3–9y follow-up, no T-cell lymphomas reported

2017–2021



FDA/EMA approvals; 15-year long-term follow-up mandated for all products

Nov 2023



FDA safety signal: 22 T-cell malignancies reported (>27,000 US doses infused)

Mar 2024



FDA finalizes class-wide boxed warning across all 6 approved CAR-T products

2024



Large cohort/registry analyses published

2025



EMA evaluation: 38 suspected T-cell malignancy cases among ~42,500 patients treated worldwide

2026



Converging reviews: risk is real but rare, mostly not vector-driven

SPM after CAR-T: about 6% at 2 years, no excess vs standard of care

5,517 patients with lymphoma or myeloma · 25 studies (18 clinical trials, 7 real-world) · 326 SPMs

OVERALL INCIDENCE

6.0% 95% CI 4.8–7.4%
FU 21.7 mo

By disease · p = 0.56

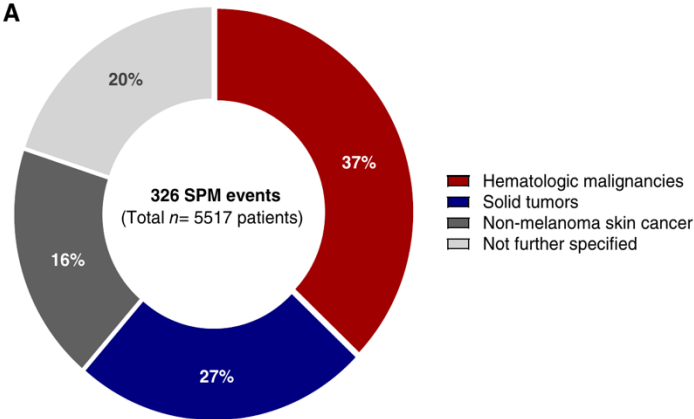
Indolent	8.7%
Myeloma	6.0%
LBCL	5.3%
Mantle cell	4.3%

By CAR-T product · p = 0.95

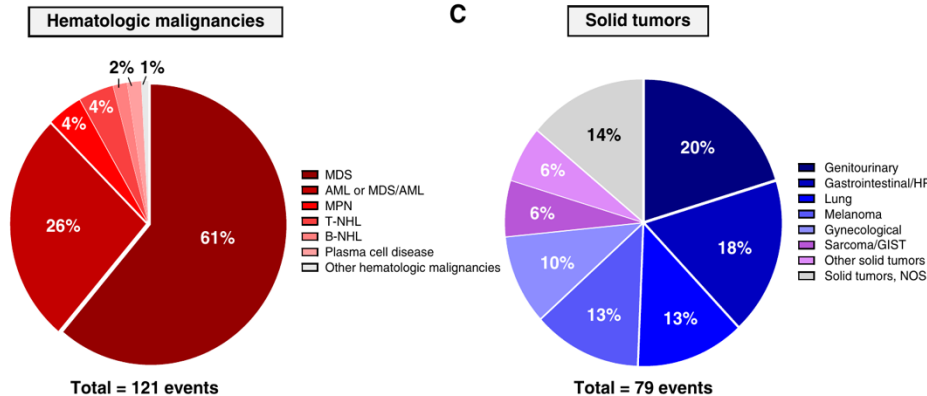
Axi-cel	7.2%
Brexu-cel	7.1%
Liso-cel	6.7%
Tisa-cel	5.8%
Ide-cel	5.5%
Cilta-cel	5.2%

TYPES OF SPM

A

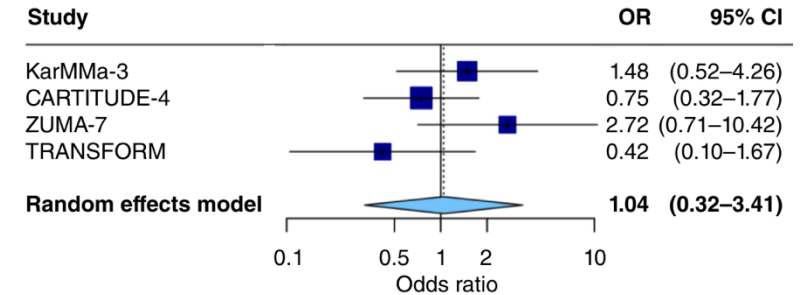


C



T-cell lymphomas: 5 cases = 0.09%

VS STANDARD OF CARE



SPM 5.0% with CAR-T vs 4.9% with SOC (33/660 vs 29/593)

PREDICTORS OF SPM

⌚ Longer follow-up	p = 0.035
📅 More prior lines	p = 0.016
👤 Trial vs real-world	p = 0.049

Not associated: CAR-T product, disease, age, prior transplant

B-cell lymphoma survivors have a 5-fold higher risk of T-cell lymphoma, regardless of CAR-T cells therapy

Population data from 2000–2016, before commercial CAR-T · risk highest in the first year after diagnosis

SEER 2000–2016 · PRE-CAR-T ERA

4.7×

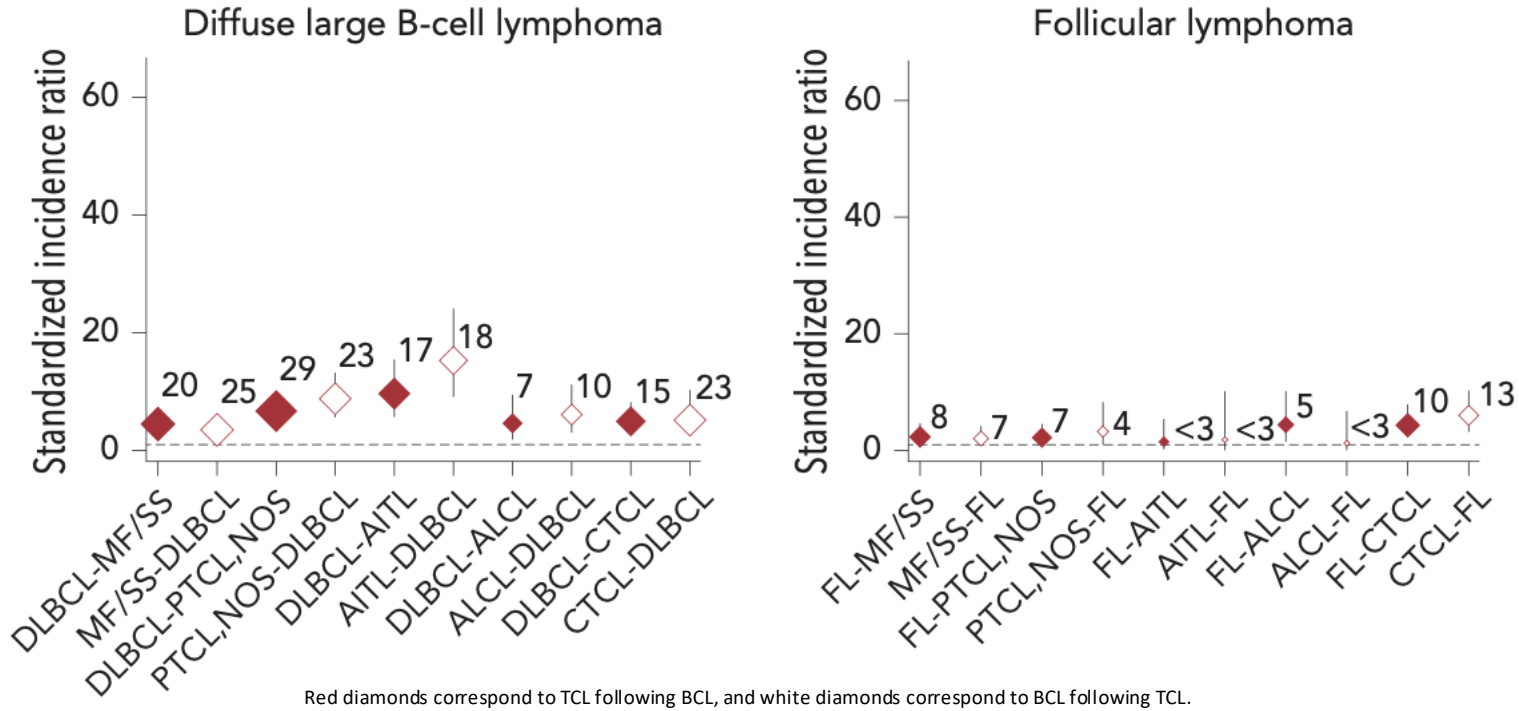
risk of T-cell lymphoma after a B-cell lymphoma, vs the general population

288,478 B-cell lymphomas

354 subsequent T-cell lymphomas

Still 3.3× after 5 years

	No. of BCL patients	Observed no. of TCLs	SIR	(95% CI)
Time since first lymphoma diagnosis, y				
<1	288 478	87	7.3	(5.9, 9.0)
1-4.9	234 412	168	5.0	(4.3, 5.8)
≥5	130 725	99	3.3	(2.7, 4.0)

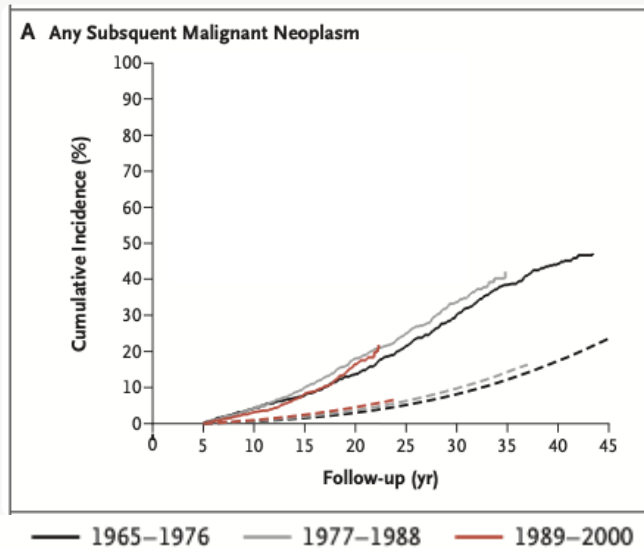


SPM are a well-known late effect of standard cancer therapy

Hematological malignancies: SPM 7.9–20% at 10 years · **myeloid neoplasms 4–6% at 10 years**

HODGKIN LYMPHOMA

N = 3,905 · 1965–2000

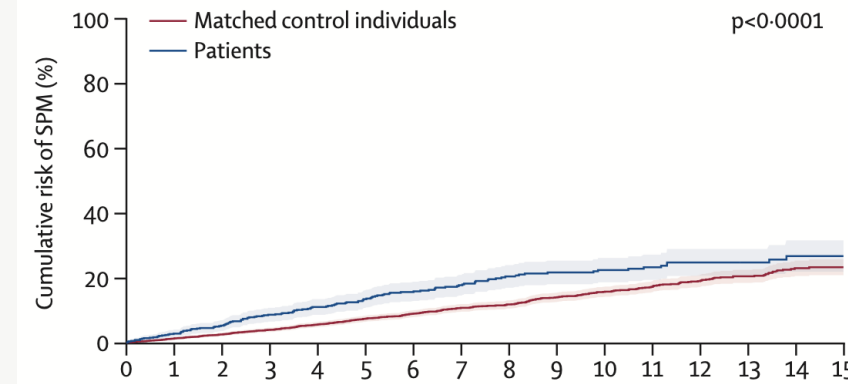


30-year cumulative incidence of SPM: 28.5%
after a median follow-up of about 20 years

Schaapveld, NEJM 2015

NHL AFTER HDT-ASCT

N=910 · MEDIAN F-UP 7.7 YEARS



3%

5-year cumulative
risk of tMN

41×

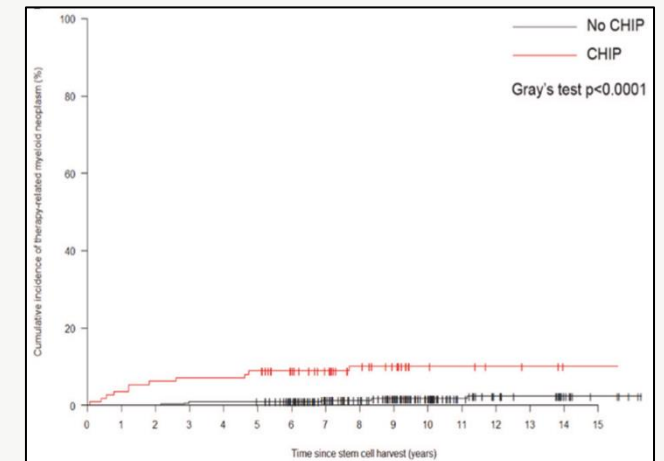
higher risk vs matched general
population

HR 10.6

ASCT vs first-line CT only

Trab, Lancet Haematol 2023

CHIP BEFORE HDT-ASCT FAVORS MYELOID NEOPLASMS



Secondary MDS/AML: **adjusted HR 6.5**

**Higher incidence in patients with clonal
hematopoiesis (CHIP) prior to ASCT**

Husby, Leukemia 2020

SPM, therapy-related myeloid neoplasms and T-cell lymphomas across the major cohorts

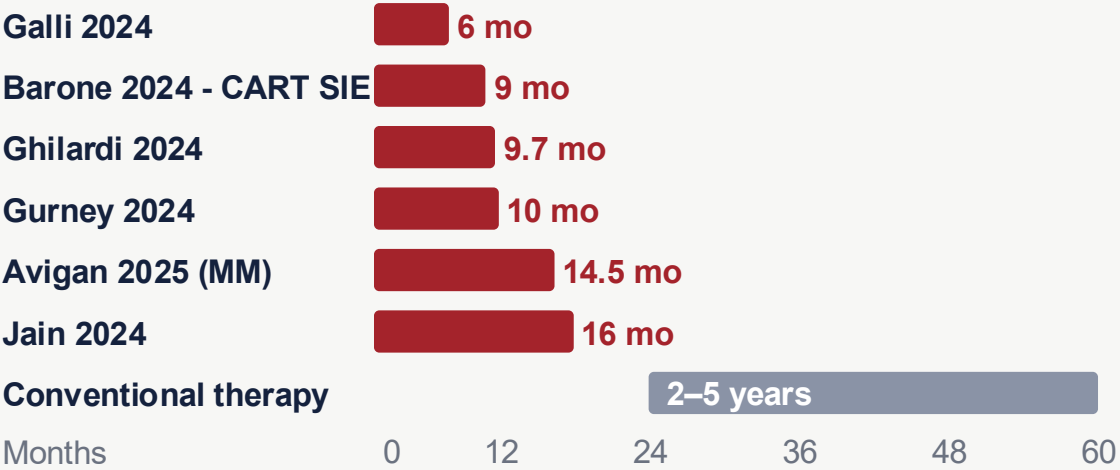
Study	Cohort (n)	SPM	TCL	tMN	F-up, median	Cumulative incidence
Elsallab, Blood 2024	12,394 (FAERS)	536 (4.3%)	17 (0.1%)	333 (2.7%)	NA	NA
Levine, Nat Med 2024	11,345 (CIBMTR)	485 (4.3%)	3 (0.03%)	NA	13 mo	NA
Dulery, Nat Med 2025	3,066 (DESCAR-T)	NA	1 (0.03%)	NA	13–18 mo	NA
Lorenc, TCT 2024	355 pts	32 (9%)	0	10 (2.8%)	19 mo	3y: 14% all / 4.5% heme
Ghilardi, Nat Med 2024	449 pts	16 (3.6%)	1 (0.2%)	3 (0.66%)	10 mo	9.5% at 5y (excl. NMSC)
Hamilton, NEJM 2024	724 pts	25 (3.4%)	1 (0.1%)	13 (1.8%)	15 mo	6.5% at 3y (heme)
Barone, BJH 2024	651 pts (CART-SIE)	28 (4.3%)	2 (0.3%)	21 (3.2%)	12.2 mo	2y: 7.0% SPM / 5.1% tMN
Jain, JCO 2024	275 pts	9%	1 (0.4%)	15 (5.4%)	5 y	NA

Across studies, myeloid neoplasms seem to appear earlier after CAR-T than after conventional therapy and survival is less than 1y

Cross-study comparison, no head-to-head data · CAR-T recipients are more pretreated and more closely monitored

Study	Patients · setting	MN, n (%)	MDS / AML	CK	TP53	Median OS, mo
CART-SIE · Barone, BJH 2024	651 · B-NHL	21 (3.2%)	17 / 4	7 (30%)	4 (19%)	10
Gazeau, Leukemia 2025	539 · B-NHL	29 (5.4%)	18 / 11	~65%	80% MDS · 33% AML	4.5
Alkhateeb, Blood Cancer J 2022	189 · NHL	10 (5.3%)	8 / 2	4/10	4/9	nr
Sillito, Haematologica 2025	403 · B-NHL	10 (2.5%)	8 / 2	nr	1/8	8.1
Lorenc, TCT 2024	355 · B-NHL	10 (2.8%)	10 / 0	nr	nr	nr
Jain, JCO 2024	275 · LBCL	15 (5.4%)	nd	nr	nr	nr
Hamilton, NEJM 2024	724 · mixed	13 (1.8%)	13 MDS/AML	nr	nr	nr
Ghilardi, Nat Med 2024	449 · mixed	3 (0.7%)	2 / 1	nr	nr	nr
Galli, BJH 2024	55 · B-NHL	3 (5.5%)	2 / 1	nr	nr	nr
Avigan, CCR 2025	213 · MM	~9%	nr	nr	80%	nr
Lymphoma series, pooled ‡		~4%	76% / 24%	~50%	19–80%	4.5–10

MEDIAN TIME TO MYELOID NEOPLASM



After CAR-T: **about 1 year** · after cytotoxic therapy and ASCT: 2–5 years

Galli, BJH 2024 · Barone, BJH 2024 · Ghilardi, Nat Med 2024 · Gurney, JAMA Oncol 2024 · Avigan, CCR 2025 · Jain, JCO 2024 · Sillito, Haematologica 2025 · Elsallab, Blood 2024 · Al-Juhaishi 2019

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Confirmed T-cell lymphomas after CAR-T

Reference	Disease / CAR-T	Onset	Histology	Molecular findings	CAR
Ozdemirli, NEJM 2024	MM / cilta-cel	4–8 mo	Indolent CD4+ GI TCL	Integration in SSU72	Positive
Harrison, NEJM 2025 (#1)	MM / cilta-cel	5 mo	PTCL-NOS, CD4–CD8–	Integration in PBX2; TET2	Positive
Harrison, NEJM 2025 (#2)	MM / cilta-cel	16 mo	PTCL-NOS, CD4–CD8–, leukemic	Integration in ARID1A; TET2	Positive
Perica, NEJM 2025	MM / cilta-cel	~2 mo	Indolent CD4+ GI TCL / LPD	Integration in TP53, TANGO2	Positive
Braun, Nat Med 2025	MM / cilta-cel, then talquetamab	9 mo	Leukemic PTCL, T-LGLL-like	CAR+ clones from TET2-mutated precursor	Positive
Kobbe, NEJM 2024	LBCL / tisa-cel	~1 mo	Aggressive PTCL	Multiple integration sites; pre-existing clone	Positive
Dulery, Nat Med 2025	DLBCL / tisa-cel	3 yrs	Primary cutaneous CD30+ TCL	Integration in PLAAT4	Positive
Ghilardi, Nat Med 2024	axi-cel	~3 mo	PTCL	TCR clone detectable pre-infusion	Negative
Hamilton, NEJM 2024	axi-cel	54 days	EBV+ TCL	Shared DNMT3A/TET2 CHIP	Negative
Tatetsu, IJH 2025	liso-cel	8 mo	PTCL-NOS	CAR not detected	Negative
CART-SIE data, unpublished	Axi-cel	9 mo	T-LGL	CAR not detected	Negative

+ 3 reported cases of clonal T-cell proliferations (mostly CAR-negative) after CAR T-cell therapy with a self-limited course, including spontaneous regression without lymphoma-directed treatment

Adapted from Stella F et al. Haematologica 2026, Tables 2–3

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Udine, 8-9 Ottobre 2026

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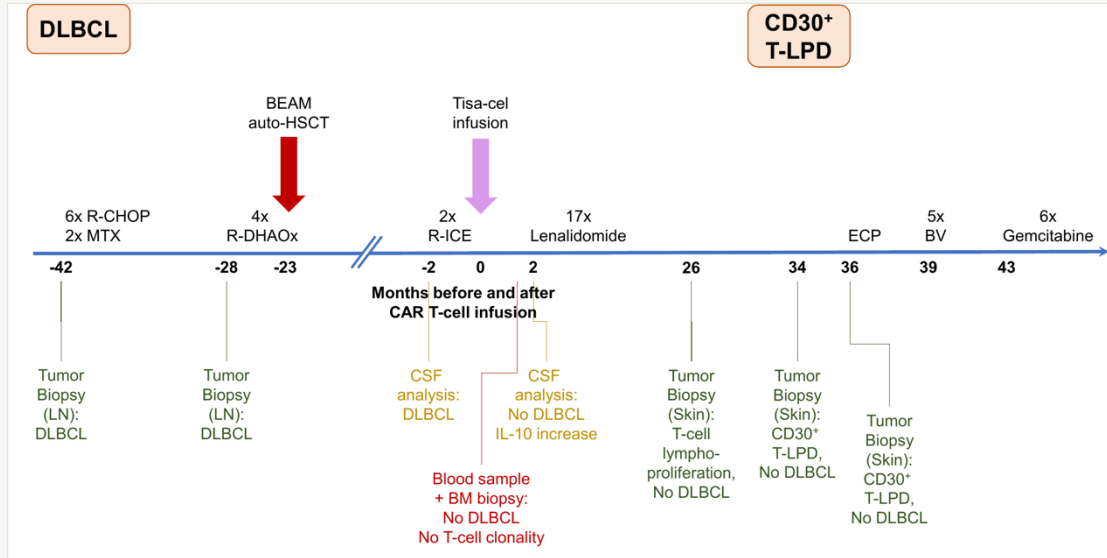
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CAR-positive does not (always?) mean vector-driven

Two CAR+ T-cell lymphomas, each with a single integration site

DULERY ET AL. · NAT MED 2025 · DESCAR-T · TISA-CEL, DLBCL

73-year-old woman · primary cutaneous CD30+ T-cell lymphoproliferation, 34 months after infusion



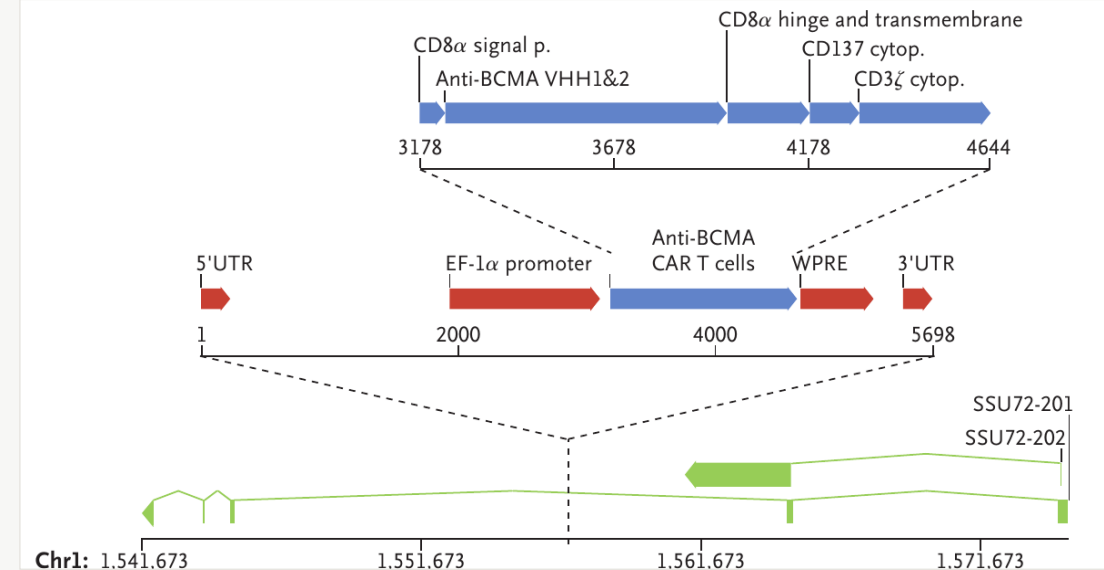
- CAR clone integrated in intron 2 of **PLAAT4**, a tumor suppressor, same orientation: **separates promoter from catalytic core**
- Only T-cell malignancy among 3,066 patients (0.03%)

Insertional mutagenesis most likely cause?

Dulery R et al. Nat Med 2025 · Ozdemirli M et al. N Engl J Med 2024

OZDEMIRLI ET AL. · NEJM 2024 · CILTA-CEL, MYELOMA

71-year-old woman · indolent CD4+ cytotoxic T-cell lymphoma of the small bowel, ~5 months after infusion



- Single integration site in **SSU72**: **gene not disrupted**: second allele intact, both alleles equally expressed, normal splicing
- Other hits: >500 somatic CNVs (KRAS, MYB, CBLB, CDKN2A, ATM)

Integration unlikely to be the direct cause

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Udine, 8-9 Ottobre 2026

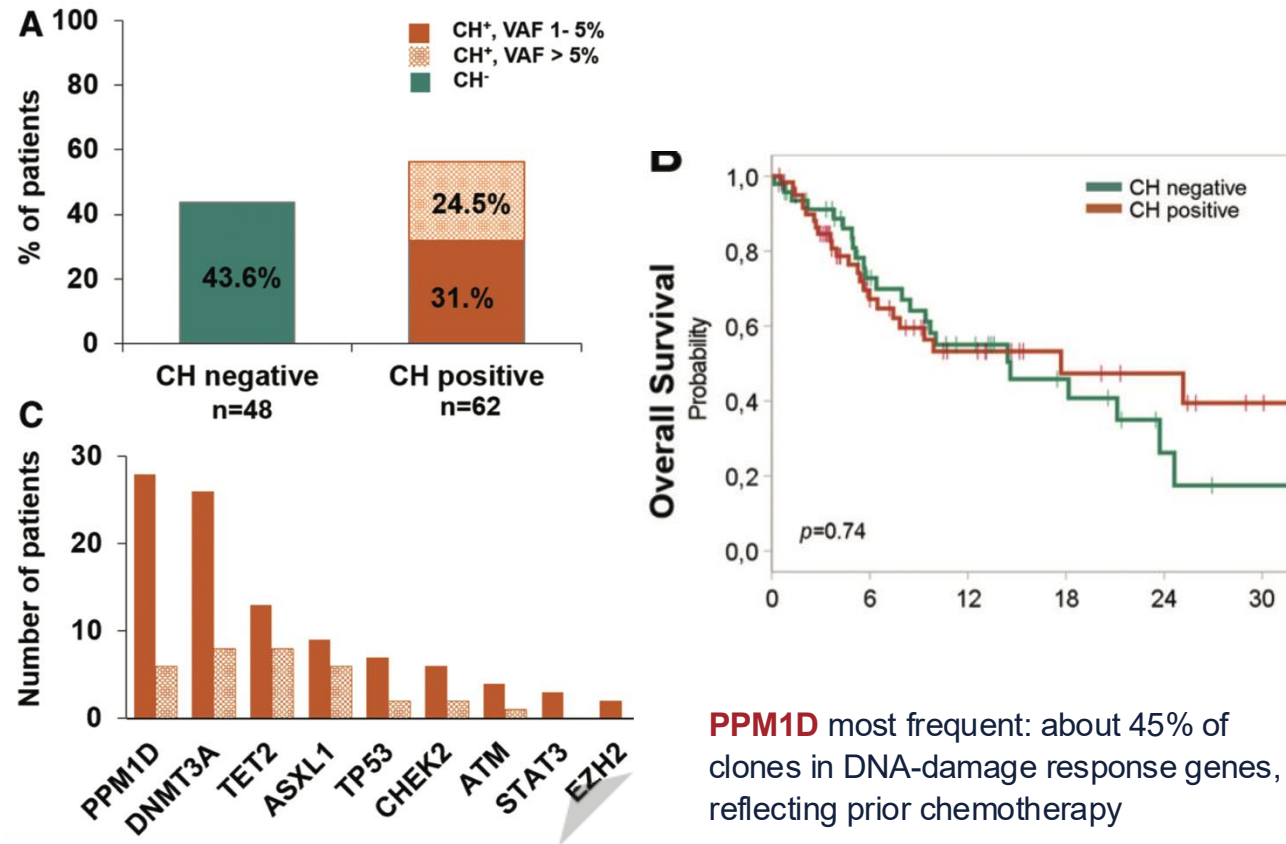
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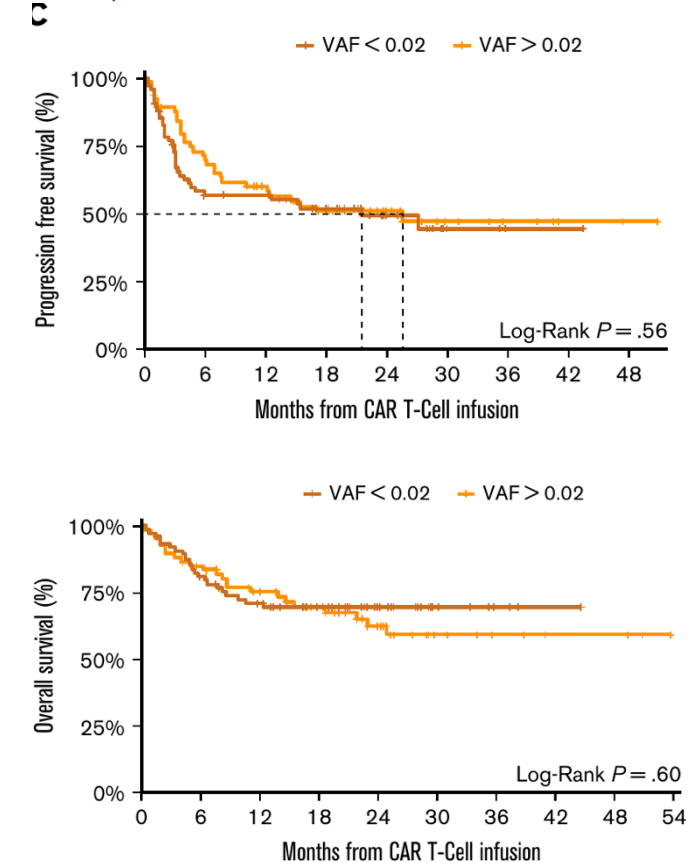
CH found in about 50% patients at infusion, without affecting survival outcomes

CH at infusion: 34% (Teipel) · 39% (Avigan, MM) · 40% (Galli) · 48% (Miller) · 56% (Panagiota)

PANAGIOTA, HEMASPHERE 2023 · 110 PATIENTS



MILLER, BLOOD ADV 2021 · 144 NHL



Panagiota V, HemaSphere 2023 · Miller PG, Blood Adv 2021 · Teipel R, Blood Adv 2022 · Galli E, BJH 2024 · Avigan ZM, CCR 2025

Rischio di seconde neoplasie dopo CAR-T? | A. Barone — GITMO 2026, Udine

Udine, 8-9 Ottobre 2026

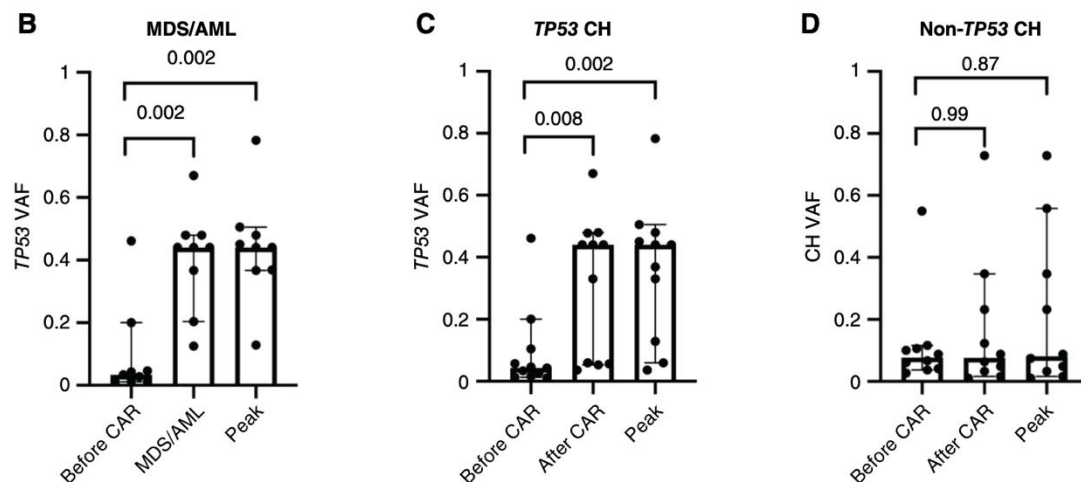
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CAR-T drives clonal expansion, with post-CAR-T myeloid neoplasms mostly arising from pre-existing clones

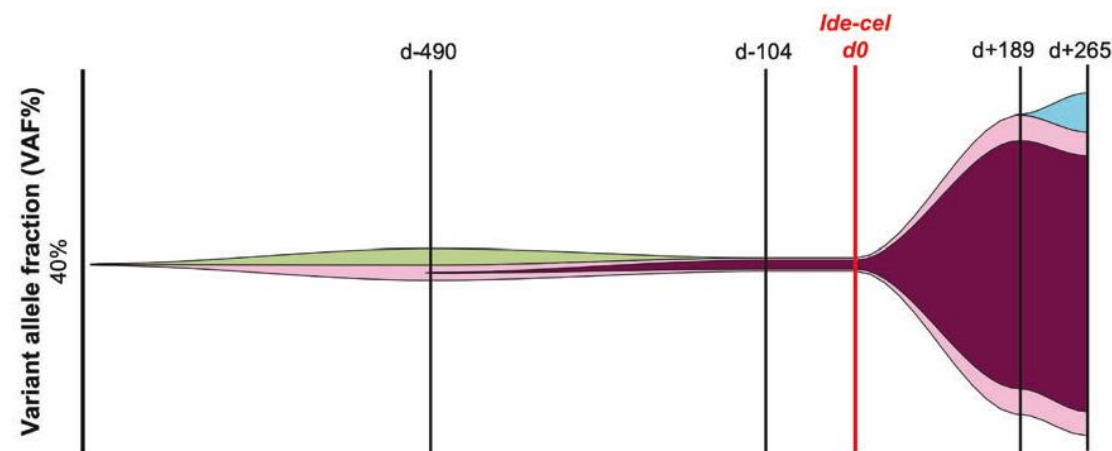
Avigan ZM et al. Clin Cancer Res 2025 · Waldschmidt JM et al. Leukemia 2026

AVIGAN, CCR 2025 · TP53 CH IN MYELOMA



- **TP53-mutated CH at baseline led to MDS/AML in about 2/3 of patients**, with TP53 clones expanding from a median VAF of 3.4% to 44% after anti-BCMA CAR-T.
- TP53 clones were already present in stem cells collected for prior ASCT.
- **Non-TP53 clones (DNMT3A, TET2, PPM1D) remained stable**

WALDSCHMIDT ET AL. · MYELOMA, ANTI-BCMA · LEUKEMIA 2026



Days to CAR-T	-490	-104	+189	+266
TP53^{R273H} (VAF, %)	1.79	1.55	34.9	35.4
TP53^{S215dupl} (VAF, %)	0	1.05	28.9	29.8
ETV6^{N156K} (VAF, %)	1.92	0	0	0
NRAS^{G12S} (VAF, %)	0	0	0	4.6

CAR T therapy may be needed as a second stimulus in intensively treated patients to drive expansion of preselected CH clones

Rischio di seconde neoplasie dopo CAR-T? | A. Barone — GITMO 2026, Udine

Udine, 8-9 Ottobre 2026

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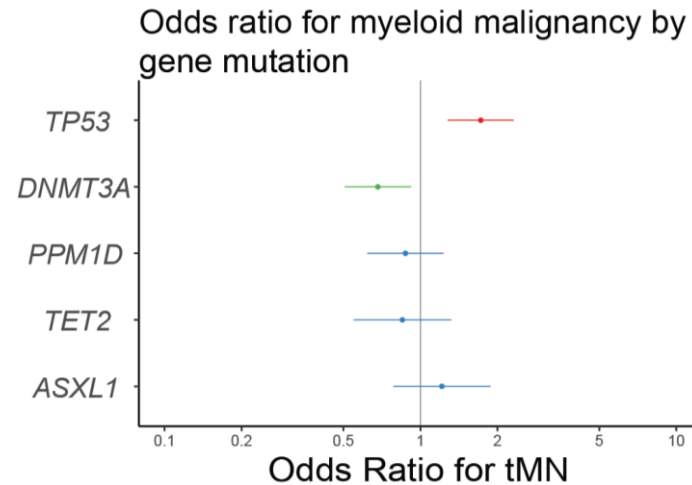
An inflammatory environment after CAR-T therapy may favor clonal expansion?

Stanford · 169 lymphoma patients, 1,124 serial cfDNA and blood samples · 31 cytopenic post-CAR marrows · 17 tMN among 533 CAR19-treated NHL

KEY FINDINGS

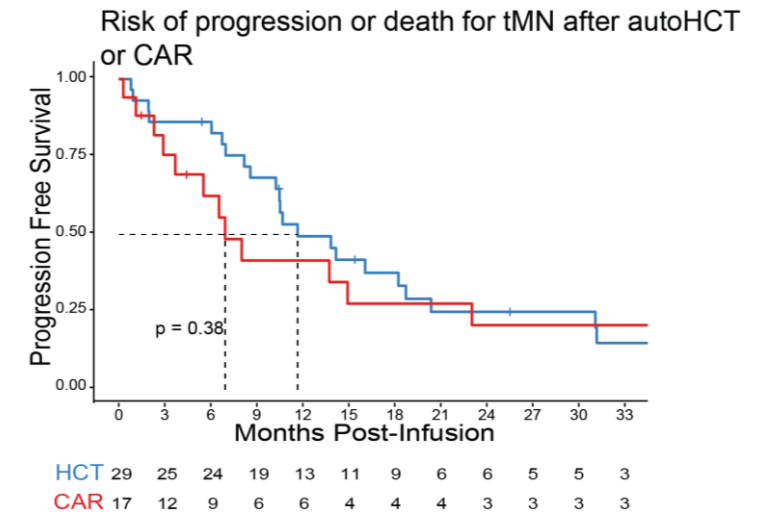
- Chemotherapy before CAR-T **increases clonal hematopoiesis**, especially TP53 and PPM1D clones
- After CAR19, **pre-existing clones expand** (TP53, PPM1D, DNMT3A), mostly in the first 3 months
- **Clones grow 5–10× faster than expected at baseline**
- Most tMN arise from mutations **already present at infusion** (15 of 19)
- **TP53** is the main driver of transformation to MDS/AML

TP53 PREDICTS tMN



TP53 ↑ risk · DNMT3A ↓ risk

POST-CAR ≈ POST-ASCT tMN

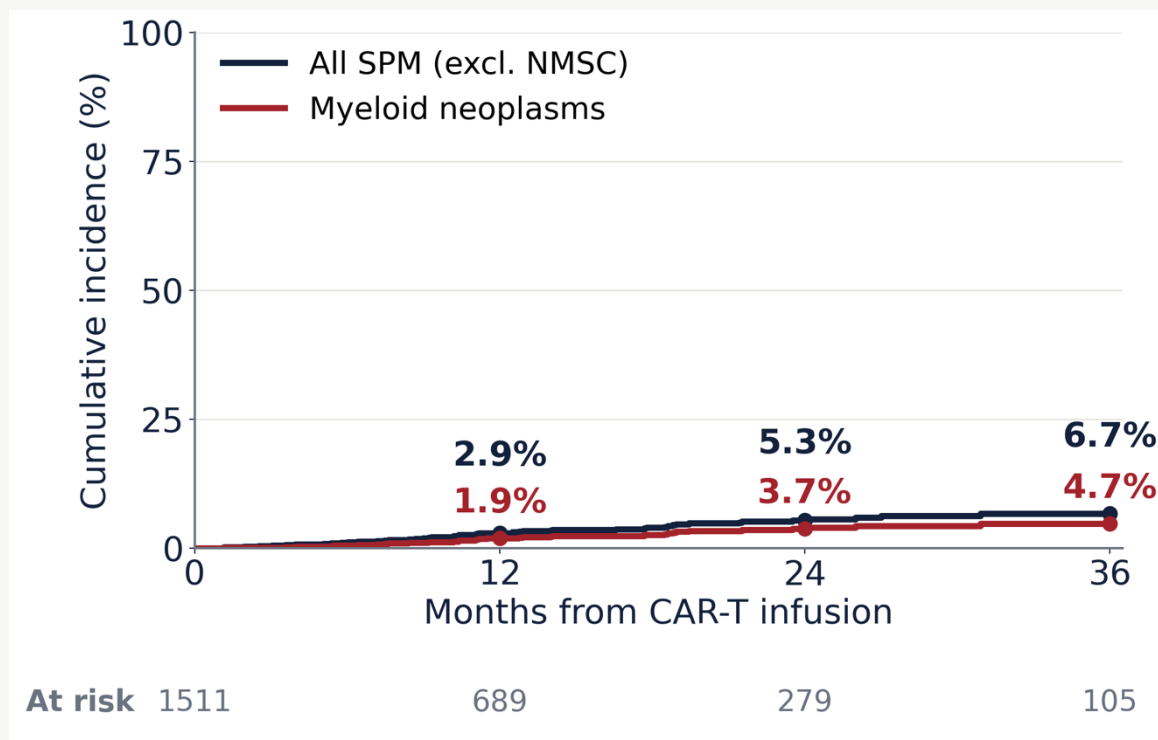


Authors' hypothesis: post-CAR marrow shows an interferon-driven inflammatory infiltrate (CD8+ effector T cells), which may favor clonal expansion

CART-SIE updated analysis (Jul 2026): SPM in 57 of 1511 patients (3.8%), 65% are myeloid neoplasms, TCL 0.1%

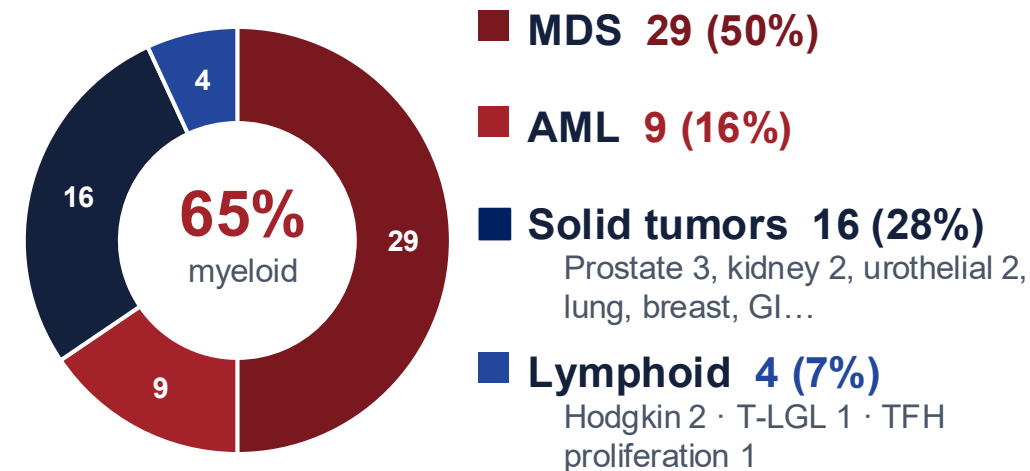
Median follow-up 15.3 months

CUMULATIVE INCIDENCE



CART-SIE study (NCT06339255), unpublished updated analysis

TYPES · 58 SPM IN 57 PATIENTS (EXCL. NMSC)



+ 6 non-melanoma skin cancers

Median onset, all SPM
10.4 mo

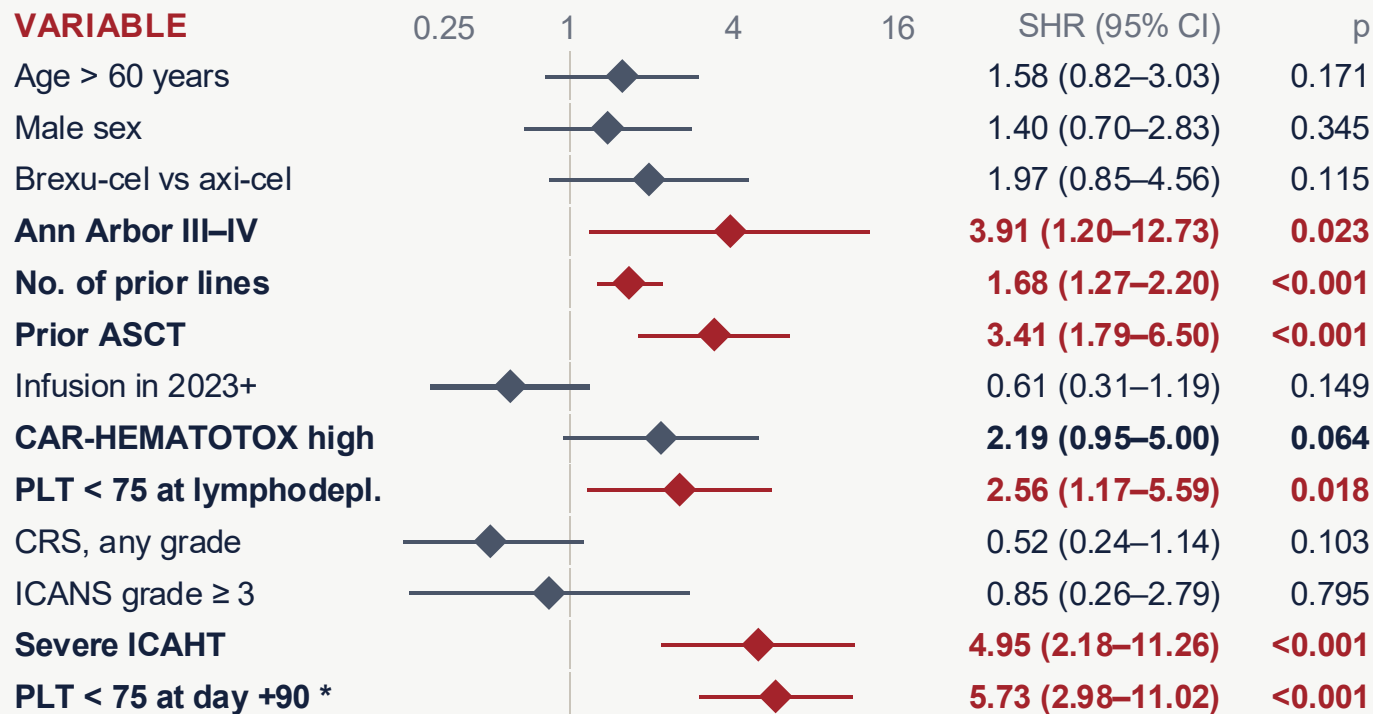
Median onset, myeloid
11.1 mo

2-year incidence of myeloid neoplasms by product

Axi 2.9% **Tisa 4.1%** **Brexu 5.9%** **Liso 0/53**

CART-SIE Study: previous treatment burden flags patients at higher risk of tMN

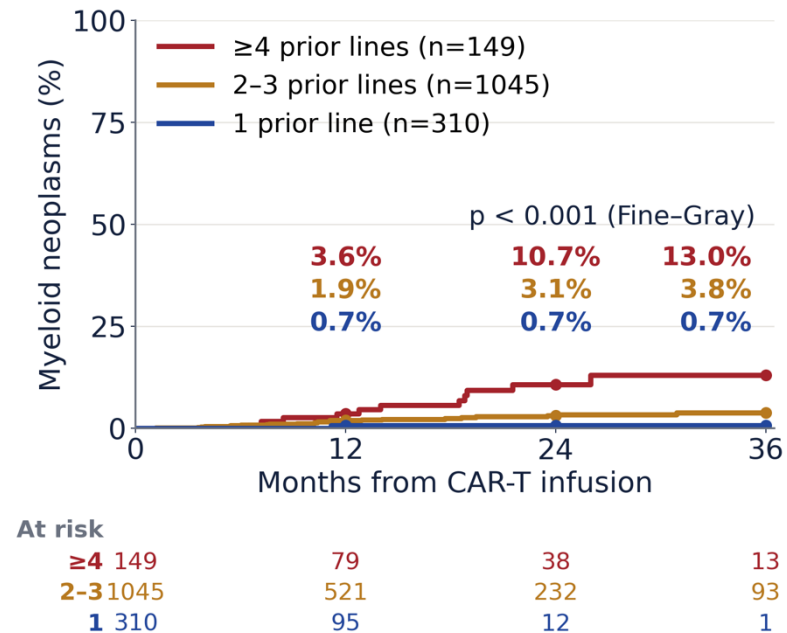
Fine-Gray models, death as competing event · 38 myeloid neoplasms in 1,511 patients



Univariable · * landmark at day +90 · LD = lymphodepletion · SHR = subdistribution hazard ratio

CART-SIE study (NCT06339255), unpublished updated analysis

MYELOID NEOPLASMS BY PRIOR LINES

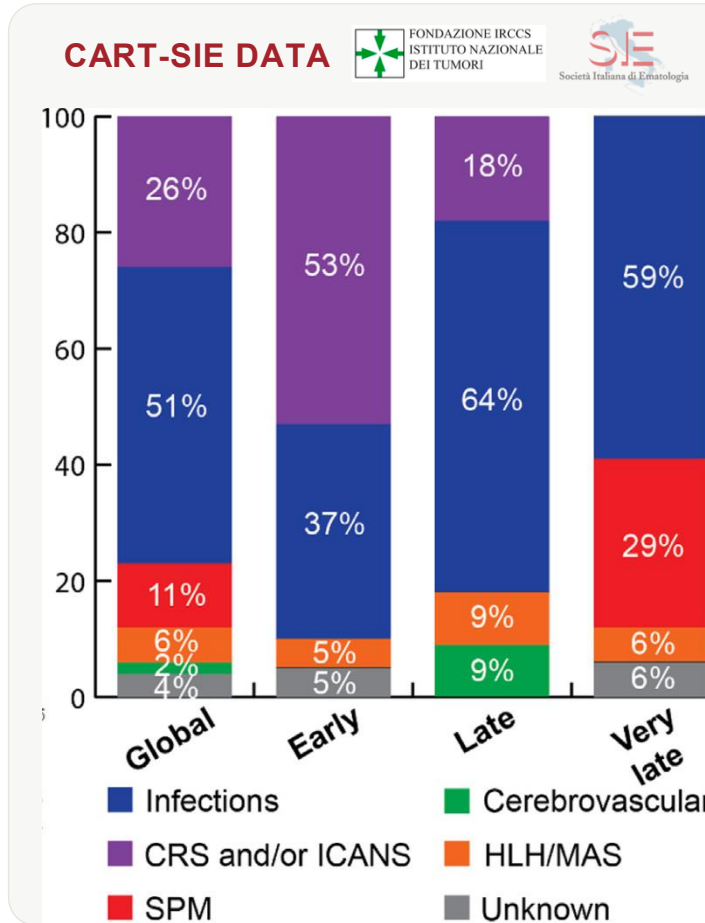
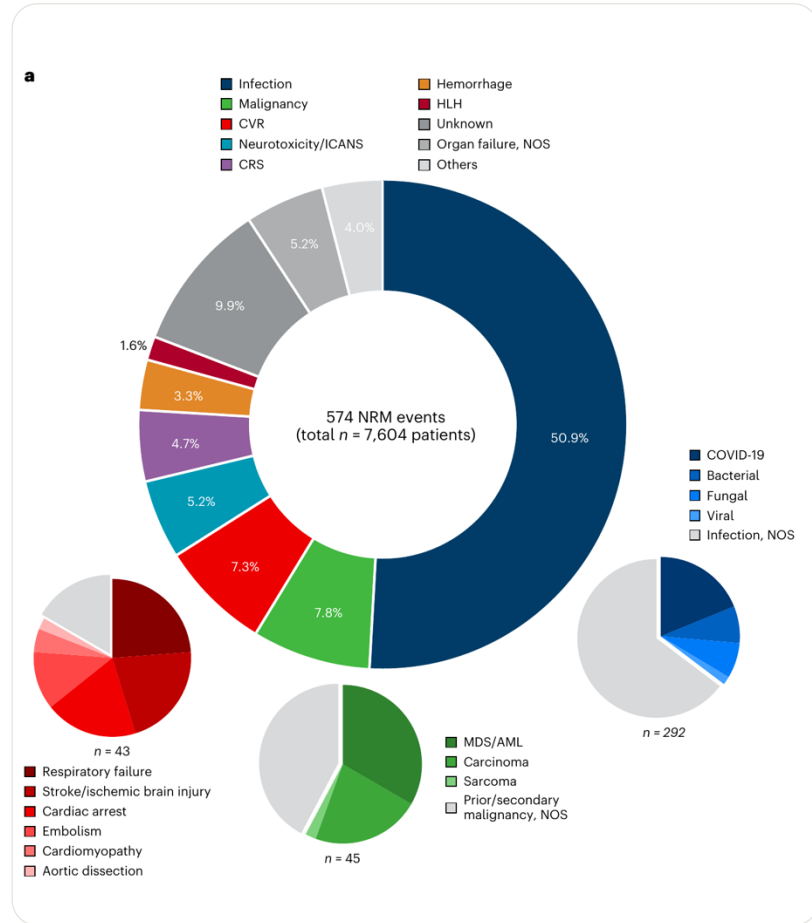


Multivariable	SHR (95% CI)	p
Prior lines (each)	1.45 (1.08–1.96)	0.015
PLT < 75 at LD	2.16 (0.99–4.73)	0.054
Prior ASCT	2.41 (1.21–4.81)	0.013

Second malignancies are the second cause of non-relapse death

Meta-analysis: 46 studies (18 trials, 28 real-world) · 7,604 patients · 574 non-relapse deaths

CART SIE DATA: 932 evaluable patients · median follow-up 17.8 months · 47 NRM events (5%), 5 due to SPM



11%
of NRM due to SPM

515 d
median time from infusion to death from SPM

29%
of very late NRM (> 90 days)

1.8%
NRM from SPM at 2y

SPM as time-dependent covariate for NRM

Univariable **HR 2.32 (1.01–5.34), p 0.047**

Multivariable * **HR 1.80 (0.58–5.58)**

* with CRS ≥ 3, ICANS ≥ 3, infections, steroids

Updated cohort, July 2026 (n = 1,511)

SPM cause 10 of 76 NRM deaths, and 8 of 19 beyond the first year

SPM after CAR-T cells?

The risk is real, mostly myeloid, and largely driven by the patient's history

- 1 ~6% SPM at 2 years — **no excess vs standard of care** in randomized trials (5.0% vs 4.9%)
- 2 Mostly myeloid (2/3) — **pre-existing clones (TP53, PPM1D) selected by prior therapy, expanded after CAR-T**
- 3 T-cell lymphomas are rare (~1/1,000) — vector integration is often one element of **multi-hit oncogenesis** rather than a sufficient causal explanation.
- 4 SPM matter for survival — in CART-SIE, **the leading cause of non-relapse death beyond year 1**
- 5 In practice — **Routine pre-CAR-T screening for clonal hematopoiesis is not indicated as an exclusion criterion, but targeted testing in high-risk patients supports risk stratification and long-term monitoring**

OPEN QUESTIONS

- > **Why do tMN seem to appear earlier after CAR-T than after standard therapy?**
- > **Will we see a lower frequency of tMN with CAR-T cells moving in earlier lines of therapy?**



Acknowledgements



All the Italian qualified centers for CAR-T treatment, the referral centers, patients, families and nurses.

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