9° WORKSHOP
IN EMATOLOGIA TRASLAZIONALE
DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Bologna, Aula "G. Prodi", 19-20 maggio 2025

Neoplasie secondarie e MDS post CAR-T

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Regione Lombardia

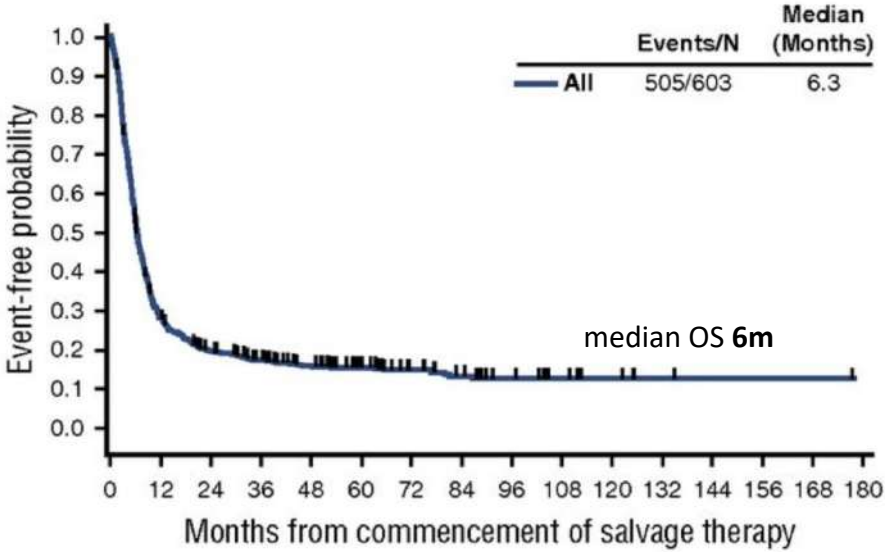
Disclosures di Nicola Polverelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kite Pharma			x		x		
Novartis			x		x	x	

Outcomes of R/R DLBCL and ALL prior to CART/Bite availability

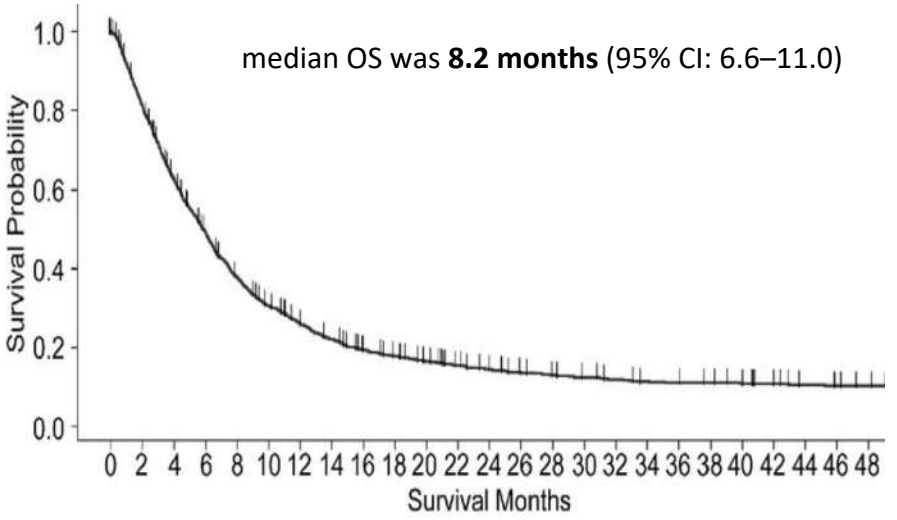
R/R DLBCL

(Primary refractory, refractory to 2° line or later, relapsed ≤12 mo from ASCT)



R/R B-ALL

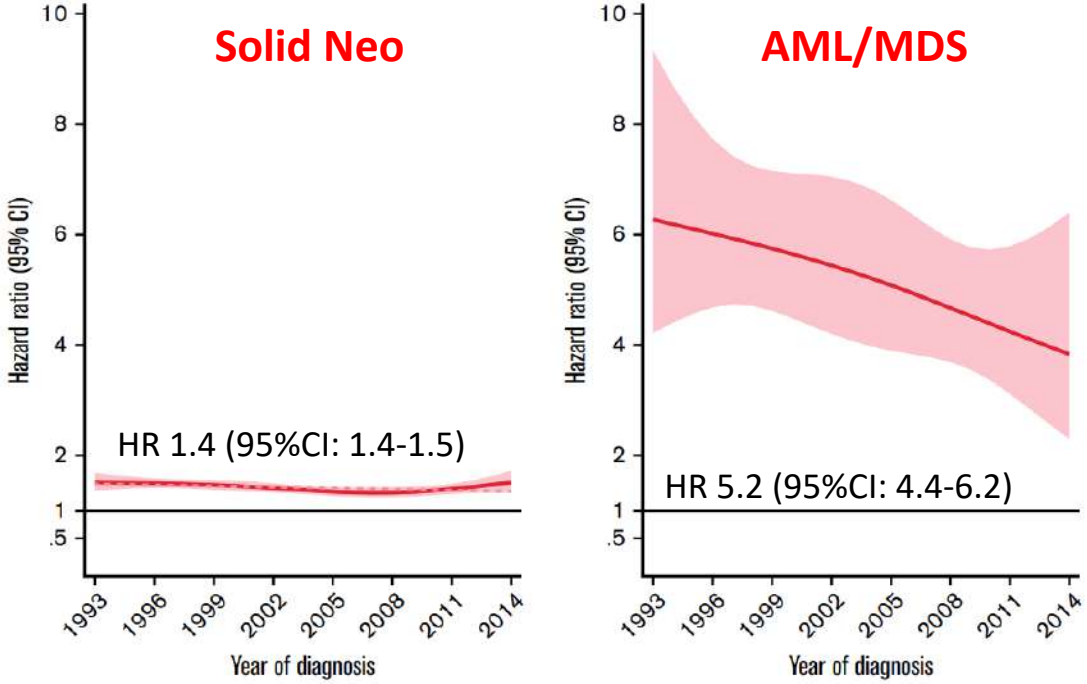
(Ph-negative relapsed/refractory B-precursor ALL patients)



Crump M et al ***Blood. 2017***;130(16):1800-8; Gökbuget N et al***. Haematologica 2016***; 101(12): 1524-1533

The incidence of SPMs in NHL: the Sweedish registry

Among 32100 NHL patients, 3619 solid tumors and 217 MDS/AML cases were observed.



Second Neoplasms	HR (CI95%)	p
CML/MPNs	1.4 (1.0-2.0)	0.036
Hodgkin Lymphoma	8.7 (5.4-13.4)	<0.001
Multiple Myeloma	1.0 (0.7-1.4)	0.854
Lymphatic Leukemia*	3.7 (2.1-6.6)	<0.001

*ALL and lymphoblastic/lymphocytic leukemia unspecified

Joelsson J et al. ***Blood Adv. 2022***; 6(8):2657-2666.

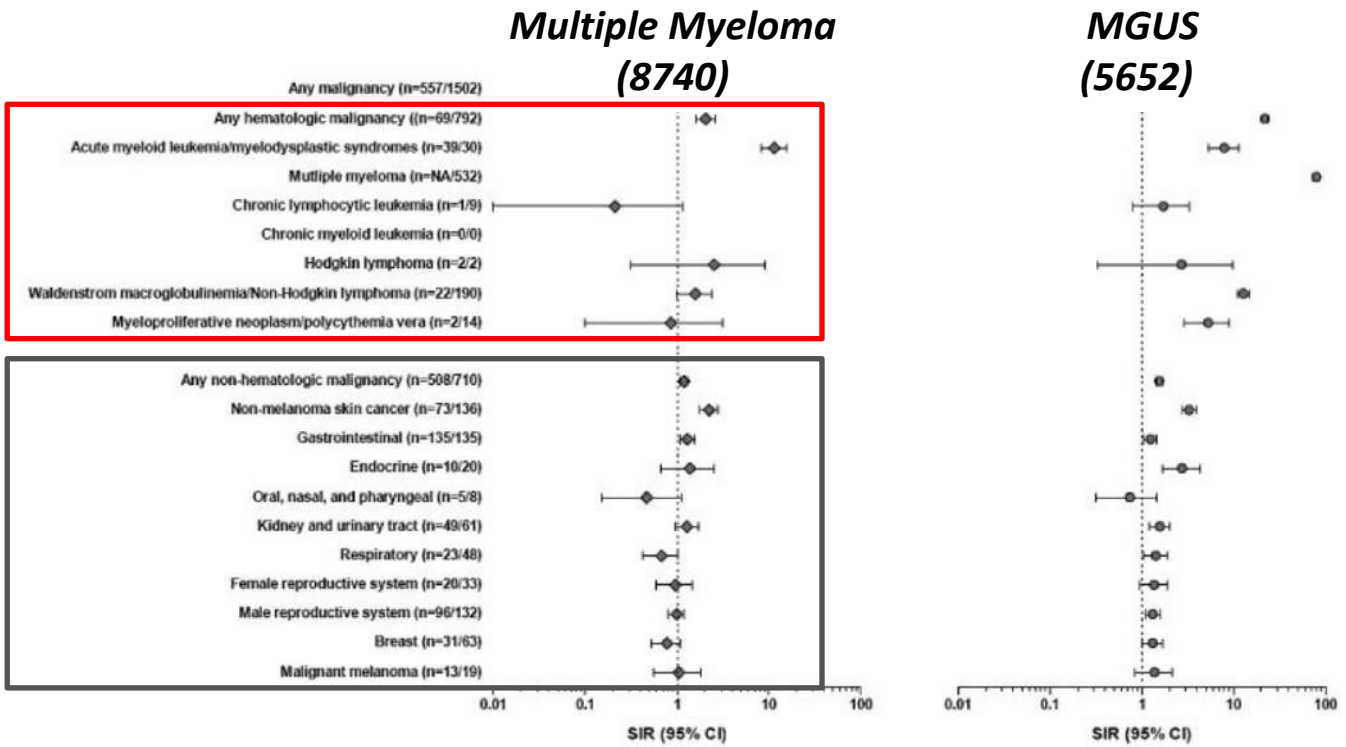
SPMs in Multiple Myeloma in the pre-CART era

Hemato

HR 2.04 (95% CI 1.59-2.58)

Solid

HR 1.19 (95% CI 1.09-1.30)

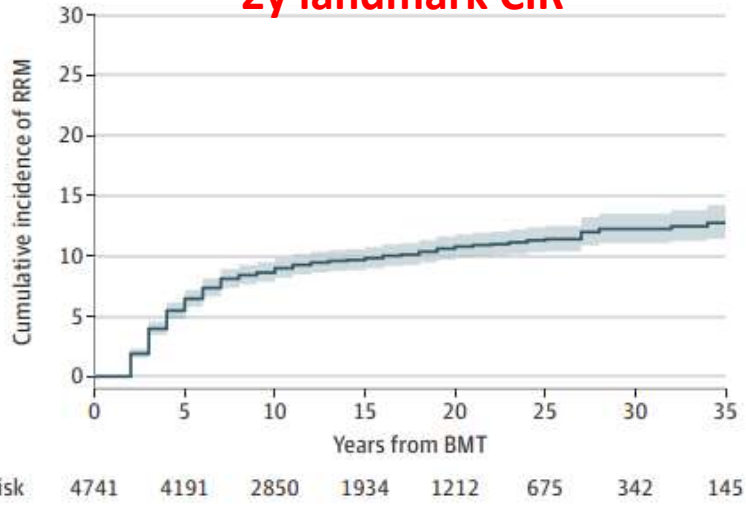


Mailankody S et al. ***Blood 2011;*** 118 (15): 4086–4092; Razavi P et al. ***Blood Cancer Journal 2013***; 3, e121; Jonsdottir G et al. ***Haematologica 2016***; 101(4):

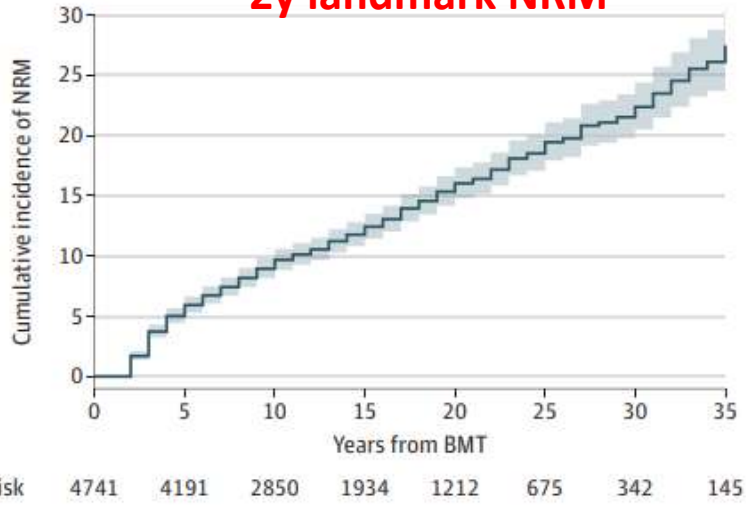
The issue of non relapse mortality after allo-HCT

4741 pts (>2y after alloHSCT) HSCT Jan 1974 - Dec 2014. Cut-off March 2020.

2y landmark CIR



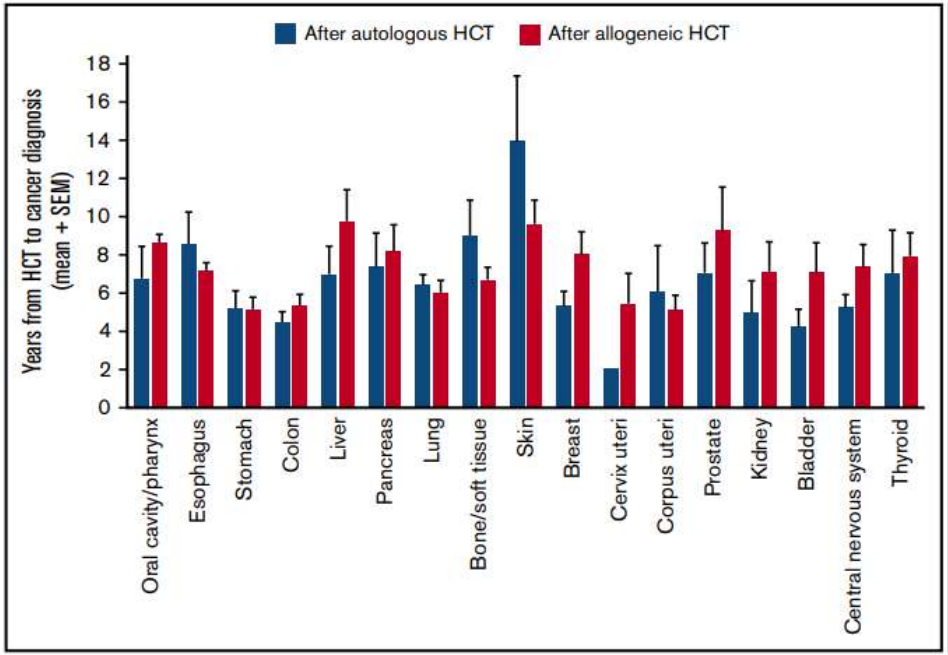
2y landmark NRM

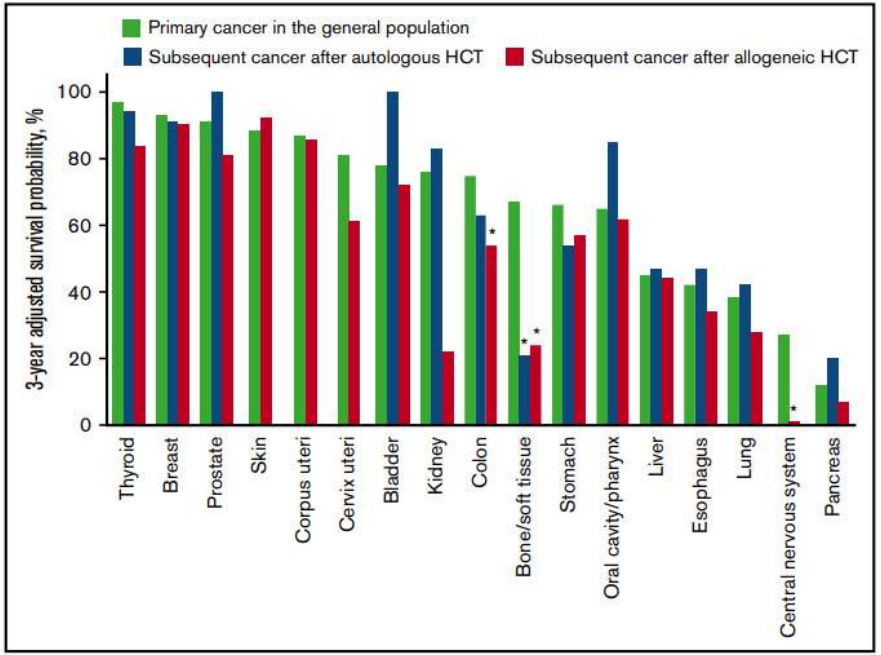


Leading **causes of NRM** included infection (30-year cumulative incidence: 10.7%; SMR, 52.0) and **second cancers** (30-year cumulative incidence: 7.0%; SMR, 4.8)

Bhatia S et al. ***JAMA Oncol. 2021***;7(11):1626-1634

Second Cancers in auto and allo-HCT vs General Population

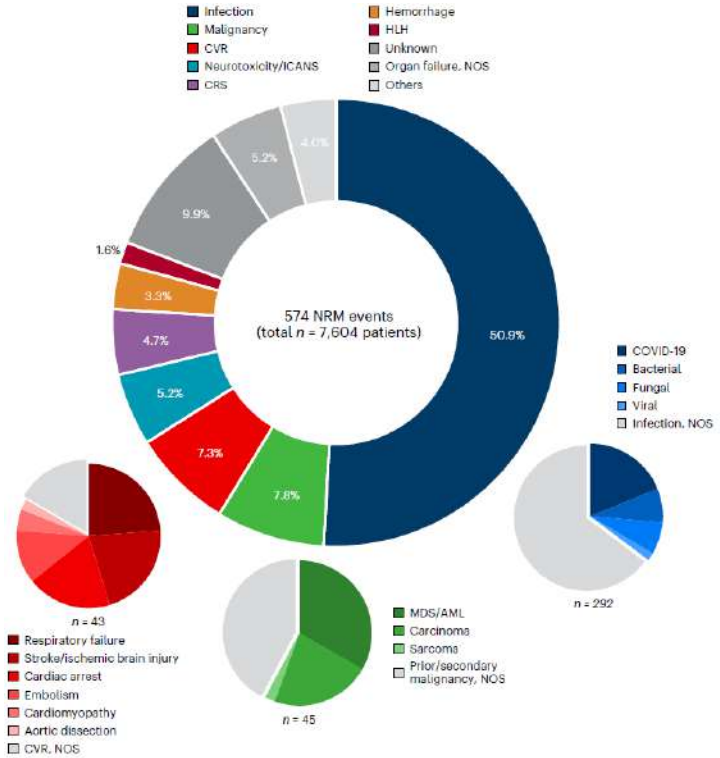




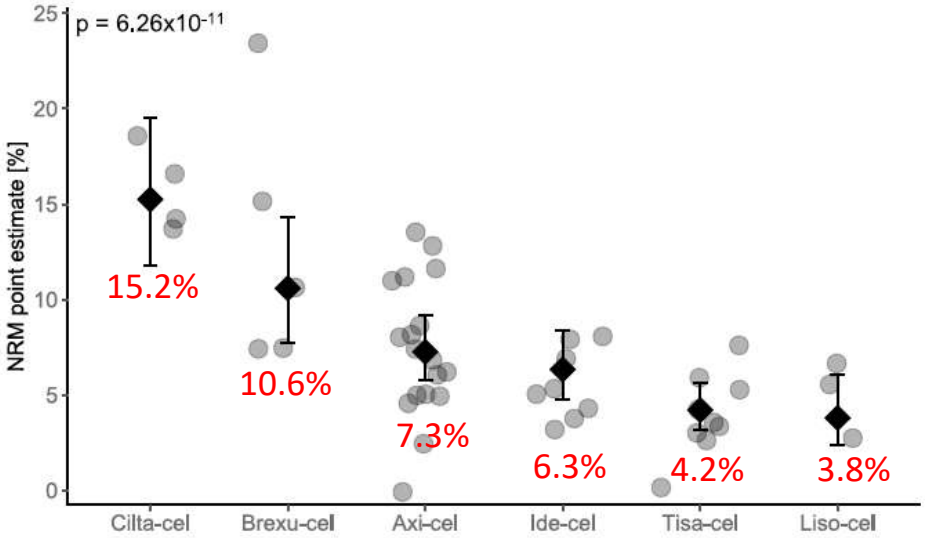
31867 transplanted patients in Japan (21189 allo-HCT) for 713 SC.
Median age at diagnosis of SC was 55y vs 67y of general population.

Inamoto Y et al. ***Blood Adv 2018***; 2 (15): 1901–1913.

Non-relapse mortality in CART

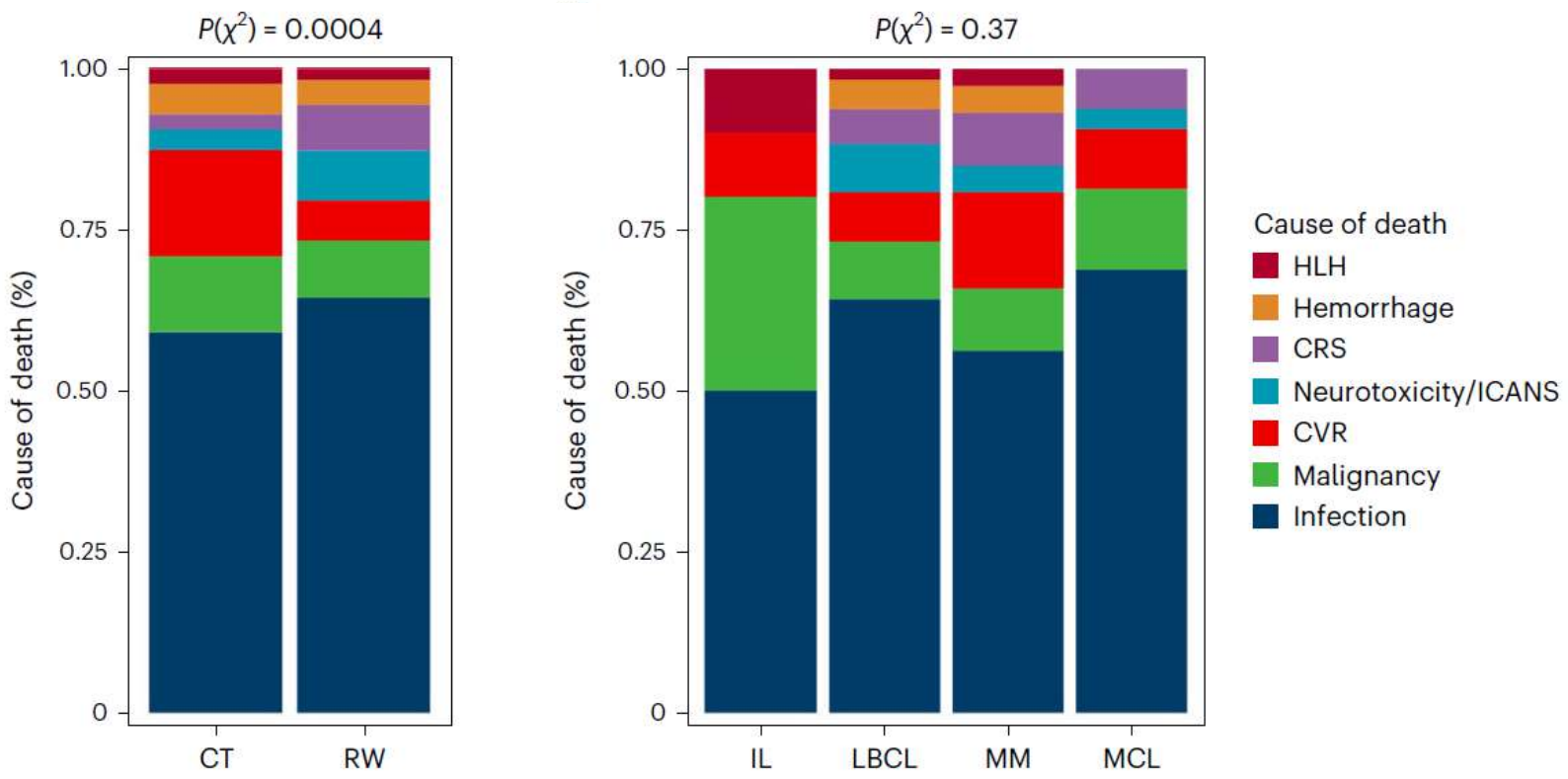


NRM at 13 months estimates varied across **disease**: MCL 10.6%, MM 8.0%, LBCL 6.1%, indolent lymphomas 5.7%



Cordas Dos Santos DM et al. ***Nat Med 2024***;30(9):2667-2678.

Causes of NRM: Comparison by Study Type and Underlying Disease



Cordas Dos Santos DM et al. ***Nat Med 2024***;30(9):2667-2678.

Secondary T-cell malignancies after CAR-T infusion

PERSPECTIVE

Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy

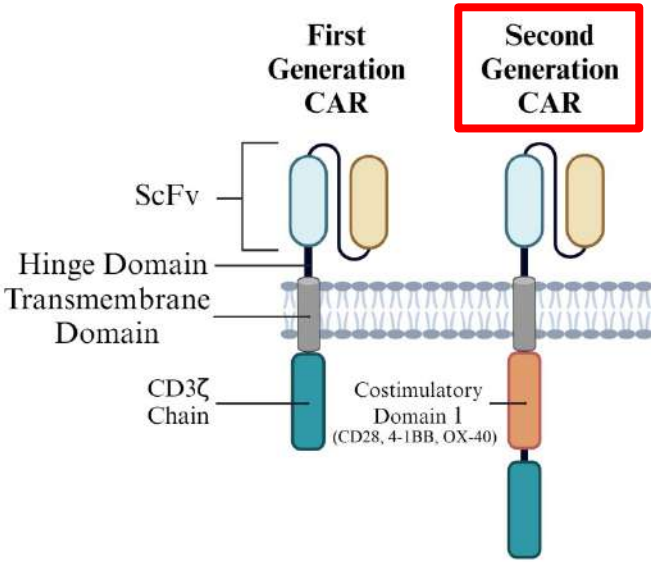
Authors: Nicole Verdun, M.D., and Peter Marks, M.D., Ph.D. Author Info & Affiliations

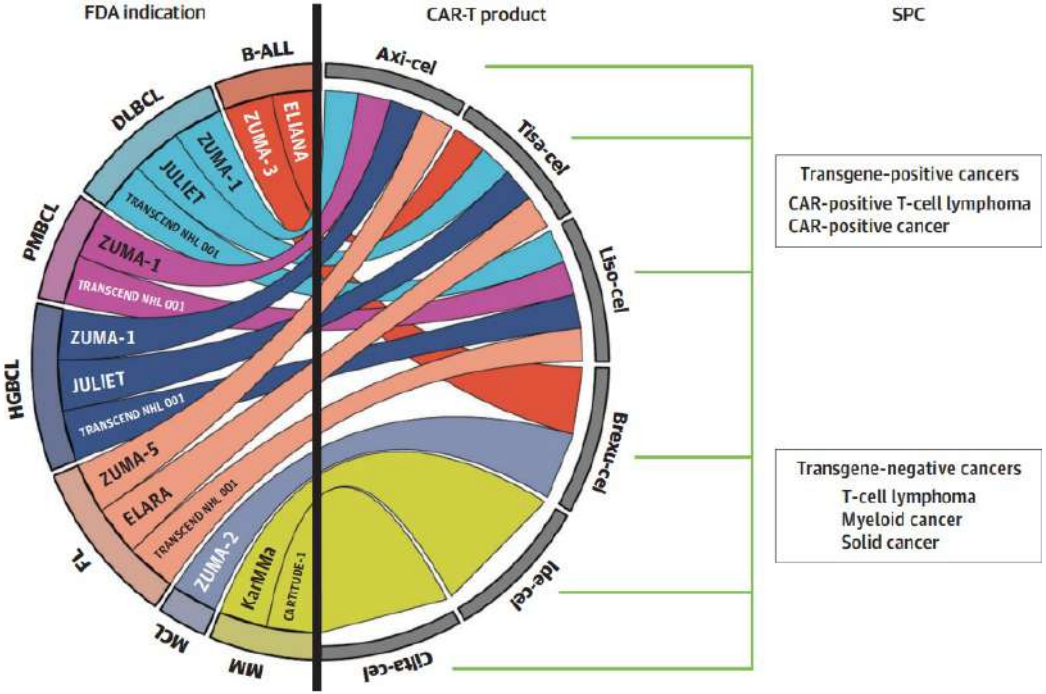
FDA Alert (November 2023): Twenty-two cases of **T-cell malignancies** were identified in patients treated with **CD19-** or **BCMA-**targeting **CAR-T cells**, all occurring **within two years** post-infusion.

Potential Genotoxicity: At least **three cases** showed evidence of **clonal vector integration**, raising concerns about **insertional genotoxicity**.

Verdun N et al. ***N Engl J Med 2024***;390:584-58

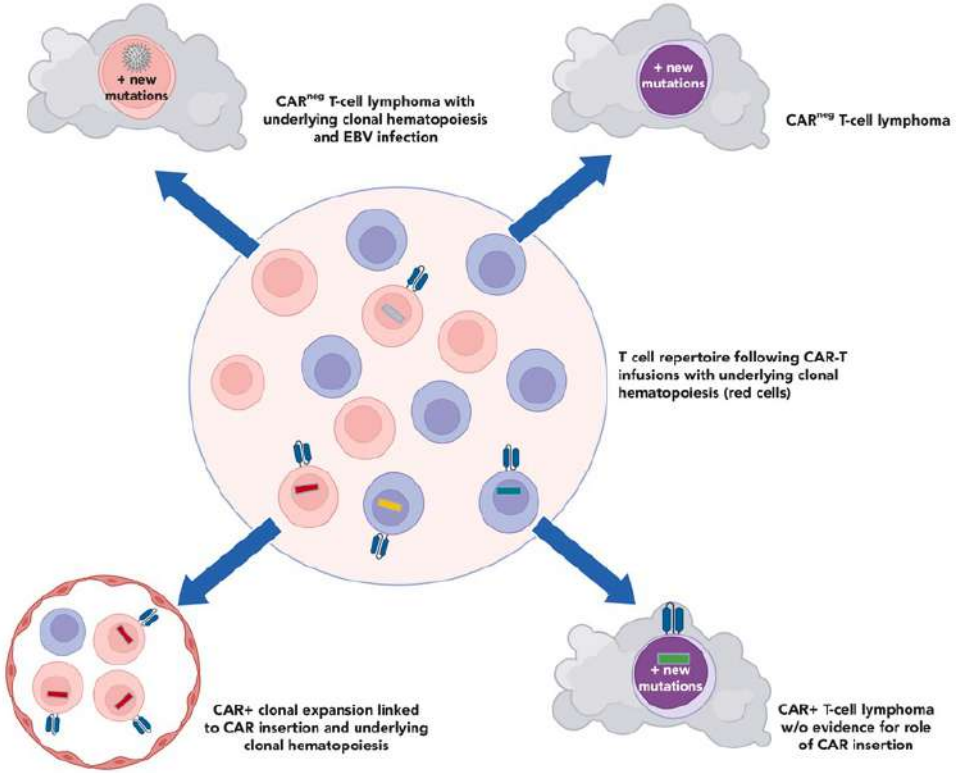
Components of approved CAR-T and SPMs





Khan SH et al. ***Front Immunol 2025***; 15:1489827; Pathel S et al. ***JAMA Oncol. 2025***;11(2):174-181

Secondary T-cell malignancies: mechanisms of mutagenesis



Vector Integration and Insertional Oncogenesis

Clonal Expansion of Transduced T Cells with Pre-existing or Acquired Mutations

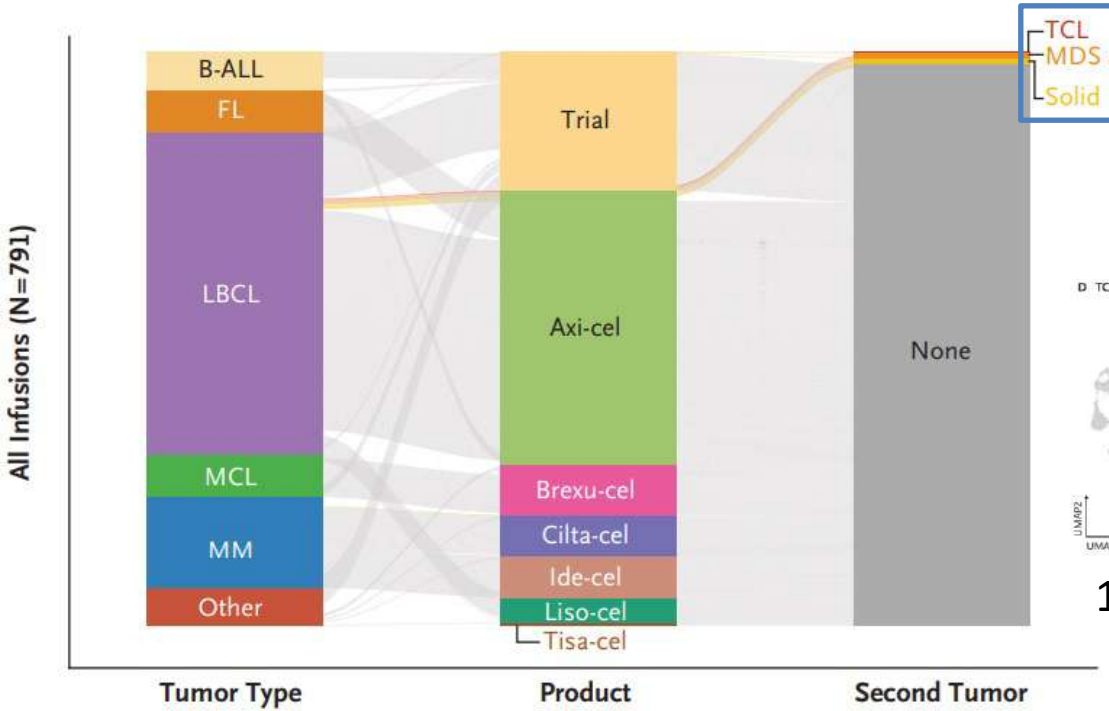
Immune Dysregulation and Cytokine Milieu Post-CAR T Therapy

Host Factors and Underlying Disease

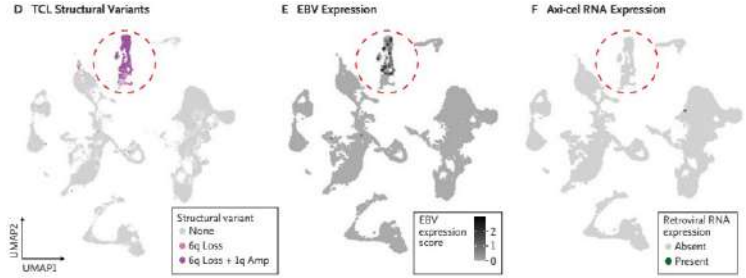
Hu J & Dunbar C. ***Blood 2024***; 144 (24): 2473–2481.

Secondary malignancies after CAR-T infusion

724 unique patients at Stanford University Medical Center (2016-2024)



24 cases (3,4%)

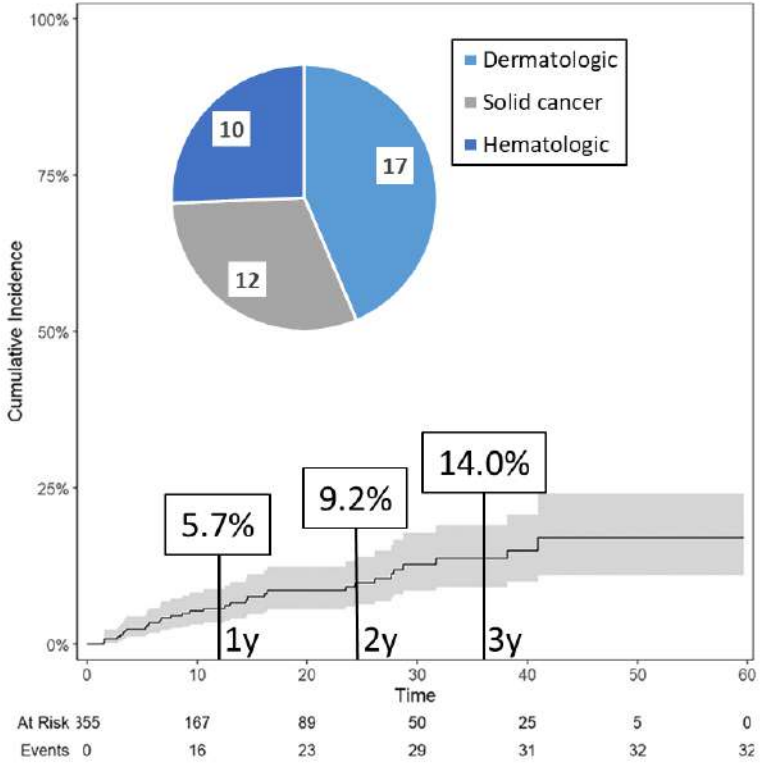


1 case of TCL not arising from CART

Hamilton MP et al. ***N Engl J Med 2024***; 390(22):2047-2060.

The incidence of SPMs in NHL after CART: MSKCC experience

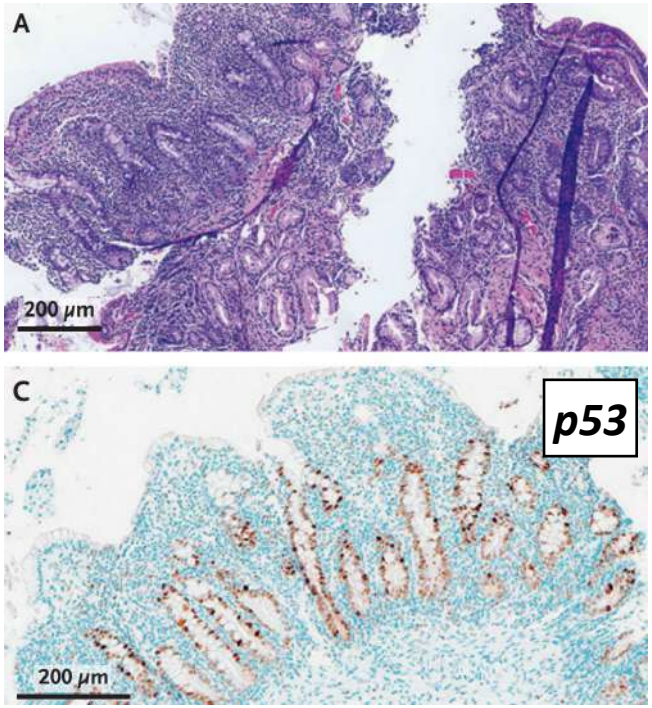
Total	355 (100)
Age, median (range)	65 (56-82)
Gender (male)	65%
Histology	
Large B-cell lymphoma	87%
Follicular lymphoma	4%
Mantle cell lymphoma	9%
Prior auto-HCT	21%
3 or less lines	65%
CAR T product	
Axicabtagene ciloleucel	188 (53)
Brexucabtagene autoleucel	18 (5)
Lisocabtagene maraleucel	73 (21)
Tisagenlecleucel	76 (21)
Median follow-up, m (IQR)	*19.3 (7.5-33.2)*

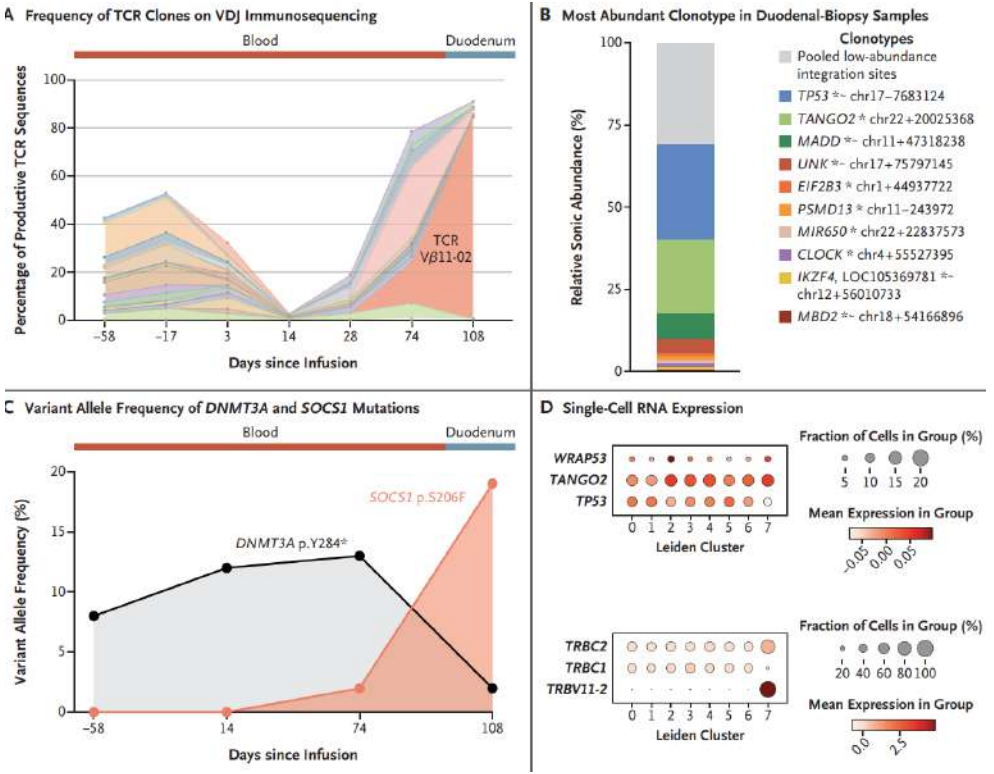


No T cell malignancies recorded

Lorenc R et al. ***Transplantation and Cellular Therapy 2024***; 30: 9901000

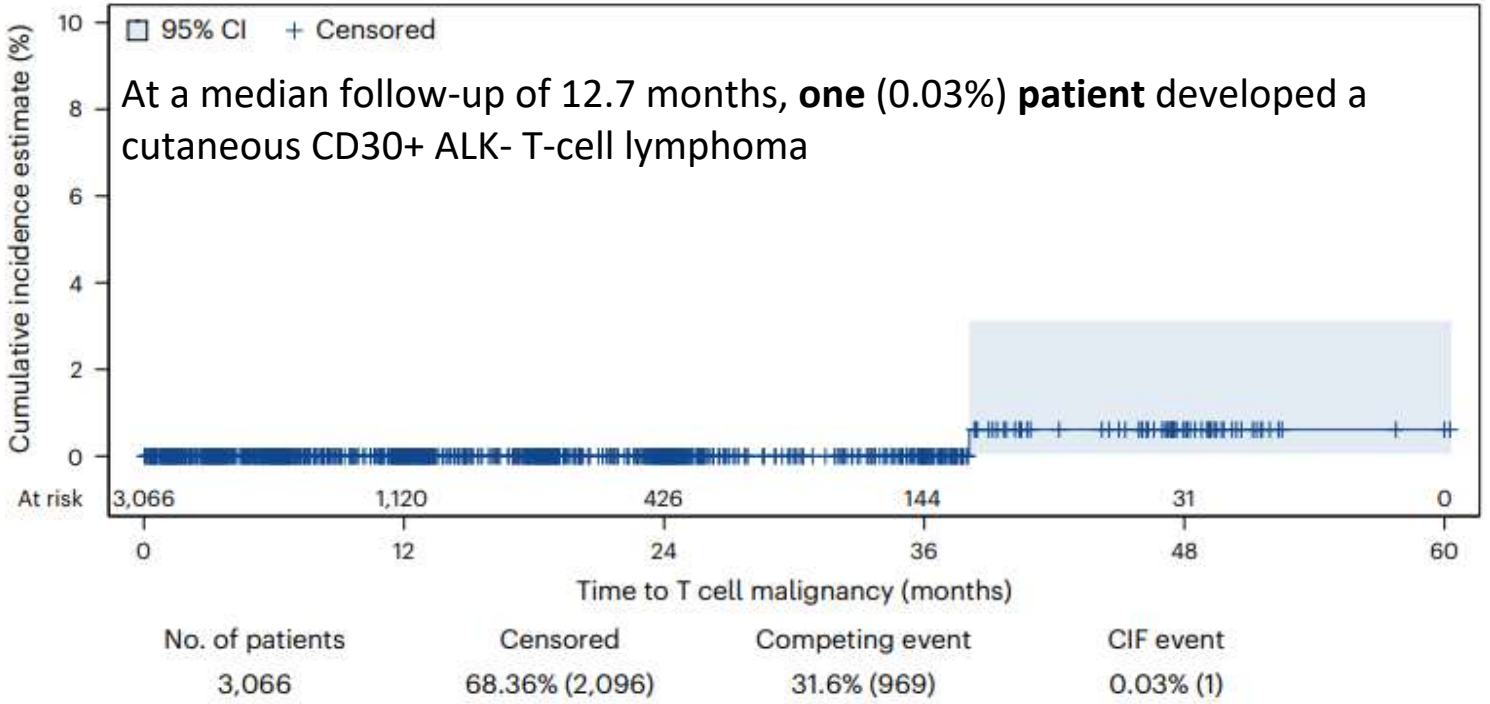
CD4+ T-Cell Lymphoma Harboring a CAR integration in TP53





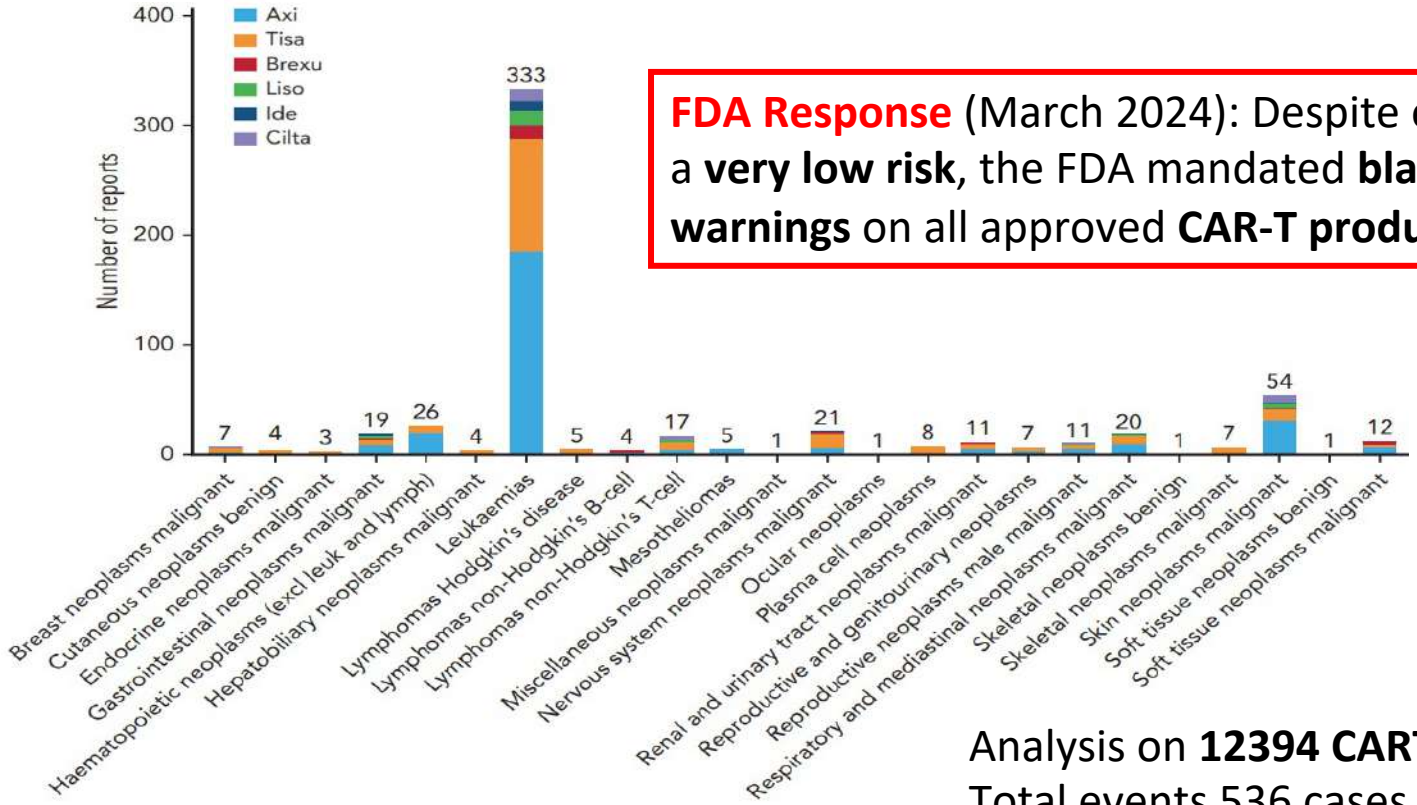
Perica K et al. ***N Engl J Med 2025***;392:577-83.

Secondary T-cell malignancies after CAR-T: DESCAR-T registry



Dulery R et al. ***Nat Med 2025**; 31: 1130–1133*

SPMs: FDA Adverse Events Reporting System



FDA Response (March 2024): Despite estimating a **very low risk**, the FDA mandated **black box warnings** on all approved **CAR-T products**.

Analysis on **12394 CART patients**
Total events 536 cases (**4.3%**)

Elsallab M et al. ***Blood 2024***; 143: 2099-2105

Incidence and risk factors for secondary malignancies after CART

CIBMTR data (8040 pts) over a median follow-up of 12 months: second malignancies occurred in **4.4% of treated patients**

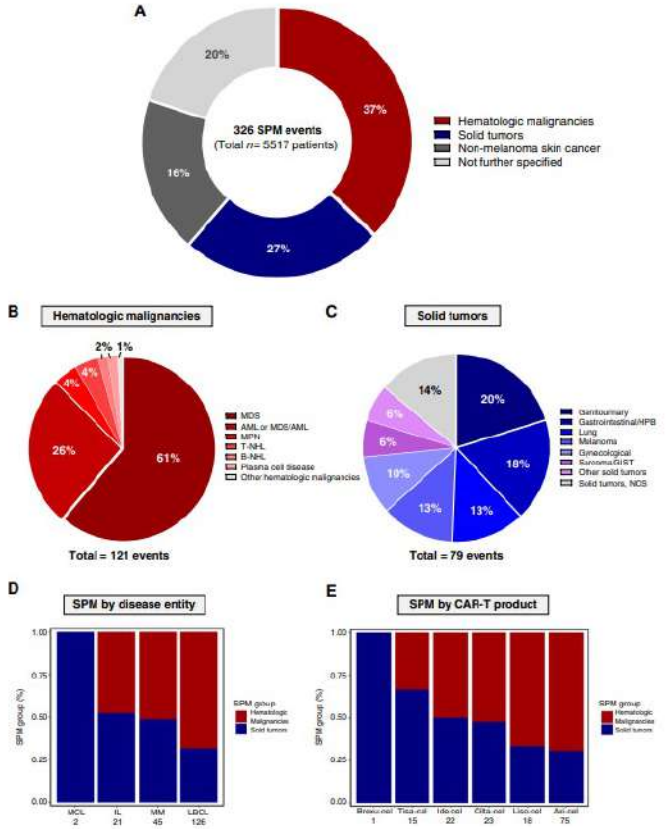
Meta-analysis in 5517 patients: **6% at 22 months**; **37% hematological malignancies. No differences as compared to SOC**

Risk factors:

- enrollment in clinical trials

- longer follow-up

- more lines of previous therapy



Levine BL et al. ***Nat Med. 2024***;30(2):338–341; Tix et al. ***Clin Cancer Res. 2024***;30:4690–700.

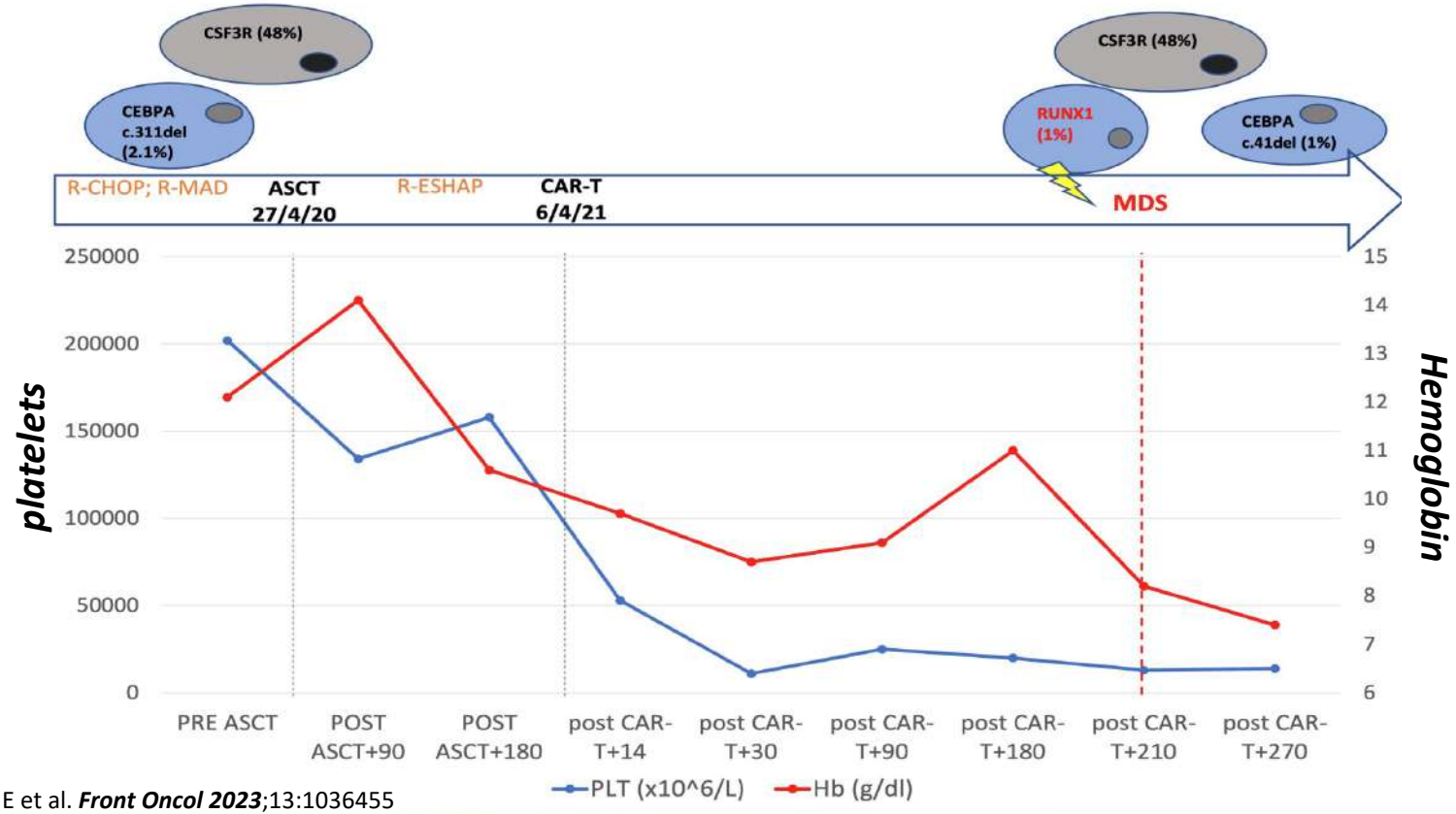
Second malignancies after CAR-T in Europe: EBMT survey

EBMT survey on **secondary hematological neoplasm**.
The survey was open from 09/11/2023 to 30/06/2024

122 centers participated representing **28 countries**
CART performed: **7261**
Secondary primary **neoplasms**: **83 (0,1%)**
T cell malignancy: **1 (0,0001%)**

Under preparation

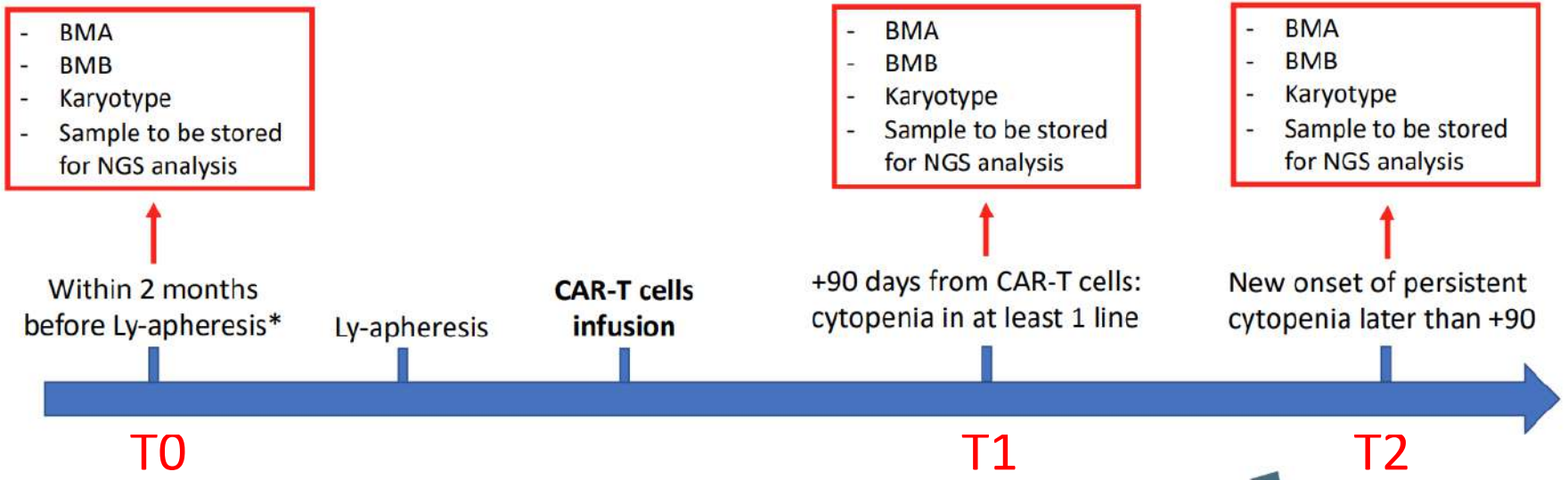
Secondary MDS: the role of clonal hematopoiesis



Accorsi-Buttini E et al. ***Front Oncol 2023***;13:1036455

Secondary MDS/AML after CART: the ClonHema-CAR-T project

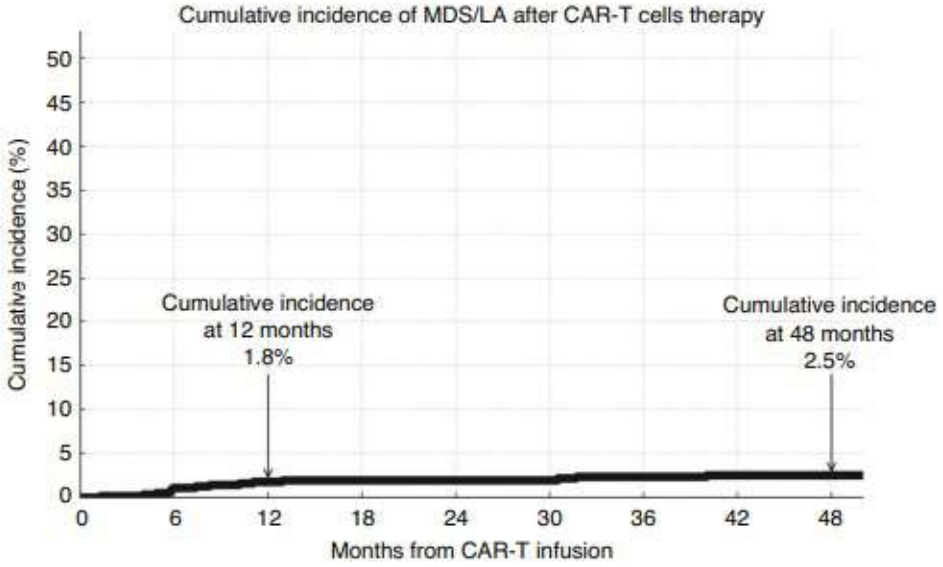
Study of clonal hematopoiesis on patients undergoing CAR-T cells therapy (ClonHema-CAR-T Study). Involving 15 Italian GITMO Centers

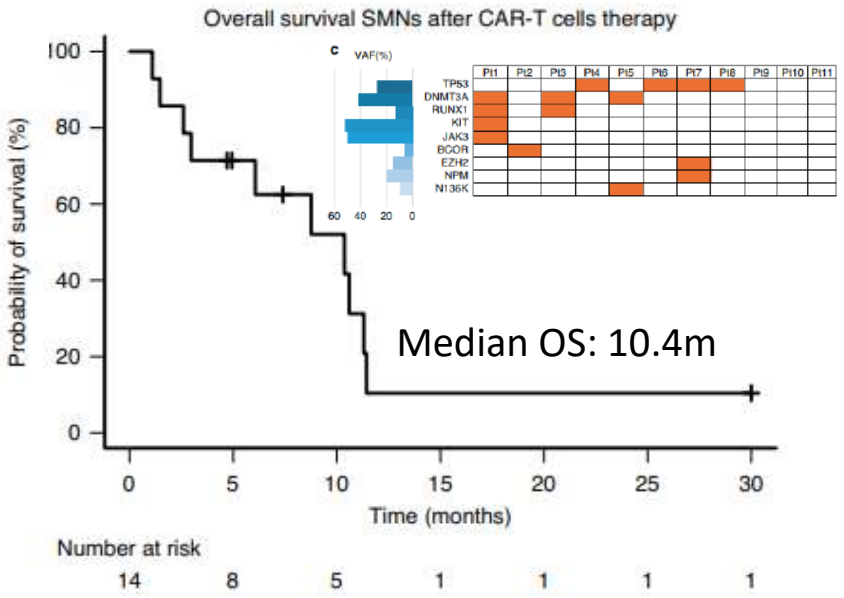


GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

Incidence of MDS/AML after CART: the ClonHema experience

555 patients submitted to commercial CART from Nov 2019 to May 2024. **Median f-up 29m**.





Farina M et al. ***Bone Marrow Transplantation 2025***; 60:702–704

Conclusions

Patients with **hematological malignancies** have a **higher risk** of developing second primary **malignancies** (SPMs), both solid and hematologic, **compared to the general population**, **regardless** of **CAR-T** therapy.

The **incidence** of SPMs following CAR-T treatment is **relatively low**; however, specific **oncogenic mechanisms** have been **described** and should be carefully considered when managing these patients.

All patients undergoing CAR-T therapy should receive thorough **counseling** and long-term **surveillance** within a **multidisciplinary care model** to enable **early detection** of SPMs.

In this context, further **research** is **warranted** to better elucidate the underlying mechanisms of therapy-related oncogenesis

Bishop M. ***Hematology Am Soc Hematol Educ Program 2024;*** (1):109-115.

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